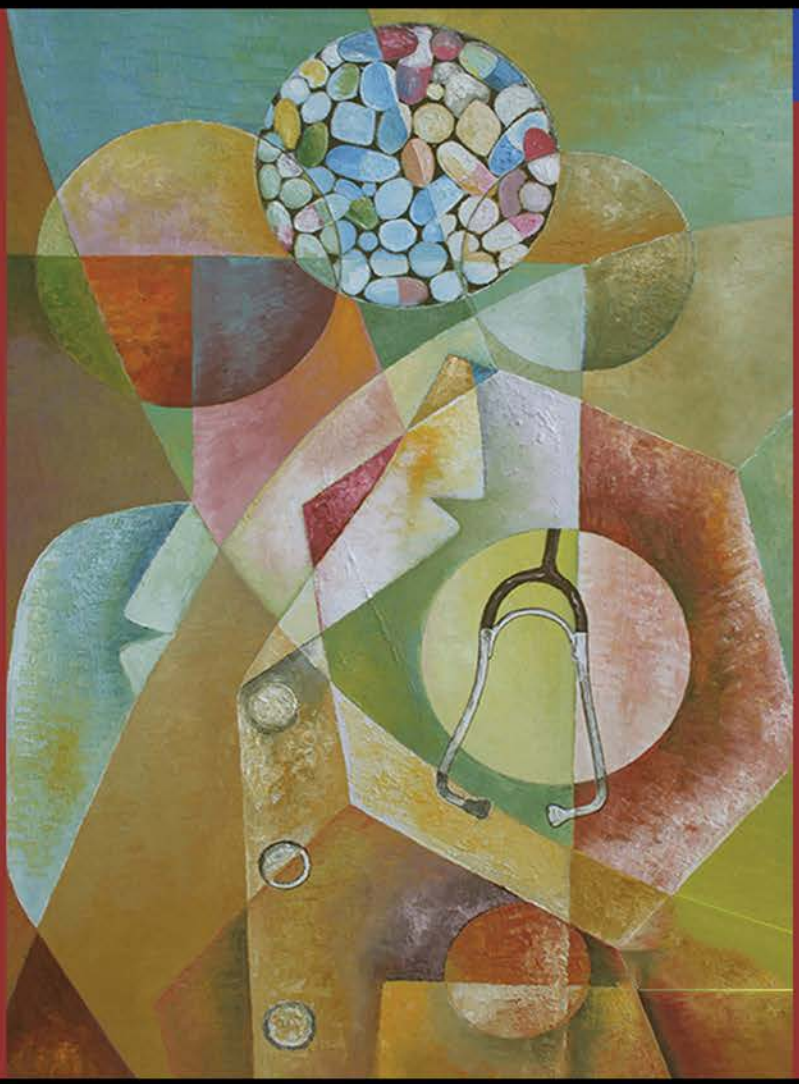
FIFTH EDITION

Pharmacotherapy

Principles & Practice



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Mc Graw Hill Education

Pharmacotherapy Principles & Practice

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Pharmacotherapy Principles & Practice

FIFTH EDITION

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PREFACE

Effective use of pharmacotherapy is vital for preventing and treating acute and chronic medical conditions. Although biomedical research continues to develop and provide medications with enormous potential to improve health, these same medications are often overused, underused, or misused, leading to suboptimal or unsafe results. It is our responsibility as health care practitioners to optimize positive health outcomes and limit adverse pharmacotherapeutic effects.

Provision of high quality, cost-effective pharmacotherapy requires an integration of scientific knowledge and clinical practice skills combined with a fiduciary responsibility to put the patient's needs first. The development of mature pharmacotherapists occurs through structured learning processes that include formal coursework, independent study, mentorship, interprofessional experiences, and direct involvement in the care of actual patients.

The fifth edition of *Pharmacotherapy Principles & Practice* is designed to provide student learners and health care practitioners with essential knowledge of the pathophysiology and pharmacotherapeutics of disease states likely to be encountered in routine practice. Chapters are written by content experts and peer reviewed by pharmacists, nurse practitioners, physician assistants, and physicians who are authorities in their professional disciplines.

Pharmacotherapy Principles & Practice, fifth edition, opens with an introductory chapter followed by chapters on pediatrics, geriatrics, and palliative care. Most of the remainder of the book consists of disease-based chapters that review disease epidemiology, etiology, pathophysiology, clinical presentation and diagnosis, and nonpharmacologic therapy, followed by an emphasis on clear therapeutic recommendations for medication selection, desired outcomes expected, dosing, and patient monitoring. The following features were designed in collaboration with educational design specialists to enhance learning and retention:

- *Structured learning objectives* at the beginning of each chapter, *w*ith information in the text that corresponds to each learning objective identified by a vertical rule in the margin, allowing the reader to quickly find content related to each objective.
- *Key concepts related to the disease, patient assessment, and treatment* highlighted with an easily identifiable icon throughout the chapter.
- *Patient encounters* that facilitate development of critical thinking skills and lend clinical relevance to the scientific foundation provided.
- A newly designed *patient care process* section modeling the Joint Commission of Pharmacy Practitioners (JCPP) Pharmacists' Patient Care Process that provides specific recommendations about the process of care for an individual patient involving five steps: collecting information, assessing information, developing a care plan, implementing the care plan, and following-up: monitor and evaluate.
- *Up-to-date literature citations* for each chapter to support treatment recommendations.
- *Tables, figures, and algorithms* that enhance understanding of pathophysiology, clinical presentation, medication selection, pharmacokinetics, and patient monitoring.
- *Medical abbreviations and their meanings* at the end of each chapter to facilitate learning the accepted shorthand used in real-world health care settings.
- *Self-assessment questions and answers for each chapter* in the Online Learning Center to facilitate self-evaluation of learning.
- *Laboratory values* expressed as both conventional units and Système International (SI) units.
- *Appendices* that contain: (1) conversion factors and anthropometrics; (2) common medical abbreviations; (3) glossary of medical terms (the first use of each term in a chapter appears in bold, colored font); and (4) prescription writing principles.
- *A table of common laboratory tests and reference ranges* appears on the inside covers of the book.

A companion textbook, *Pharmacotherapy Principles and Practice Study Guide: A Case-Based Care Plan Approach*, is available to further enhance learning by guiding students through the process of applying knowledge of pharmacotherapy to specific patient cases. This study guide contains approximately 100 patient cases that correspond to chapters published in the textbook.

The Online Learning Center at www.ChisholmPharmacotherapy.com provides self-assessment questions, grading and immediate feedback on the questions, and reporting capabilities. The complete textbook and study guide are available to subscribers of the publisher's AccessPharmacy site (www.accesspharmacy.com), an online educational resource for faculty and students of the health professions.

We are extremely grateful for the commitment and dedication of more than 190 contributing authors and more than 100 peer reviewers of the chapters in this new edition. We also thank the many educators, schools/colleges, and health care institutions that have adopted this textbook in courses or use it as a reference in practice settings. In closing, we extend our sincere thanks to the McGraw-Hill Education editorial team for their hard work and commitment to bringing this new edition to our readership.

The Editors
August 2018

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Editors Emeriti

The following individuals were founding editors and participated in the first four editions. Their contributions have been invaluable and are greatly appreciated:

- Barbara G. Wells, PharmD, FASHP, FCCP
- Joseph T. DiPiro, PharmD, FCCP

Original Artwork

Title: The Art of Pharmacotherapy

Cover illustration and design copyright © 2018 by Obi-Tabot Tabe, PharmD. The image is taken from an 18′ × 24′ oil painting by Obi-Tabot Tabe, PharmD, a painter, graphic designer, scientific illustrator, and pharmacist. The painting is housed at the University of Pittsburgh School of Pharmacy.

Dr. Tabe, originally from Cameroon, is a graduate of the University of Pittsburgh School of Pharmacy. The pharmacist scope of practice is expanding, and pharmacists are taking on a greater patient care role in collaborative drug therapy with physicians and other healthcare professionals. The painting depicts the collaborative relationship between the disciplines of pharmacy and medicine in the art of pharmacotherapy. Basic dispensing functions, drug information services, solutions to patient- and medication-related problems, and decisions regarding drug prescribing, monitoring and drug regimen adjustments are all collaborative efforts in pharmacotherapy. The intersecting circles represent collaboration between pharmacists, physicians, and other healthcare professionals in the art of pharmacotherapy. The subtle greens and blues in the painting, including carbon rings and molecular structures, represent natural and synthetic medicines. The pills (tablets and capsules) in one of the circles represent the knowledge and expertise of the pharmacist in drug information services and drug therapy; the stethoscope represents the clinical environment; and the pharmacokinetic curves represent the vitality to drug monitoring and adjustments.

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On the occasion of her retirement, we especially acknowledge the many years of dedicated service provided by Ms. Laura Libretti, Administrative Assistant at McGraw-Hill Education.

Part I

Basic Concepts of Pharmacotherapy Principles and Practices

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1 Introduction

Jack E. Fincham

INTRODUCTION

Health professionals are given significant responsibilities in our health care system. These roles may be taken for granted by patients until a pharmacist, nurse practitioner, physician assistant, physician, or others perform assigned tasks that make positive impacts upon patients and patients' families lives in countless ways. The exemplary manner in which health professionals provide necessary care to patients is a hallmark of health professional practice and delivery of US health care. Patients are thus well served, and fellow health professionals share knowledge and expertise specific to their profession. However, there are significant problems remaining in the US health care system from a structural standpoint. In 2016, the United States spent 17.2% of the gross domestic product (GDP) on health care,[1] yet the United States ranks 37th in the world when considering outcomes of care. Comparing the United States to similar industrialized countries, we rank 11th out of 11 comparator countries, and have poorer health outcomes.[2] The reasons for why the United States compares poorly with other countries will be discussed in the following paragraphs.

Tremendous uncertainty surrounds the current health care system in the United States. Efforts to repeal and replace the Patient Protection and Affordable Care Act (ACA) have failed at the US Congressional level. Bipartisan calls for improving the current ACA have met with both encouragement and disdain, depending upon the point of view of those speaking. Regardless of the form of health care delivery and insurance for such, the very bright note to point out is the realization of the excellence of the delivery and outcomes of care provided by US health care professionals. Health professionals improve the health of Americans daily through many efforts and accomplishments.

A significant issue in the United States is that countless other Americans in our midst are underinsured. They may have partial coverage after a fashion, but, for these Americans, the high price of deductibles, co-pays, and monthly payments for insurance create an economic dilemma each time they seek care or pay premiums. In a comprehensive report from Kalorama Information,[3] it was noted that consumer out-of-pocket health care costs have risen from $250 per year in 1980 to over $1400 in 2016. It was also noted in this report that those in less comprehensive health care coverage insurance plans have delays in treatment, which lead to increasing costs in the long term. Recently, Howard Bauchner, MD, the editor-in-chief of JAMA and The JAMA Network, has called for health professionals and professional organizations to speak with one voice and support health care coverage as a right for all.[4]

Recent US Center for Medicare and Medicaid (CMS) expenditure data projections posit that, in 2025 in the United States, a total of $4.72 trillion will be spent on health care.[5] The projection for spending on prescription drugs in 2025 is estimated to total $1.7 billion.[6]

There are tremendous opportunities for health professionals due to the implementation of outcome measures (clinical, economic, humanistic) via the ACA. For the first time in the structure of the US health care system there is now a tangible, significant effort to enhance the quality and outcomes of health care delivered.

The use of medications in the health care system provides enormous help to many; lives are saved or enhanced, and lifespans are lengthened. Many other uses of medications lead to significant side effects, worsening states of health, and premature deaths. So, how to separate these disparate pictures of drug use outcomes? You, within your practices and within your networks in the health care workplace, can help to promote the former and diminish the latter. The authors of the chapters in this book have written informative, current, and superb chapters that can empower you to positively influence medication use.

DRUG USE IN THE HEALTH CARE SYSTEM

Prescription medications are used daily; 48.5% of the population uses one prescription drug daily, 21.7% use three or more drugs daily, and 10.6% use five or more prescription drugs daily.[7] Problems occurring with the use of drugs can include:

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

Clinicians are often called upon to resolve problems that occur due to undertreatment, overtreatment, or inappropriate treatment. Individuals can purchase medications through numerous outlets. Over-the-counter (OTC) medications can be purchased virtually anywhere. OTCs are widely used by all age groups. Prescription medications can be purchased through traditional channels (community chain and independent pharmacies), from mail-order pharmacies, through the Internet, from physicians, from health care institutions, and elsewhere. Herbal remedies are marketed and sold in numerous outlets. The monitoring of the positive and negative outcomes of the use of these drugs, both prescription and OTC, can be disjointed and incomplete. Clinicians and health professionals need to take ownership of these problems and improve patient outcomes resulting from drug use.

Although clinicians are the gatekeepers for patients to obtain prescription drugs, patients obtain prescription medications from numerous sources. Patients may also borrow from friends,

relatives, or even casual acquaintances. In addition, patients obtain OTC medications from physicians through prescriptions, on advice from pharmacists and other health professionals, through self-selection, or through the recommendations of friends or acquaintances. Through all of this, it must be recognized that there are both formal (structural) and informal (word-of-mouth) components at play. Health professionals may or may not be consulted regarding the use of medications, and, in some cases, are unaware of the drugs patients are taking.

External variables may greatly influence patients and their drug-taking behaviors. Coverage for prescribed drugs allows those with coverage to obtain medications with varying cost sharing requirements. However, many do not have insurance coverage for drugs or other health-related needs.

Self-Medication

Self-medication can be broadly defined as a decision made by a patient to consume a drug with or without the approval or direction of a health professional. The self-medication activities of patients have increased dramatically in the late 20th and early 21st centuries. Many factors affecting patients have continued to fuel this increase in self-medication. There have been many prescription items switched to OTC classification in the last 50 years, which is dramatically and significantly fueling the rapid expansion of OTC drug usage. In addition, patients are increasingly comfortable with self-diagnosing and self-selection of OTC remedies.

Through the rational use of drugs, patients may avoid more costly therapies or expenditures for other professional services. Self-limiting conditions, and even some chronic health conditions (eg, allergies and dermatologic conditions), if appropriately treated through patient self-medication, allow the patient to have a degree of autonomy in health care decisions.

Compliance Issues

Noncompliance with prescription regimens is one of the most understated problems in the health care system. Approximately 10% of initial prescriptions written by physicians are never filled.[8] Reasons can include trying too soon to obtain a new prescription, prior approval requirements, the prescribed drug may not be covered under the patient's insurance, and so on. The effects of noncompliance have enormous ramifications for patients, caregivers, and health professionals. Noncompliance is a multifaceted problem with a need for interprofessional, multidisciplinary solutions. Interventions that are organizational (how clinics are structured), educational (patient counseling, supportive approach), and behavioral (impacting health beliefs and expectations) are necessary. Compliant behavior can be enhanced through your actions with the patients for whom you provide care. Sometimes what is necessary is referral to specific clinicians for individualized treatment and monitoring to enhance compliance. The case histories provided in this textbook will allow you to follow what others have done in similar situations to optimally help patients succeed in improving compliance rates and subsequent positive health outcomes.

Drug Use by the Elderly

The major source of payment for prescription drugs for those aged 65 years and older in the United States is the Medicare Part D Drug Benefit. Seniors have benefitted tremendously from this component. Estimates place the expenditure for Medicare Part D to be $94 billion in 2017; this is 15.6% of Medicare expenditures.[9] Since the inception of Medicare Part D, recipients have had to pay costs after initial minimum threshold amounts are reached, then enter the so-called "donut hole" requiring payment out of pocket until a certain amount would be paid, and then coverage for payment would ensue. This so-called donut hole closes in 2020, which will provide more benefits for more enrollees. Enhanced use of pharmacoeconomic tenets to select appropriate therapy, while considering cost and therapeutic benefits for seniors and others, will become even more crucial for clinicians in the future.

Unnecessary drug therapy and over medication are problems with drug use in the elderly. Cost estimates are projected to be $1.3 billion per year for elderly patient polypharmacy alone.[10] A joint effort by health professionals working together is the best approach to aiding seniors in achieving optimal drug therapy. Evaluation of all medications taken by seniors at each patient visit can help prevent polypharmacy from occurring.

IMPACTING THE PROBLEMS OF DRUG USE

Medication Errors

There is a tremendous opportunity in medication use and monitoring for working to reduce medication errors. Untold morbidity and mortality occur due to the many errors in medication use. Studies have shown that reconciling the medications that patients take, with coordination by various caregivers providing care, can help reduce medication errors in patient populations.[8]

The incorporation of three key interventions—computerized physician order entry (CPOE), additional staffing, and bar coding—has been shown in an institutional setting to help reduce medication errors.[11]

Avoiding Prescribing Cascades

Prescribing cascades occur in health care when the side effect from a medication is interpreted as a new condition, and a second drug is prescribed to "treat" the side effect. Prescribing cascades are important because they can be prevented.[12]

Impacting the Opioid Crisis

The use and misuse of prescription opioid analgesic medications are at an all-time high and are increasing, and the negative consequences of this epidemic are many.[13] According to the Centers for Disease Control and Prevention (CDC), 91 Americans die daily from an opioid overdose, including prescription opioids and heroin.[14] The opioid crisis is not limited to the United States; it is a North American crisis as well, with the Canadian government providing funding to address the problem.[14,15] The CDC has published and promoted prescribing guidelines to help stem inappropriate prescribing of opioids for chronic pain.[16] Health professionals will play a vital role in reversing this epidemic and enhancing the health of many and society as well.

SUMMARY

Health professionals are at a crucial juncture facing an uncertain, yet promising future. The skills and knowledge that enable effective practice have never been more daunting among the numerous health professions. Technology can further empower health professionals to play an effective role in helping patients and fellow health professionals to practice safe and effective medicine. Health care reform has the potential to dramatically impact your practices in the health care system for the length of your careers.

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

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

REFERENCES

1. Organization for Economic Cooperation and Development, Paris, France; *OECD Health Statistics*. Available from: http://stats.oecd.org/Index.aspx?DataSetCode=SHA. Updated June 2017. Accessed November 3, 2017.
2. Schneider EC, Sarnak DO, Squires D, Shah A, Doty MM. Mirror, Mirror 2017: International Comparison Reflects Flaws and Opportunities for Better U.S. Health Care, The Commonwealth Fund, August, 2017.
3. Out-of-Pocket Healthcare Expenditures in the United States. Rockville, MD: Kalorama Information; April, 2017.
4. Bauchner H. Health care in the United States: a right or a privilege. JAMA. 2017;317(1):29.
5. National Health Expenditure (NHE) Data. United States Centers for Medicare and Medicaid Services. Available from: https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html, Table 5. Updated June 14, 2017. Accessed November 3, 2017.
6. National Health Expenditure (NHE) Data, Table 11. United States Centers for Medicare and Medicaid Services. Available from: https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html. Updated June 14, 2017. Accessed November 3, 2017.
7. National Center for Health Statistics. Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD, 2014.
8. Aitken H, Valkova S. Exhibit 1: Avoidable U.S. healthcare costs add up to $213 billion. Avoidable Costs in U.S. Healthcare: The $200 Billion Opportunity from Using Medicines More Responsibly. Report by the IMS Institute for Healthcare Informatics, June, 2013: p. 3.
9. The Medicare Part D Prescription Drug Benefit. The Henry J. Kaiser Family Foundation. Available from http://www.kff.org/medicare/fact-sheet/the-medicare-prescription-drug-benefit-fact-sheet. Accessed November 9, 2017.
10. Karnon J, McIntosh A, Dean J, et al. Modelling the expected net benefits of interventions to reduce the burden of medication errors. J Health Serv Res Policy. 2008;13:85–91.
11. Franklin BD, O'Grady K, Donyai P, Jacklin A, Barber N. The impact of a closed-loop electronic prescribing and administration system on prescribing errors, administration errors and staff time: a before-and-after study. Qual Saf Health Care. 2007;16:279–284.
12. Kalisch LM, Caughey GE, Roughead EE, Gilbert AL. The prescribing cascade. Aust Prescr. 2011;34:162–166.
13. Fincham JE. The opioid epidemic: healthcare utilization and cost considerations. Am Health Drug Benefits. 2017;10(2):79–86.
14. Drug overdose deaths in the United States continue to increase in 2015. US Centers for Disease Control and Prevention. Available from: www.cdc.gov/drugoverdose/epidemic. Updated August 31, 2017. Accessed November 3, 2017.
15. Government of Canada announces $6 million in emergency funding to combat opioid crisis in Alberta. Available from: www.canada.ca/en/health-canada/news/2017/03/government_of_canadaannounces6millioninemergencyfundingtocombato.html. Accessed November 3, 2017.
16. CDC Guideline for Prescribing Opioids for Chronic Pain. US Centers for Disease Control and Prevention. Available from: www.cdc.gov/drugoverdose/prescribing/guideline.html. Updated August 31, 2017. Accessed November 3, 2017.

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2 Geriatrics

Jeannie K. Lee, Damian M. Mendoza, M. Jane Mohler, and Corinne M. Self

LEARNING OBJECTIVES

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

LO
1. Explain changing aging population demographics.
2. Discuss age-related pharmacokinetic and pharmacodynamic changes.
3. Identify drug-related problems and associated morbidities commonly experienced by older adults.
4. Describe major components of geriatric assessment.
5. Recognize interprofessional patient care functions in various geriatric practice settings.

INTRODUCTION

The growth of the aging population and increasing lifespan require that health care professionals gain knowledge necessary to meeting the needs of this patient group. Despite the availability and benefit of numerous pharmacotherapies to treat their diseases, older patients commonly experience drug-related problems, resulting in additional morbidities. Therefore, it is essential for clinicians serving older adults across all health care settings to understand the epidemiology of aging, age-related physiological changes, drug-related problems prevalent in the elderly, comprehensive geriatric assessment, and interprofessional approaches to geriatric care.

EPIDEMIOLOGY AND ETIOLOGY

As humans age, they are at increasing risk of disease, disability, and death for three reasons: (a) genetic predisposition; (b) reduced immunological surveillance; and (c) the accumulated effects of physical, social, environmental, and behavioral exposures over the life course. Elders experience variably increasing vulnerability (homeostenosis) as they age, resulting in heterogeneity in health states and care requirements. While resilient elders can maintain high levels of physical and cognitive functioning, others suffer functional decline, frailty, disability, or premature death. There is an urgent need for all clinicians to better understand the epidemiology of aging in order to comprehensively provide high value services to optimize the function and health-related quality of life of older adults.[1]

Sociodemographics

▶ *Population*

KEY CONCEPT Our population is rapidly growing older. In 2015, 47.8 million US residents were 65 years and older (nearly 15% of the total population), with projections to more than double to 98 million by 2060.[2] Almost 6.3 million people were 85 years or older (the "oldest-old"), and nearly 77 thousand persons were aged 100 or older.[3] Those 85+ years individuals are projected to triple from 6.3 million in 2015 to over 14.6 million in 2040.[3] In 2015, older women aged 65 years and above (26.7 million) outnumbered older men (21.1 million), with a ratio of 100 women to 79 men; this ratio widens as elders age. In addition, minority elders are projected to increase to 21.1 million in 2020.[3] With changing aging population demographics, surviving baby boomers will be disproportionally female, more ethnically/racially diverse, better educated, live alone, and have more financial resources than were elders in previous generations.

LO 1

▶ *Economics*

More elders are enjoying higher economic prosperity than ever before, with only 10% living below the poverty line.[4] However, major inequalities persist, with older blacks and those without high school diplomas reporting fewer financial resources.[4] Considerable disparities exist, and may prevent less advantaged elders from being able to purchase all prescribed medications.

▶ *Education and Health Literacy*

By 2007, more than 75% of US elders had graduated from high school, and nearly 20% had a bachelor's degree or higher. Still, substantial educational differences exist among racial and ethnic minorities. While more than 80% of non-Hispanic white elders had high school degrees in 2007, 72% of Asians, 58% of blacks, and 42% of Hispanic elders were graduates.[5] Nearly 40% of people 75 years or older have low health literacy, more than any other age group.[4] Despite these limitations, the Pew Trust reports that today, 67% of adults aged 65 years and older say they use the Internet,[6] and large health care systems are increasingly offering online health information to older health consumers. These advances are important because communication between health care providers and elders is vital in providing quality care, supporting self-care, and in negotiating transitions of care.

Health Status

▶ *Life Expectancy*

Although Americans are living longer than ever before, an estimated average of 78.74 years overall in 2015, US life expectancy lags behind that of many other industrialized nations.[5] Life expectancy has increased; elders who survive to age 65 can expect to live an average of 19.3 more years.[4] Disparities in mortality persist, in 2014 life expectancy at birth for the white population

was 3.4 years longer than for the black population, a decrease of 1.8 years since 2004.[4] Nearly 35% of US deaths in 2000 were attributed to three risk behaviors: smoking, poor diet, and physical inactivity. Currently, only 9% of Americans older than 65 years smoke; however, nearly 54% of men and 21% of women are former smokers.[4,7] Overweight elders 65 to 74 years of age increased from 57% to 73% in 2004 largely due to inactivity and a diet high in refined foods, saturated fats, and sugared beverages.[4] Despite the proven health benefits of regular physical activity, more than half of the older population is sedentary; 47% of those 65 to 74 years and 61% older than 75 years report no physical activity and only 12% of people aged 65 years and older report participating in leisure-time aerobic and muscle-strengthening activities that meet US physical activity guidelines.[4,8]

The 2016 National Health Interview Survey indicated that in 2012–2014, older non-Hispanic White people were more likely to report good to excellent health than were non-Hispanic Black and Hispanic peers (80% vs 65% and 66%, respectively).[9] Approximately 80% of older adults have at least one chronic condition, and 50% have at least two. The prevalence of certain chronic conditions differs by sex, with women reporting higher levels of arthritis (54% vs 43%), and men reporting higher levels of heart disease (37% vs 26%) and cancer (24% vs 19%).[6] In 2014, the leading causes of death were heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer disease, diabetes, unintentional injuries (mostly falls), and influenza and pneumonia regardless of sex, race, or ethnicity.[4] Figure 2–1 specifies the most common chronic conditions of older adults by sex. Frailty is a common biological syndrome in the elderly. Once frail, elders may rapidly progress toward failure to thrive and death. Only 3% to 7% of elders between the ages of 65 and 75 years are frail, increasing to more than 32% in those older than 90 years.[10]

Health Care Utilization and Cost

KEY CONCEPT Older Americans use more health care services than younger Americans do. Although older adults with one or more hospital stays decreased from 2000 to 2014 (18% vs 15.2%), they accounted for more than half of hospitalizations overall, with longer lengths of stay corresponding to increasing age.[11] In 2010 there were 1.3 million (3.6%) US nursing home residents aged 65 and older, and as the aged live longer, more will require assistance, which will be increasingly performed in the home. Health care costs among older Americans are greater than the cost for someone younger than 65 years. In 2015, older Americans spent 12.9% of their total expenditures on health

Patient Encounter Part 1

UA is a 78-year-old woman who moved to the United States after she retired to help care for her three grandchildren. Though UA finished high school in Brazil, she speaks very little English and has limited health literacy, even with the interpretation service. UA comes to the Interprofessional Geriatrics Clinic to receive comprehensive care of her multimorbidity and polypharmacy. Her past medical history includes hypertension, diabetes, dyslipidemia, stroke, hypothyroidism, arthritis, depression, insomnia, and peripheral neuropathy. UA uses 16 medications for her multiple chronic conditions and herbal supplements for "brain health." She is overweight, though reports trying to eat "healthy." She walks the family dog for about 30 minutes once a week and daily when her daughter's family is out of town.

What information is consistent with epidemiology of aging?

Which of UA's medical conditions are commonly found in older adults?

What additional information do you need before conducting a comprehensive medication review?

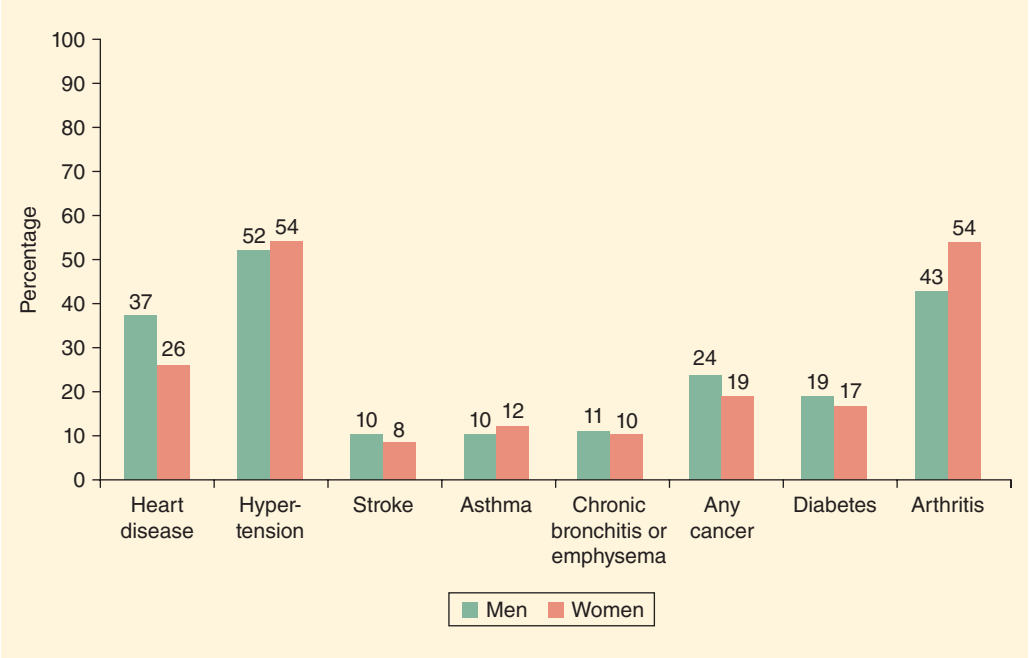


FIGURE 2–1. Percentage of people 65 years and older who reported having selected chronic conditions, by sex, 2005 to 2006. Note: Data are based on a 2-year average from 2005 to 2006. Reference population: These data refer to the noninstitutionalized population. (From Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey.)

compared with 7.8% among all consumers.[3] Medicare plays a major role in health care costs, accounting for 20% of total US health spending in 2012, 27% of spending on hospital care, and 23% of spending on physician services.[12]

By applying the epidemiology of aging, clinicians can better intervene with pharmacotherapy to postpone disease, disability, and mortality, and promote health, functioning, and health-related quality of life.

AGE-RELATED CHANGES

In basic terms, pharmacokinetics is what the body does to the drug, and pharmacodynamics is what the drug does to the body. KEY CONCEPT All four components of pharmacokinetics—absorption, distribution, metabolism, and excretion—are affected by aging; the most clinically important and consistent is the reduction of renal elimination of drugs.[13] As people age, they can become more frail and are more likely to experience altered and variable drug pharmacokinetics and pharmacodynamics. Even though this alteration is influenced more by a patient's clinical state than their chronological age, the older patient is more likely to be malnourished and suffering from diseases that affect pharmacokinetics and pharmacodynamics.[14] Older adults can develop significant drug-related problems when alterations in pharmacokinetics and pharmacodynamics are not appropriately accounted for in prescribing and monitoring of medications.[13] Clinicians have the responsibility to use pharmacokinetic and pharmacodynamic principles to improve the care of older patients and avoid adverse effects of pharmacotherapy. Due to the multitude of changes described below, many medications used to treat chronic conditions in older adults should be started at 50% of the recommended initial adult dose, and doses titrated slowly. This is a general recommendation to consider when initiating medications such as antihypertensives and antidepressants, but does not apply to the treatment of acute illness (eg, antibiotics for pneumonia).

LO 2

Pharmacokinetic Changes

▶ *Absorption*

Multiple changes occur throughout the GI tract with aging, but little evidence indicates that drug absorption is significantly altered. The changes include decreases in overall surface of the intestinal epithelium, gastric acid secretion, and splanchnic blood flow.[13] Peristalsis is weaker and gastric emptying delayed. These changes slow absorption in the stomach, especially for enteric-coated and delayed-release preparations. Delays in absorption may lead to a longer time required to achieve peak drug effects, but it does not significantly alter the amount of drug absorbed, and drug movement from the GI tract into circulation is not meaningfully changed.[13,14] However, relative **achlorhydria** can decrease the absorption of nutrients such as vitamin B_{12}, calcium, and iron.[14]

Aging facilitates atrophy of the epidermis and dermis along with a reduction in barrier function of the skin. Tissue blood perfusion is reduced, leading to decreased or variable rates of transdermal, subcutaneous, and intramuscular drug absorption. Therefore, intramuscular injections should generally be avoided in older adults due to unpredictable drug absorption.[13] Additionally, because saliva production decreases with age, medications that need to be absorbed rapidly by the buccal mucosa are absorbed at a slower rate. Yet, for most drugs, absorption is not significantly affected in older patients and the changes described are clinically inconsequential.[14,15]

▶ *Distribution*

The main physiological changes that affect distribution of drugs in older adults are changes in body fat and water, and changes in protein binding. Lean body mass can decrease by 12% to 19% through loss of skeletal muscle in older adults. Thus, blood levels of drugs primarily distributed in muscle increase (eg, digoxin), presenting a risk for overdose.[14] While lean muscle mass decreases, adipose tissue can increase with aging by 18% to 36% in men and 33% to 45% in women. Therefore, fat-soluble drugs (eg, diazepam, amitriptyline, amiodarone, valproic acid, and verapamil) have increased volume of distribution (V_d), leading to higher tissue concentrations and prolonged duration of action. Greater V_d leads to increased half-life and time required to reach steady-state serum concentration.[13,14]

Total body water decreases by 10% to 15% by age 80. This lowers V_d of hydrophilic drugs (eg, aspirin, digoxin, morphine, lithium, and ethanol) leading to higher plasma drug concentrations than in younger adults when equal doses are used.[13,14] Thus lower doses are needed to prevent toxicity. Toxic drug effects may be enhanced when dehydration occurs and when the extracellular space is reduced by diuretic use.

Likewise, plasma albumin concentration decreases by 10% to 20%, although disease and malnutrition contribute more to this decrease than age alone.[13] In patients with an acute illness, rapid decreases in serum albumin can increase drug effects. Examples of highly protein-bound drugs include warfarin, phenytoin, and diazepam.[14] For most chronic medications, these changes are not clinically important because although the changes affect peak level of a single dose, mean serum concentrations at steady state are not altered unless clearance is affected.[14] For highly protein-bound drugs with narrow therapeutic indices (eg, phenytoin), however, it is important to appropriately interpret serum drug levels in light of the older patient's albumin status. In a malnourished patient with hypoalbuminemia, a higher percentage of the total drug level consists of free drug than in a patient with normal serum albumin. Thus, if a hypoalbuminemic patient has a low total phenytoin level and phenytoin dose is increased, the free phenytoin concentration may rise to a toxic level.

▶ *Metabolism*

Drug metabolism is affected by age, acute and chronic diseases, and drug–drug interactions. The liver is the primary site of drug metabolism, which undergoes changes with age; though the decline is not consistent, older patients have decreased metabolism of many drugs.[13,16] Liver mass is reduced by 20% to 30% with advancing age, and hepatic blood flow is decreased by as much as 50%.[15] These changes can drastically reduce the amount of drug delivered to the liver per unit of time, reduce its metabolism, and increase the half-life.[14] Metabolic clearance of some drugs is decreased by 20% to 40% (eg, amiodarone, amitriptyline, warfarin, and verapamil), but it is unchanged for drugs with a low hepatic extraction.[14] Drugs that have high **extraction ratios** have significant first-pass metabolism, resulting in higher bioavailability for older adults. For example, the effect of morphine is increased due to a decrease in clearance by around 33%. Similar increases in bioavailability can be seen with propranolol, levodopa, calcium channel blockers, tricyclic antidepressants, and statins. Thus, older patients may experience a similar clinical response to that of younger patients using lower doses of these medications.[14-16]

The effect of aging on liver enzymes (cytochrome P450 system [CYP450]) may lead to a decreased elimination rate of drugs that undergo oxidative phase I metabolism, but this is controversial.[13] Originally, it was thought that the CYP450 system was impaired

in older adults, leading to decreased drug clearance and increased serum half-life, but studies have not consistently confirmed this. Thus variations in the CYP450 activity may not be due to aging but to lifestyle (eg, smoking), illness, or drug interactions.[14-16] A patient's nutritional status plays a role in drug metabolism as well. Frail elderly have a more diminished drug metabolism than those with healthy body weight.[13,16] Aging does not affect drugs that undergo phase II hepatic metabolism, known as conjugation or glucuronidation, but conjugation is reduced with frailty. Temazepam and lorazepam are examples of drugs that undergo phase II metabolism.[14]

▶ *Elimination*

Clinically, the most important pharmacokinetic change in older adults is the decrease in renal drug elimination.[13] As people age, renal blood flow, renal mass, glomerular filtration rate, filtration fraction, and tubular secretion decrease. After age 40, there is a decrease in the number of functional glomeruli, and renal blood flow declines by approximately 1% yearly. From age 25 to 85 years, average renal clearance declines by as much as 50% and is independent of the effects of disease.[13,14] Still, the impact of age on renal function is variable and not always linear. Longitudinal studies have suggested that a percentage (up to 33%) of older adults do not experience this age-related decline in renal function.[15] Clinically significant effects of decreased renal clearance include prolonged drug half-life, increased serum drug level, and increased potential for **adverse drug reactions (ADRs)**.[13] Special attention should be given to renally eliminated drugs with a narrow therapeutic index (eg, digoxin, aminoglycosides). Monitoring serum concentration and making appropriate dose adjustment for these agents can prevent serious ADR resulting from drug accumulation.[14] It is important to note that despite a dramatic decrease in renal function (creatinine clearance) with aging, serum creatinine may remain fairly unchanged and remain within normal limits. This is because older patients, especially the frail elderly, have decreased muscle mass resulting in less creatinine production for input into circulation.[13,14] Because chronic kidney disease can be overlooked if a clinician focuses only on the serum creatinine value, overdose and ADR can occur.

Thus, creatinine clearance should be calculated when starting or adjusting pharmacotherapy in older adults. Clearance measure using 24-hour urine collection is impractical, costly, and often done inaccurately. The Cockcroft-Gault equation is the most widely used formula for estimating creatinine clearance (mL/min) for adjusting drug doses. See Chapter 25 (Table 25–2) for more details.

$$\text{Creatinine clearance} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine} \times 72} \times (0.85 \text{ if female})$$

This equation is also used by most drug manufacturers to determine renal dosing guidelines. The Cockcroft-Gault equation provides the best balance between predictive ability and bias in a study that compared it with the Modification of Diet in Renal Disease (MDRD) and Jelliffe "bedside" clearance equations.[14] The Cockcroft-Gault equation can overestimate renal function in obese individuals. In these cases an adjusted body weight should be used in the calculation [AjBW = IBW + 0.4(ABW – IBW)]. Understand that the predictive formulas can also significantly overestimate actual renal function in chronically ill, debilitated older patients.

Pharmacodynamic Changes

Pharmacodynamics refers to the actions of a drug at its target site and the body's response to that drug. Compared to pharmacokinetics, there is much less data on age-related pharmacodynamic changes. KEY CONCEPT In general, the pharmacodynamic changes that occur in older adults tend to increase their sensitivity to drug effects. Most pharmacodynamic changes in the elderly are associated with a progressive reduction in homeostatic mechanisms and changes in receptor properties. Although the end result of these changes is an increased sensitivity to the effects of many drugs, a decrease in response can also occur. The changes in the receptor site include alterations in binding affinity of the drug, number or density of active receptors at the target organ, structural features, and postreceptor effects (biochemical processes/signal transmission). These include receptors in the adrenergic, cholinergic, and dopaminergic systems, as well as γ-*aminobutyric acid* (GABA) and opioid receptors.[13-15]

▶ *Cardiovascular System*

Decreased homeostatic mechanisms in older adults increase their susceptibility to orthostatic hypotension when taking drugs that affect the cardiovascular system and lower the arterial blood pressure. This is explained by a decrease in arterial compliance and baroreceptor reflex response, which limits their ability to compensate quickly for postural changes in blood pressure. It has been estimated that 5% to 33% of older adults experience drug-induced orthostasis. Examples, other than typical antihypertensives, that have a higher likelihood of causing orthostatic hypotension in geriatric patients are tricyclic antidepressants, antipsychotics, loop diuretics, direct vasodilators, and opioids.[13-15] Older patients have a decreased β-adrenergic receptor function, and they are less sensitive to β-agonist and β-adrenergic antagonist effects in the cardiovascular system and possibly in the lungs, but their response to α-agonists and antagonists is unchanged.[14,15] Increased hypotensive and heart rate response (to a lesser degree) to calcium channel blockers (eg, verapamil) are reported. Increased risk of developing drug-induced QT prolongation and **torsade de pointes** is also present.[15] Therefore, clinicians must start medications at low doses and titrate slowly, closely monitoring the patient for any adverse effects.

▶ *Central Nervous System*

Overall, geriatric patients exhibit a greater sensitivity to the effects of drugs that gain access to the CNS, especially anticholinergic medications. In most cases, lower doses result in adequate response, and higher incidence of adverse effects may be seen with standard and high doses. For example, lower doses of opioids provide sufficient pain relief for older patients, whereas conventional doses can cause oversedation and respiratory depression.[13,14] The blood–brain barrier becomes more permeable as people age; thus more medications can cross the barrier and cause CNS adverse effects. Examples of problematic medications include benzodiazepines, antidepressants, antipsychotics, neuroleptics, and antihistamines. There is a decrease in the number of cholinergic neurons as well as nicotinic and muscarinic receptors, decreased choline uptake from the periphery, and increased acetylcholinesterase.[14,15] Older adults have a decreased ability to compensate for these imbalances of the neurotransmitters, which can lead to movement and memory disorders. Older adults have an increased number of dopamine type 2 receptors, making them more susceptible to delirium from anticholinergic

and dopaminergic medications. At the same time, they have a reduced number of dopamine and dopaminergic neurons in the substantia nigra of the brain resulting in higher incidence of extrapyramidal symptoms from antidopaminergic medications (eg, antipsychotics).[13,15]

▶ *Fluids and Electrolytes*

Fluid and electrolyte homeostatic mechanism is decreased in the older adult population. Older adults experience more severe dehydration with equal amounts of fluid loss compared with younger adults. The multitude of factors involved include decreased thirst and cardiovascular reflexes, decreased fluid intake, decreased ability of the kidneys to concentrate urine, increased atrial natriuretic peptide, decreased aldosterone response to hyperkalemia, and decreased response to antidiuretic hormone. The result is an increased incidence of hyponatremia, hyperkalemia, and prerenal azotemia, especially when the older patient is taking a diuretic (eg, hydrochlorothiazide, furosemide). Angiotensin-converting enzyme inhibitors have an increased potential to cause hyperkalemia and acute renal failure in older adults. Thus these agents need to be started with low doses, titrated slowly, and renal function should be monitored frequently.[13]

▶ *Glucose Metabolism*

An inverse relationship between glucose tolerance and age has been reported. This is likely due to reduced insulin secretion and sensitivity (greater insulin resistance). Consequently, the incidences of hypoglycemia are increased when using sulfonylureas (eg, glyburide, glipizide) from age-related impairment to counter-regulate the hypoglycemic response.[13] Due to an impaired autonomic nervous system, older patients may not distinguish symptoms of hypoglycemia such as sweating, palpitations, or tremors. They do experience neurological symptoms of syncope, ataxia, confusion, or seizures.

Patient Encounter Part 2

UA was recently hospitalized for urinary tract infection. Her daughter (interpreter) states that one of the hospital staff thought UA may need to double up her gabapentin dose due to complaints about pain and stop lisinopril because she was coughing. UA brought in medications used at home since the hospital discharge: (1) lisinopril 20 mg by mouth in the morning, (2) amlodipine 5 mg by mouth in the morning and evening, (3) hydrochlorothiazide 25 mg by mouth in the morning, (4) sertraline 100 mg by mouth in the evening, (5) glyburide 10 mg by mouth in the morning and evening, (6) gabapentin 600 mg by mouth twice a day, (7) atorvastatin 10 mg in the evening, (8) levothyroxine 50 mcg by mouth in the morning, (9) zolpidem 10 mg by mouth at bedtime, (10) calcium-vitamin D 600 mg-500 units by mouth in the morning and evening, (11) acetaminophen 500 mg 2 tablets by mouth every 4 hours as needed for pain, (12) pantoprazole 20 mg by mouth in the morning, (13) vitamin C 5000 mg by mouth in the morning, (14) ibuprofen 200 mg 2 tablets three times a day, (15) gingko biloba 240 mg by mouth in the morning, (16) diphenhydramine 25 mg by mouth at bedtime.

She is allergic to penicillin (hives) and intolerant to lisinopril (cough).

UA does not smoke; has one or two drinks a night.

VS: BP 110/56, P: 70 bpm, RR: 14, T: 38.4°C (101.1°F)

Ht: 5′2″ (157 cm), Wt: 66 kg, Pain 2/10

Labs: Na 141 mEq/L (mmol/L), K 4.2 mEq/L (mmol/L), Cl 98 mEq/L (mmol/L), CO_2 25 mEq/L (mmol/L), BUN 20 mg/dL (7.1 mmol/L), creatinine 1.5 mg/dL (133 µmol/L), glucose 98 mg/dL (5.4 mmol/L), $HgbA_{1c}$ 6.5% (0.065; 48 mmol/mol Hgb)

What is UA's estimated creatinine clearance?

What steps should be taken prior to increasing UA's gabapentin dose?

What drug-related problems are included in UA's medication list?

DRUG-RELATED PROBLEMS

KEY CONCEPT Comorbidities and polypharmacy complicate health status of older adults, particularly inappropriate medications that lead to drug-related problems. It is reported that 28% of hospitalizations in older adults are due to medication-related problems including nonadherence and ADRs. Studies indicated that over 58% of community-dwelling and hospital older adults were prescribed at least one potentially inappropriate medication.[17] Drug-related problems result in poor health outcomes for older adults such as adverse drug withdrawal effects, therapeutic failure, and adverse drug events.[18] Collaboration among interprofessional providers and older patients can ensure appropriate therapy, minimize adverse drug events, and maximize medication adherence and health outcomes.

LO 3

Polypharmacy

Polypharmacy is defined as taking multiple medications concurrently (four to ten medications or more have been used as criteria in studies). Polypharmacy is prevalent among older adults with 39% reporting the use of 5 or more medications in 2012 compared with polypharmacy use by 24% in 1999, signifying a dramatic increase.[19] In 2010, 38% of people aged 62–85 years used at least one over-the-counter (OTC) medication and 64% used at least one supplement.[20] The common use of dietary supplements and herbal products in this population adds to polypharmacy. In nursing home settings, 50.7% of patients with severe cognitive impairment received polypharmacy (5–9 medications) and 16.9% received excessive polypharmacy (≥ 10 medications) in the Services and Health for Elderly in Long Term Care (SHELTER) study.[21] As expected, polypharmacy contributes to increased outpatient visits and hospitalizations with an approximately 30% higher medical costs.[17] Among various reasons for polypharmacy, an apparent one is an older patient receiving multiple medications from different providers who treat the patient's comorbidities without coordinated care. Thus medication reconciliation becomes increasingly important as the aging population continues to grow.

A complete evaluation of all medications should be conducted by health care providers at each older patient visit to prevent inappropriate polypharmacy. Efforts should be made to reduce polypharmacy by discontinuing any medication without indication. However, clinicians should also understand that appropriate polypharmacy is indicated for older adults who have multiple diseases, and support should be provided for optimal adherence. Drug-related problems associated with polypharmacy can be identified by performing a comprehensive medication review (see Patient Care Process).

Inappropriate Prescribing

Inappropriate prescribing is defined as prescribing medications that cause a significant risk of an adverse event when there is an effective and safer alternative. A systematic review in 2012 reported that the median rate of inappropriate medication prescribing among elderly patients in the primary care setting was 19.6%.[22] The potentially inappropriate medications in older adults have been associated with negative outcomes such as confusion, falls, and mortality.[23] At times, medications are continued long after the initial indication has resolved. The clinician prescribing for older adults must understand the rate of adverse reactions and drug–drug interactions, the evidence available for using a specific medication, and patient use of OTC medications and herbal supplements.[17]

Screening tools have been developed to help the clinician identify potentially inappropriate medications in older adults. The most utilized in the United States is the Beers criteria.[23] The 2015 Beers Criteria includes medications or medication classes that are potentially inappropriate in older patients, listed in five categories: (a) medications to avoid in most older adults, (b) medications to avoid in older adults with certain diseases/syndromes, (c) medications to use with caution, (d) non-anti-infective medications with important drug interactions, and (e) non-anti-infective medications to avoid or renal-dose based on kidney function.[23]

Common medications included in the Beers criteria are:[23]

- Benzodiazepines such as lorazepam and diazepam (risk of cognitive impairment, delirium, falls, fractures, and motor vehicle accidents)
- First generation antihistamines, such as diphenhydramine and hydroxyzine (risk of confusion, dry mouth, constipation, and other anticholinergic symptoms)
- Tertiary tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline (risk of sedation, orthostatic hypotension, and anticholinergic symptoms)
- Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen (risk of GI bleeding and ulcers)

Practical strategies for appropriate medication prescribing include establishing a partnership with patients and their care partners to enable them to understand and monitor medication effects. Clinicians should perform drug–drug and drug–disease interaction screening, use time-limited trials to evaluate the benefits and risks of new medications, and trial off medications to assess need.[22]

Undertreatment

Much has been written about the consequences of overmedication and polypharmacy in older adults. However, underutilization of medications is just as harmful, resulting in reduced functioning, and increased morbidity and mortality. There are instances when a drug is truly contraindicated, when a lower dose is indicated, or when prognoses dictate withholding therapy. Outside of these scenarios, many elders do not receive therapeutic interventions that would provide benefit.[18,24] Undertreatment is prevalent across diverse settings in the community, hospitals, and long-term care facilities.[25] This occurs for many reasons including: multimorbidity, polypharmacy, cost, concerns of nonadherence, fear of adverse effects and associated liability, limited evidence in the age group, starting low and failing to increase to an appropriate dose, skepticism regarding secondary prevention benefits, or ageism.[25] Common categories of geriatric undertreatment are listed in Table 2–1.

Table 2–1

Common Categories of Geriatric Undertreatment

Therapy	Concern
Anticoagulation in patients with atrial fibrillation	Overly concerned with risk of bleeding or the risk of falls if anticoagulated
Malignant and nonmalignant pain	Hesitant to prescribe opioids due to possible cognitive and bowel side effects, concerns about addiction; patients may often be hesitant to use opioids
Antihypertensive therapy	Underestimate the benefit on stroke and cardiovascular event prevention, and/or fail to add the second or third medication needed to attain control
β-Blocker treatment in heart failure	Concerned about complications in high-risk patients despite the substantial evidence of mortality benefit
Statin treatment for ASCVD	Underestimate benefit or have concerns about adverse events

ASCVD, atherosclerotic cardiovascular disease.

A clinical assessment to weigh the potential benefit versus harm of the older patient's complete medication regimen is required. Once obvious contraindications have been dismissed, the patient's (a) goals and preferences, (b) prognosis, and (c) time to therapeutic benefit should be taken into consideration to determine whether the pharmacotherapy meets treatment goals. Underprescribing can best be avoided by using clinical assessment strategies, improving adherence support, and liberalizing financial coverage of drugs.

Adverse Drug Reaction

ADR is defined by the World Health Organization as a reaction that is noxious and unintended, which occurs at dosages normally used in humans for prophylaxis, diagnosis, or therapy. (See the glossary for the American Society of Health-System Pharmacists' definition of an ADR.[26]) ADRs increase with polypharmacy use, and are the most frequently occurring drug-related problem among older nursing home residents. A brown bag medication review study found that 25% of community-dwelling older adults using at least five medications experienced ADRs.[27] Similarly, another study evaluating ADRs in patients after hospital discharge showed that 18.7% of them experienced an adverse drug event within 45 days.[28]

Seven predictors of ADRs in older adults have been identified[29]: (a) taking more than four medications; (b) more than 14-day hospital stay; (c) having more than four active medical problems; (d) general medical unit admission versus geriatric ward; (e) alcohol use history; (f) lower Mini-Mental State Examination score (confusion, dementia); and (g) two to four new medications added during a hospitalization. Similarly, there are four predictors for severe ADRs experienced by older adults[30]: (a) use of certain medications including diuretics, NSAIDs, antiplatelet medications, and digoxin; (b) number of drugs taken; (c) age; and (d) comorbidities. Suggested strategies to preventing ADRs in older adults are described in Table 2–2.[30] Particular caution must

Table 2–2[30]

Strategies to Prevent Adverse Drug Reactions in Older Adults

- Evaluating comorbidities, frailty, and cognitive function
- Identifying caregivers to take responsibility for medication management
- Evaluating renal function and adjusting doses appropriately
- Monitoring drug effects
- Recognizing that clinical signs or symptoms can be an ADR
- Minimizing number of medications prescribed
- Adapting treatment to patient's life expectancy
- Realizing that self-medication and nonadherence are common and can induce ADRs

ADR, adverse drug reaction.

Adapted, with permission, from Merle L, Laroche ML, Dantoine T, Charmes JP. Predicting and preventing adverse drug reactions in the very old. Drugs Aging. 2005;22(5):375–392.

be taken when prescribing drugs that alter cognition in older adults, including antidepressants, antihistamines, antipsychotics, benzodiazepines, opioids, and muscle relaxants.[30]

One of the most damaging ADRs that frequently occur in older adults is medication-related falls. Falls are associated with a poor prognosis ranging from premature institutionalization to early death, and polypharmacy is a risk factor. Multiple medications included in the Beers Criteria are related to falls.[23] For example, multiple studies of benzodiazepines found significant association with falls including an increased risk after a new prescription for benzodiazepines and twofold risk with combined use of two or more benzodiazepines.[31] Other agents having strong association with increased fall risk include sedative hypnotics, neuroleptics, antidepressants, and antipsychotics.[31] A comprehensive fall prevention intervention should include deprescribing by slow medication taper with close monitoring to prevent or resolve ADRs.

Nonadherence

America's other drug problem is the term given to medication nonadherence by the National Council on Patient Information and Education. Nonadherence to chronic medications is prevalent and escalates health care costs associated with worsening disease and increased hospitalization. *Medication adherence* describes a patient's medication-taking behavior, generally defined as the extent to which one adheres to an agreed regimen derived from collaboration with their health care provider.[32]

Table 2–3

Factors Influencing Medication Nonadherence

Three or more chronic medical conditions	Significant cognitive or physical impairments
Five or more chronic medications	Recent hospital discharge
Three times or more per day dosing or 12 or more medication doses per day	Caregiver reliance
Four or more medication changes in past 12 months	Low health literacy
Three or more prescribers	Medication cost
	History of medication nonadherence
	Living alone in the community

KEY CONCEPT Older adults are at greater risk for medication nonadherence due to the high prevalence of multimorbidities, cognitive deficit, polypharmacy, and financial barriers. Numerous barriers to optimal medication adherence exist and include patient's lack of understanding, provider's failure to educate, polypharmacy leading to **complex regimen** and inconvenience, treatment of asymptomatic conditions (such as hypertension and dyslipidemia), and cost of medications.[32] Factors influencing medication nonadherence are listed in Table 2–3.

Following is a list of six "how" questions to ask when assessing medication adherence:[33]

1. How do you take your medicines?
2. How do you organize your medicines to help you remember to take them?
3. How do you schedule your meal and medicine times?
4. How do you pay for your medicines?
5. How do you think the medicines are working for your conditions?
6. How many times in the last week/month have you missed your medicines?

Although no single intervention has found to improve adherence consistently, older person-centered multicomponent interventions, such as combining education, convenience, and regular follow-up, have resulted in a positive impact on medication adherence and associated health outcomes.[34] Future research needs to include adherence studies evaluating belief-related variables, such as personal and cultural beliefs, in larger and more ethnically diverse samples of older populations.

Patient Encounter Part 3

UA is now 88 years old and has been living at a long-term care facility for a year. Even though she was overweight most of her life, she has lost 7 kg in the past 6 months and developed a new coccyx ulcer. She is currently on multiple medications including: (1) aspirin 81 mg by mouth daily, (2) hydrochlorothiazide 25 mg by mouth daily, (3) metformin 500 mg by mouth twice daily, (4) levothyroxine 25 mcg by mouth daily, (5) ibuprofen 600 mg by mouth daily, (6) docusate sodium 100 mg by mouth twice daily, (7) lorazepam 1 mg by mouth twice daily, (8) atorvastatin 40 mg by mouth daily, (9) amitriptyline 10 mg by mouth at bedtime.

Today her pain score is 7/10.

What recommendations can be made about UA's medication regimen at this time?

Which quality indicators should be of concern in UA?

GERIATRIC ASSESSMENT

LO 4

The term *geriatric assessment* is used to describe the comprehensive interprofessional team evaluation of the frail or complex older adult's health including multimorbidity with functional and cognitive status. Such a team may include, but is not limited to, a geriatrician, nurse, pharmacist, case manager/social worker, physical therapist, occupational therapist, speech therapist, psychologist, dietician, dentist, optometrist, and audiologist. Assessment may be performed in a number of care settings and by a series of evaluations after which the team will conduct an interprofessional case conference to discuss the patient's care plan.

Table 2–4

Activities of Daily Living and Instrumental Activities of Daily Living

ADLs			
Transfers	Dressing	Mobility	Eating
Bathing	Toileting	Grooming	
IADLs			
Using transportation		If still driving, assess driving ability (including cognitive function, medications that can impair driving ability, vision, neuromuscular conditions that may interfere with reaction time, ability to turn head) at the time of license renewal	
Using the telephone		Check for emergency phone numbers located near the telephone	
Management of finances		Assess the ability to balance checkbook and pay bills on time	
Cooking		Check for safe operation of appliances and cooking tools as well as ability to prepare balanced meals	
Housekeeping		Check for decline in cleanliness or neatness	
Medication administration		Assess organization skills and adherence	

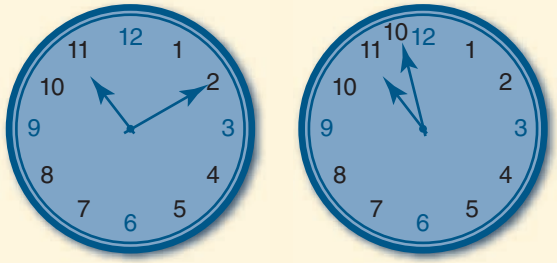
ADL, activity of daily living; IADL, instrumental activity of daily living.

Three item recall

1. Ask the patient if you may test his or her memory.
2. Give the patient 3 words (eg, apple, table, penny) to repeat and remember.
3. Have the patient repeat the 3 words from memory later (eg, after the clock drawing test).

Clock drawing test

1. Have the patient draw the face of a clock, including numbers.
2. Instruct the patient to place the hands at a specific time, such as 11:10.



Correct | Incorrect hands and inserted number

A positive dementia screen

1. Failure to remember all 3 words.
2. Failure to remember 1–2 words plus an abnormal clock drawing.

FIGURE 2–2. The mini-cog mental status examination. (Adapted from Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive "vital signs" measure for dementia screening in multi-lingual elderly. Int J Geriatr Psychiatry. 2000;15(11):1021–1027.)

Patient Interview

KEY CONCEPT The clinical approach to assessing older adults frequently goes beyond a traditional "history and physical" used in general internal medicine practice.[35] Functional status must be determined, which includes the activities of daily living (ADL) and instrumental activities of daily living (IADL) (see Table 2–4). Cognitive assessment, which may require collateral history from family, friends, or other caregivers, is important in determining the patient's capacity to manage their medications and consent to medical treatment.[36] The mini-cog mental status examination[37] shown in Figure 2–2 is a quick tool to assess patient's cognitive abilities. Patients commonly have decreased visual acuity, hearing loss, dysphagia, and impaired dexterity. Decreased skin integrity, another common problem, greatly increases risk for pressure ulcers. Sexual function is a sensitive but important topic and should be specifically inquired about. Cardiac, renal, hepatic, and digestive insufficiencies can have significant implications for pharmacotherapy. Inadequate nutrition may lead to weight loss and impaired functioning at the cellular or organ level. See Table 2–5 for common problems experienced by older adults.

It is important to recognize "geriatric syndromes" such as cognitive impairment, functional impairment, polypharmacy, delirium, frailty, falls, osteoporosis, insomnia, and incontinence. In the older adult, common diseases may present with atypical symptoms, such as thyroid dysfunction or infection presenting as delirium. It is also important to assess for caregiver stress and be aware of older patients' support systems, which may include family, friends, social or religious networks, home health agencies, and hired caregivers. Such networks may facilitate older adults to continue to live independently. Safety should be assessed and includes a home safety assessment by an occupational therapist and a driving assessment for patients with cognitive or functional limitations. In addition, look for signs and symptoms of elder abuse, neglect, or exploitation. Health professionals are required to report suspicion of elder mistreatment to Adult Protective Services.[38]

Drug Therapy Monitoring

Geriatric patients often have multiple medications, medical comorbidities, and prescribers. It is essential that there be a

Table 2–5

The *Is* of Geriatrics: Common Problems in Older Adults

Immobility	Instability
Isolation	Intellectual impairment
Incontinence	Impotence
Infection	Immunodeficiency
Inanition (malnutrition)	Insomnia
Impaction	Iatrogenesis
Impaired senses	

Hajjar ER, Gray SL, Slattum PW, Hersh LR, Naples JG, Hanlon JT. Geriatrics. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017. https://accesspharmacy.mhmedical.com/book.aspx?bookid=1861 Accessed August 2, 2017.

single provider who oversees the patient's pharmacotherapy. Particularly challenging in the geriatric population is identifying the cause(s) of medication nonadherence. Providers assessing older patients' medication regimens should keep the following questions in mind:

- Are medications skipped or reduced due to cost?
- Can the patient benefit from sample drugs? Starting a patient on a free drug sample may increase patient costs in the long term because samples typically are newer, expensive drugs.[39]
- Is there an educational barrier such as low health literacy?
- Does the patient speak English but only read in another language?
- Can the patient see labels and written instructions?
- Does the patient have hearing problems? Patients might not admit they cannot hear instructions.
- Can the patient manipulate pill bottles, syringes, inhalers, eye/ear drops?
- Has the patient's cognitive functioning worsened over time such that they can no longer follow the medication regimen?

Older patients require more frequent monitoring for adverse effects: symptoms, abnormal laboratory results, drug interactions, and drug levels.

On the subject of cost, the providers need to be aware of the patient's Medicare Part C or D plan, and what type of coverage these plans afford. What is the copayment for generic, formulary, and nonformulary drugs? Is the patient responsible for all drug costs during the Medicare "donut hole" period? (In basic part D plans, patients pay increasing percentages of drug costs up to $7,425 per year.[40]) Many Medicare patients, especially the socioeconomically challenged, have limited understanding of the complex Medicare drug benefit. This problem is compounded when the prescriber also does not understand the patient's insurance program.[39] Providers can assist patients by prescribing generic medications that are offered through retail pharmacy discount plans ($4 retail pharmacy programs do not bill insurance, thus are not counted toward their Medicare part D deductible) and help patients apply for the medication assistance programs offered by drug manufacturers.

Documentation

A clear, current, and accurate medication list must be available to the patient and all individuals involved in their care. It is particularly important for geriatric patients to bring medication containers for reconciliation by a provider. Medication adherence may require verification with the pharmacist, caregivers, or family. Transitions in patient care, such as hospital to sub-acute nursing facility or home, lead to medication errors because medications may have been deleted or added.[41] It is standard of care to conduct medication reconciliation upon hospital admission and discharge to ensure that the medication list is up to date.

Patient Education

Geriatric patients often have difficulty understanding and retaining provider instructions. "Ask me 3" cues the patient to ask three important questions of their providers to improve health literacy[42]:

1. What is my main problem?
2. What do I need to do?
3. Why is it important for me to do this?

The provider can assess patient grasp of medication instructions by asking the patient to repeat instructions initially and again in 3 minutes (teach-back method).

KEY CONCEPT Addressing deficits in vision, hearing, swallowing, cognition, motor impairment, and health literacy can lead to enhanced medication adherence. Specific drug formulations, such as metered-dose inhalers, ophthalmic/otic drops, nasal sprays, and subcutaneous injections, will require detailed education and practice. Patients who cannot swallow tablets or capsules need instructions on which tablets are safe to crush and which capsules are safe to open and sprinkle on food. Patients and/or caregivers need to be advised of potential ADRs and when to notify the provider.

GERIATRIC PRACTICE SITES

LO 5

Some say geriatrics has become a nonspecialty due to the aging population. Clinicians with geriatric certification or training practice in nearly all settings of health care, primary care to various spectrums of specialty care and long-term care. A couple of interprofessional practice sites are highlighted here.

Ambulatory Clinic and Home-Based Primary Care

Ambulatory geriatric clinics are established to provide a multitude of primary care needs specifically tailored to older adults. Home-based primary care is delivered in the home or independent living facility of homebound patients to facilitate independent living as long as possible. Patients are usually referred by their primary care physicians due to the desire for increased access to services, complex care needs due to multimorbidity and polypharmacy, and need for a comprehensive geriatric assessment. It is common for the onset of cognitive impairment to be the catalyst for a referral to such services. Interprofessional team care is the norm in these settings, which benefits patients with varied needs. The interprofessional teams hold regular meetings to discuss care plans of the patients. The geriatrician, who has specialized training in treating older adults, assesses physical, medical, emotional, and social needs. The clinical pharmacist focuses on optimizing the medication regimen by conducting comprehensive medication reviews; making evidence-based disease state management recommendations; screening and resolving drug-related problems; and educating patients, caregivers, and members of the health care team about pharmacotherapy and monitoring parameters. Nurses provide medical triage and day-to-day patient care activities such as obtaining vitals, providing wound care, educating patients, and ensuring adherence. Social workers are involved in various aspects from assessing mood and cognitive status, facilitating completion of advanced directives, and obtaining placement in higher levels of care. Physical/occupational therapists are often involved in improving the patient's functional status, providing fall prevention interventions, and maintaining a safe home environment. They provide adaptive equipment such as grab bars, raised toilet seat and shower bench for the bathroom, and cane or walker for ambulation. Dieticians evaluate the patient's nutritional status and educate on proper diet and weight management. Using these team collaborations, specialty geriatric clinical settings have developed including a multidisciplinary geriatric oncology clinic[43] and PACE centers (Programs of All-inclusive Care for the Elderly) which incorporate the interdisciplinary team as well as adult day health care in one center.[44]

Long-Term Care

Long-term care provides support for people who are dependent to varying degrees on ADLs and IADLs, numbering about

Patient Care Process

Collect Information:

- Perform a comprehensive medication review.
- Have the patient bring all medication bottles, including: prescriptions, OTC agents, vitamins, supplements, and herbal products.
- Review medical history and physical assessment.
- Ask about allergies/intolerance.
- Inquire about ADRs (Table 2–2).
- Collect adherence information using combination of methods (eg, self-report, refill history, dosage form count, demonstration of nonoral agent use).
- Ask about prevention including vaccinations.
- Collect vital signs and laboratory results.
- Inquire about functional status (Table 2–4).
- Measure cognitive status (Figure 2–2).

Assess the Information:

- Identify indication(s) for all medications.
- Assess medication doses to determine underdose/overdose.
- Screen for drug–drug/disease/supplement/herbal/food interactions.
- Check against allergies/intolerance.
- Identify ADRs.
- Assess medication adherence (Table 2–3).
- Identify untreated indication/undertreatment (Table 2–1).
- Evaluate vital signs, including pain and laboratory.
- Assess medication needs based on cognitive and functional status.
- Recognize common problems in older adults (Table 2–5).

Develop a Care Plan:

- Tailor regimen: discontinue unnecessary medications, simplify dosing times, and tailor regimen to individuals' daily routine to improve adherence.
- Develop educational materials, keeping in mind health literacy and cognitive status.
- Create solutions to any functional barriers (eg, non-child-resistant caps, tablet cutters).
- Draft referral plan to target nonpharmacological strategies (eg, diet, physical therapy, behavioral health, integrative health approaches).

Implement the Care Plan:

- Educate about medications and disease states in a health literacy-sensitive manner.
- Highlight any medication changes and tailored regimen.
- Educate on the use of nonoral agents (eg, inhalers, insulin, ophthalmic/otic drops).
- Provide a medication chart/list to include generic/brand names, indication, dose, directions for use, timing of dose, etc.
- Teach about medication storage, expiration date, and refill status.
- Emphasize adherence and what to do when a dose is missed/forgotten.
- Use medication organizers (eg, pillbox, blister pack) or other adherence aids (eg, alarm, phone reminder) when indicated.
- Implement solutions to any physical/functional barriers.
- Refer for nonpharmacological interventions.

Follow-up: Monitor and Evaluate:

- Provide a list of future appointments and follow-up.
- Promote self-monitoring (eg, recognize and report ADRs, use blood pressure monitors and glucometers).
- Encourage therapeutic lifestyle modifications including diet, exercise, and smoking cessation.
- Endorse prevention including immunizations, wellness visits, eye examinations, and dental care.
- Formulate a patient-centered and interprofessional team-based follow-up plan to track patient response, adverse events, adherence, and health outcomes.

9 million people older than 65 years in 2008.[45] Care is provided in the patient's home, in community settings such as adult care homes or assisted living facilities, and in nursing homes. Long-term care is expensive, typically several thousand dollars per month. Most care is provided at home by unpaid family members or friends. Medicare covers all or part of the cost of skilled nursing care for a limited period post hospitalization.[45] Medicare does not cover long-term care. Financing of long-term care comes from patients' and family savings and/or private long-term care insurance. When a patient's assets have been depleted, Medicaid provides basic nursing home care under long-term care insurance coverage.[45] However, this care is heavily discounted, often resulting in economizing such as lower caregiver-to-patient ratios and higher number of patients per room. Nursing homes are highly regulated by state and federal government through the Center for Medicare and Medicaid Services.[46] Initial and continuing certification of the facility depends on periodic state and federal review of the facility. Auditors' ratings are available to consumers in an online Nursing Home Report Card.[46] **Quality indicators** are used by facility administrators and government overseers to identify problem areas including[47]:

- Use of nine or more medications in single patient
- Prevalence of indwelling catheters
- Prevalence of antipsychotic, anxiolytic, and hypnotic use
- Use of physical restraints
- Prevalence of depression in patients without antidepressant therapy
- Clinical quality measures such as pressure ulcers
- Moderate daily pain or excruciating pain in residents

Long-term care geriatric practices emphasize the interprofessional team approach. The medical director leads regular meetings with disciplines delivering care. The pharmacist conducts a monthly drug review of each patient's medication list.[41] The physician is alerted to medication concerns and approves the patient's orders every 60 days. Such a team approach is vital to coordinate care for the typical frail, complex long-term care patient.

Abbreviations Introduced in This Chapter

ADL	Activities of daily living
ADR	Adverse drug reaction
GABA	γ-Aminobutyric acid
$HgbA_{1c}$	Hemoglobin A_{1c}
IADL	Instrumental activities of daily living
MDRD	Modification of diet in renal disease
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
V_d	Volume of distribution

REFERENCES

1. Institute of Medicine. Retooling for an Aging America: Building the Health Care Workforce. Washington, DC: National Academies Press, 2008.
2. 2012 National Population Projections. Washington, DC. 2012b. Available from: https://www.census.gov/data/tables/2012/demo/popproj/2012-summary-tables.html. Accessed December 5, 2017.
3. Mather M, Jacobsen LA, Pollard KM. "Aging in the United States," Population Bulletin 70, no. (2015).
4. Federal Interagency Forum on Aging-Related Statistics. Older Americans 2016: Key Indicators of Well-Being. Federal Interagency Forum on Aging-Related Statistics. Washington, DC: U.S. Government Printing Office; August 2016.
5. National Center of Health Statistics. Health, United States, 2015: With a Special Feature on Racial and Ethnic Health Disparities. Hyattsville (MD): U.S. Department of Health and Human Services; 2016.
6. Anderson M, Perrin A. Tech adoption climbs among older adults. Pew Research Center, Internet and Technology. Available from: http://www.pewinternet.org/2017/05/17/tech-adoption-climbs-among-older-adults/. Accessed December 5, 2017.
7. The health consequences of smoking—50 years of progress: a report of the surgeon general. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Printed with corrections, January 2014. Available from: https://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf. Accessed December 5, 2017.
8. National Committee for Quality Assurance (NCQA). HEDIS 2008: Healthcare Effectiveness Data & Information Set. Vol. 2, Technical Specifications for Health Plans. Washington, DC: National Committee for Quality Assurance (NCQA); 2007.
9. Summary health statistics for US adults: national health interview survey, 2015. National Center for Health Statistics. Available from: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2015_SHS_Table_P-1.pdf. Accessed December 5, 2017.
10. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. Am J Med. 2007;120(9):748–753.
11. Health, United States, 2016: with chartbook on long-term trends in health. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, NCHS. Available from: https://www.cdc.gov/nchs/data/hus/hus16.pdf#081. Accessed December 5, 2017.
12. National health expenditure data. Centers for Medicare and Medicaid Services. Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/index.html. Accessed December 5, 2017.
13. Delafuente JC. Pharmacokinetic and pharmacodynamic alterations in the geriatric patient. Consult Pharm. 2008;23:324–334.
14. Sera LC, McPherson ML. Pharmacokinetics and pharmacodynamic changes associated with aging and implications for drug therapy. Clin Geriatr Med. 2012;28:273–286.
15. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17(6):571–584.
16. McLachlan AJ, Pont LG. Drug metabolism in older people—a key consideration in achieving optimal outcomes with medicines. J Gerontol A Biol Sci Med Sci. 2012;67(2):175–180.
17. Maher RL, Hanlon JT, Hajjar ER. Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf. 2014;13(1):57–65.
18. Hajjar ER, Gray SL, Slattum PW, Hersh LR, Naples JG, Hanlon JT. Geriatrics. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017. Available from: https://accesspharmacy.mhmedical.com/book.aspx?bookid=1861. Accessed August 2, 2017.
19. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in prescription drug use among adults in the United States from 1999–2012. JAMA. 2015;314(17):1818–1831.
20. Oato DM, Wilder J, Schumm P, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs. 2011. JAMA Intern Med. 2016;176:475–482.
21. Vetrano DL, Tosato M, Colloca G, et al. Polypharmacy in nursing home residents with severe cognitive impairment: results from the SHELTER Study. Alzheimer's & Dementia. 2013;9:587–593.
22. Opondo D, Eslami S, Visscher S, et al. Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review. PLoS ONE. 2012;7(8):e43617.
23. The American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2016;64(4):920–921.
24. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2014;0:1–6.
25. Cherubini A, Corsonello A, Lattanzio F. Underprescription of beneficial medicines in older people: causes, consequences and prevention. Drugs Aging. 2012;29(6):463–475.
26. American Society of Health-System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting. Am J Health Syst Pharm. 1995;52:417–419.
27. O'Connell MB, Chang F, Tocco A, et al. Drug-related-problem outcomes and program satisfaction from a comprehensive brown bag medication review. J Am Geriatr Soc. 2015;63:1900–1905.
28. Kanaan AO, Donovan JL, Duchin NP, et al. Adverse drug events after hospital discharge in older adults: types, severity, and involvement of Beers Criteria medications. J Am Geriatr Soc. 2013;61:1894–1899.
29. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA. 2003;289:1107–1116.
30. Merle L, Laroche ML, Dantoine T, Charmes JP. Predicting and preventing adverse drug reactions in the very old. Drugs Aging. 2005;22(5):375–392.
31. de Jong MR, Van der Elst M, Hartholt KA. Drug-related falls in older patients: implicated drugs, consequences, and possible prevention strategies. Ther Adv Drug Saf. 2013;4(4):147–154.
32. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–497.
33. MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller D, Bond CA. Assessing medication adherence in the elderly: which tools to use in clinical practice? Drugs Aging. 2005;22(3):231–255.
34. Lee JK, Grace KA, Taylor, AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and

low-density lipoprotein cholesterol: a randomized controlled trial. JAMA. 2006;296:2563–2571.
35. Welsh TJ, Gordon AL, Gladman JR. Comprehensive geriatric assessment—a guide for the non-specialist. Int J Clin Pract. 2014;68(3):290–293.
36. Appelbaum PS. Clinical practice. Assessment of patients' competence to consent to treatment. N Engl J Med. 2007;357(18):1834–1840.
37. Borson S, Scanlan J, Brush M, Vitaliano P, Dokmak A. The mini-cog: a cognitive "vital signs" measure for dementia screening in multilingual elderly. Int J Geriatr Psychiatry. 2000;15(11):1021–1027.
38. Armstrong J, Mitchell E. Comprehensive nursing assessment in the care of older people. Nurs Older People. 2008;20(1):36–40.
39. Schmittdiel JA, Steers N, Duru OK, et al. Patient-provider communication regarding drug costs in Medicare Part D beneficiaries with diabetes: a TRIAD Study. BMC Health Serv Res. 2010;10:164.
40. Prescription drug coverage: general information. Centers for Medicare and Medicaid Services. Available from: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/index.html. Accessed December 5, 2017.
41. Pincus K. Transitional care management service: optimizing medication reconciliation to improve the care of older adults. J Gerontol Nurs. 2013;39:10–15.
42. Ask me 3: good questions for your good health. National Patient Safety Foundation. Available from: http://www.npsf.org/?page=askme3. Accessed December 1, 2017.
43. Overcash J. Integrating geriatrics into oncology ambulatory care clinics. Clin J Oncol Nurs. 2015;19(4):E80–E86.
44. Understanding the PACE model of care. National Pace Association. Available from: http://www.npaonline.org/start-pace-program/understanding-pace-model-care. Accessed December 1, 2017.
45. Long term care. Centers for Medicare and Medicaid Services. Available from: https://www.longtermcare.acl.gov. Accessed December 1, 2017.
46. Nursing home compare. Centers for Medicare and Medicaid Services. Available from: http://www.medicare.gov/NHCompare/. Accessed December 1, 2017.
47. Quality measures archive. Centers for Medicare and Medicaid Services. Available from: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/NursingHomeQualityInits/Quality-Measures-Archive.html. Accessed December 1, 2017.

3 Pediatrics

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LEARNING OBJECTIVES

LO

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

1. Define different age groups within the pediatric population.
2. Identify factors that affect selection of safe and effective drug therapy in pediatric patients.
3. Explain general pharmacokinetic and pharmacodynamic differences in pediatric versus adult patients.
4. Develop strategies for appropriate and effective medication administration to infants and young children.
5. Determine approaches to effectively communicate with patients and caregivers about appropriate medication use including expected outcomes, possible adverse effects, and appropriate administration.

INTRODUCTION

Pediatric clinical practice involves care of infants, children, and adolescents with the goal of optimizing health, growth, and development toward adulthood. Clinicians serve as advocates for this unique and vulnerable patient population to optimize their well-being. Care for pediatric patients is relevant in both inpatient and outpatient settings and requires additional considerations with regard to selection and monitoring of drug therapy.

KEY CONCEPT Despite the common misconception of pediatric patients as "smaller adults" where doses are scaled only for their smaller size, there are multiple factors to consider when selecting and providing drug therapy for patients in this specific population. Pediatric patients significantly differ within their age groups and from adults regarding drug administration, psychosocial development, and organ function development, which affect the efficacy and safety of pharmacotherapy.

FUNDAMENTALS OF PEDIATRIC PATIENTS

Classification of Pediatric Patients

LO 1

Pediatric patients are those younger than 18 years, although some pediatric clinicians may care for patients up to age 21. Unlike an adult patient, whose age is commonly measured in years, a pediatric patient's age can be expressed in days, weeks, months, and years. Patients are classified based on age and may be further described based on other factors, including birth weight and prematurity status (Table 3–1).[1-3]

Growth and Development

Children are monitored for physical, motor, cognitive, and psychosocial development through clinical recognition of timely milestones during routine well-child visits. As a newborn continues to progress to infant, child, and adolescent stages, different variables are monitored to assess growth compared with the general population of similar age and size. Growth charts are used to plot head circumference, weight, length or stature, weight-for-length, and body mass index (BMI) for a graphical representation of a child's growth compared with the general pediatric population. These markers of growth and development are both age- and gender-dependent; thus, the use of the correct tool for measurement is important. For children younger than 2 years, one should use the World Health Organization (WHO) growth standards (Figure 3–1).[4] For children 2 years and older, the Centers for Disease Control and Prevention (CDC) Growth Charts (Figure 3–2) are used.[5] These tools assess whether a child is meeting the appropriate physical growth milestones, thereby allowing identification of nutritional issues such as poor weight and height gain (eg, failure to thrive). Failure to thrive is defined as inadequate physical growth with weight that falls below the 5th percentile or decreases over time, crossing two or more major percentile lines. Body habitus is often evaluated at routine checkups or well-check visits, with definitions of underweight as BMI less than the 5th percentile for age, overweight as BMI between 85th to 94th percentile for age, and obese as BMI greater than 95th percentile.[6] Since these charts were developed based on a general, healthy population, growth charts may not be accurate evaluation of physical development in children with congenital diseases.

Differences in Vital Signs

Normal values for heart rate and respiratory rate vary based on age. Normal values for blood pressure vary based on gender and age for all pediatric patients, and also height percentile for patients older than 1 year. Respiratory rates are also higher in neonates and infants (30–60 breaths/min), decreasing with age to adult rates around 15 years of age (12–20 breaths/min) (Table 3–2).

Normal values for blood pressure in pediatric patients can be found in various national guidelines and other pediatric diagnostic references. In general, blood pressure increases with age, with average blood pressures of approximately 70/50 in neonates, increasing throughout childhood to approximately 110/65 in adolescents.[7] Heart rates are highest in neonates and infants, ranging from 90 to 205 beats per minute (bpm) and decrease with age, reaching adult rates (60–100 bpm) around 10 years of age.[7-9]

Table 3–1

Pediatric Age Groups, Age Terminology, and Weight Classification[1–3]

Age Group	Age
Neonate	≤ 28 days (4 weeks) of life
Infant	29 days to < 12 months
Child	1–12 years
Adolescent	13–17 years (most common definition)
Age Terminology	**Definition**
Gestational age (GA)	Age from date of mother's first day of last menstrual period to date of birth
Full term	Describes infants born at 37-weeks gestation or greater
Premature	Describes infants born before 37-weeks gestation
Small for GA	Neonates with birth weight below the 10th percentile among neonates of the same GA
Large for GA	Neonates with birth weight above the 90th percentile among neonates of the same GA
Chronological or postnatal age	Age from birth to present, measured in days, weeks, months, or years
Corrected or adjusted age	May be used to describe the age of a premature child up to 3 years of age: Corrected age = Chronological age in months – [(40 – GA at birth in weeks) × 1 month ÷ 4 weeks]. For example, if a former 29-week GA child is now 10 months old chronologically, his corrected age is approximately 7 months: 10 months – [(40 – 29 weeks) × 1 month ÷ 4 weeks] = 7.25 months
Weight Classification	**Definition**
LBW infant	Premature infant with birth weight between 1500 and 2500 g
VLBW infant	Premature infant with birth weight 1000 g to < 1500 g
ELBW infant	Premature infant with birth weight < 1000 g

ELBW, extremely low birth weight; GA, gestational age; LBW, low birth weight; VLBW, very low birth weight.

Another vital sign commonly monitored in children by their caregivers is body temperature, especially when they seem "warm to the touch." The American Academy of Pediatrics (AAP) supports the use of rectal measurement of body temperature as it is most accurate when appropriate technique is used; however, for other routes, the AAP offers an age-specific guideline on routes of measurement.[10,11] For patients aged less than 3 months, rectal measurement using a digital thermometer is recommended. For those 3 months and older, use of temporal artery measurement is an available option. The use of tympanic measurement is appropriate for those age 6 months and older. Axillary measurement is not considered first-line in this all age groups, as proper technique is important for accurate measurement and other accurate options are available. For patients age 4 or 5 years and older, oral measurement is reliable. Generally, fever is defined as temperature 100.4°F (38°C) and greater measured via rectal, otic, or temporal artery technique. For oral and axillary measurement, fever is defined as temperature 100°F (37.8°C) and 99°F (37.2°C) and greater, respectively.[11] Low-grade fevers range from 100° to 102°F (37.8°–38.9°C), with antipyretic treatment (eg, acetaminophen) considered by most pediatricians in cases of temperature greater than 38.3°C (101°F, any measurement route) accompanied by patient discomfort. Formal definition of fever, like other vital signs, is also age dependent, with a lower temperature threshold for neonates (38°C or 100.4°F) and infants (38.2°C or 100.7°F).[10,11]

Pain assessment is more challenging to assess in neonate, infants, and young children due to their inability to communicate symptoms. Indicators of possible pain include physiological changes, such as increased heart rate, respiratory rate, and blood pressure, decreased oxygen saturation, as well as behavior changes such as prolonged, high pitch crying, and facial expressions.[12] Such indicators are used in validated assessment scales, such as the FACES scale and FLACC behavioral tools.[13,14] The FACES scale is a visual analog scale, where patients aged 3 years and older can select a face that best associates with their current pain level.[13] The FLACC scale, intended for patients age 2 months to 7 years or those patients unable to communicate pain, is a scale in which a clinician scores a patient based on a series of criteria (facial expression, leg movement, activity, crying, and consolability).[14]

Fluid Requirements

Fluid requirement and balance are important to monitor in pediatric patients, especially in premature neonates and infants. Maintenance fluid requirement can be calculated based on body surface area for patients greater than 10 kg, with a range of 1500 to 2000 mL/m^2 per day. However, a weight-based method of determining normal maintenance fluid requirement for children is often used (Table 3–3).[15]

EFFECTS OF PHARMACOKINETIC AND PHARMACODYNAMIC DIFFERENCES ON DRUG THERAPY

Drug selection strategy may be similar or different depending on age and disease state, as a result of differences in pathophysiology of certain diseases and pharmacokinetic and pharmacodynamic parameters among pediatric and adult patients. It is noteworthy that pediatric patients may require the use of different medications from those used in adults affected by certain diseases. For

Patient Encounter Part 1

AB is a 30-week GA premature baby girl weighing 1.25 kg, length 38 cm, born to a 21-year-old woman today. AB is currently admitted to the neonatal intensive care unit.

What is AB's weight classification as a neonate?

Calculate AB's corrected age for TS 6 months from today.

How much maintenance fluid per day (mL) and overall rate (mL/hour) is appropriate at this time for AB?

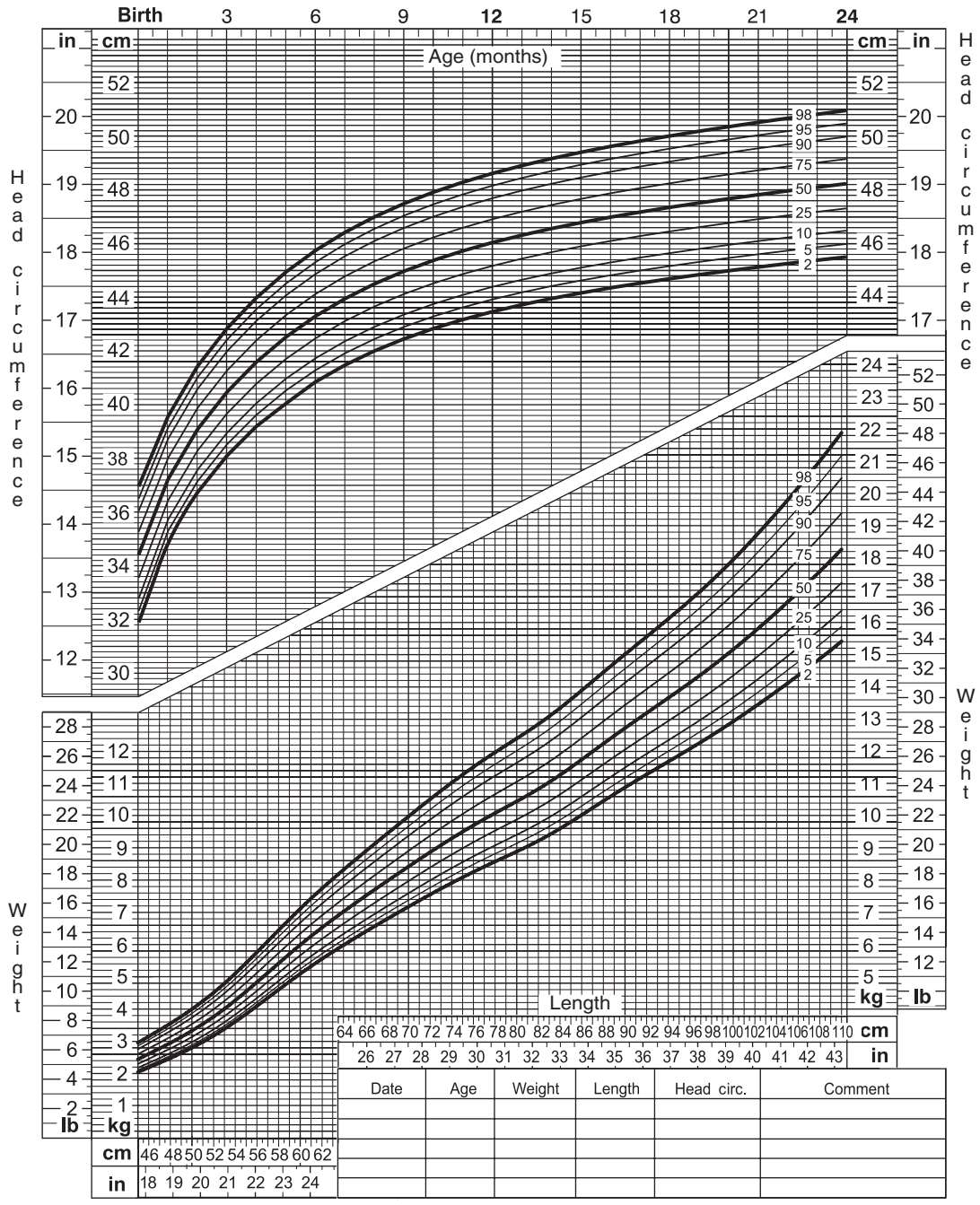

FIGURE 3–1. Example of WHO growth chart of girls, birth to 24 months: Head circumference-for-age and weight-for-length percentile, 2000. (From Centers for Disease Control and Prevention from the WHO Growth Standards. World Health Organization [WHO] Growth Standards, 2009 [updated September 9, 2010], http://www.cdc.gov/growthcharts/who_charts.htm.)

example, phenobarbital is commonly used for treatment of neonatal seizures, but seldom used for seizure treatment in adults, due to differences in seizure etiology and availability of extensive data regarding its use in neonates compared with newer antiepileptic medications. There also exist commonalties between pediatric and adult patients, such as therapeutic serum drug concentrations required to treat certain diseases. For example, gentamicin peak and trough serum concentrations needed for bacteremia treatment are the same in children and adults. Appropriate selection and dosing of drug therapy for a pediatric patient depends on a number of specific factors, such as age, weight, height, disease, comorbidities, developmental pharmacokinetics, and available drug dosage forms. Pediatric drug doses are often calculated based on body weight (eg, mg/kg/dose) compared with uniform dosing (eg, mg/day or mg/dose) for adult patients. Thus, accurate weight should be available while prescribing or dispensing medications for this patient population. Pediatric doses may exceed adult doses by body weight for certain medications due to differences in pharmacokinetics and pharmacodynamics; hence, the use of pediatric drug dosing guides is recommended.

LO 2

KEY CONCEPT Due to multiple differences, including age-dependent development of organ function in pediatric patients, the pharmacokinetics, efficacy, and safety of drugs often differ

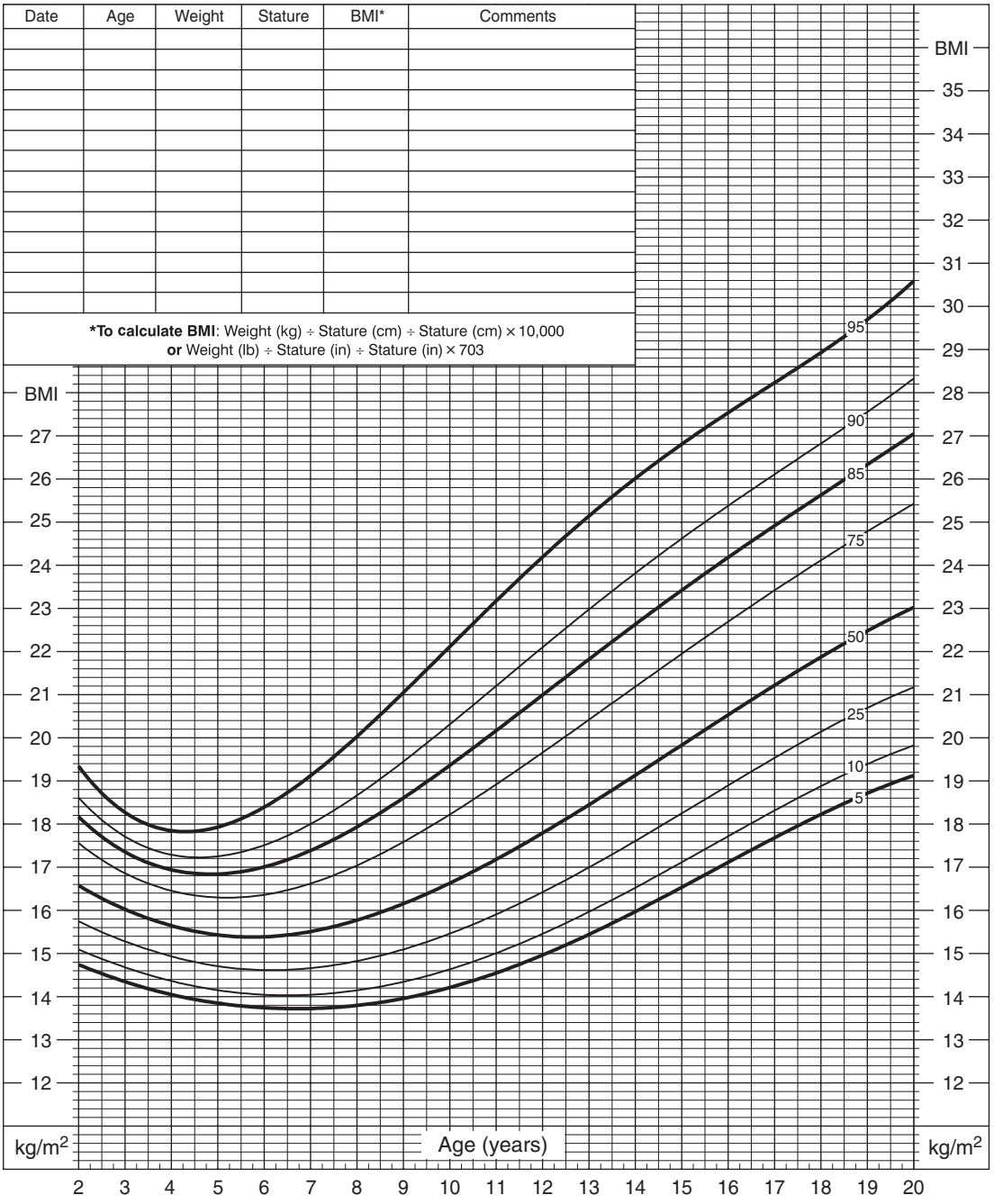

FIGURE 3–2. Example of CDC growth chart of boys, 2 to 20 years: Body mass index for age percentile, 2000. (From National Center for Health Statistics and National Center for Chronic Disease Prevention and Health Promotion. Center for Disease Control Growth Charts, 2000 [updated September 9, 2010], http://www.cdc.gov/growthcharts.)

between pediatric and adult patients; thus, pediatric dosing should not be calculated based on a single factor of difference. Equations proposed to estimate pediatric doses based on adjusted age or weight, such as the Clark's, Fried's, or Young's rule, should not be routinely used to calculate pediatric doses because they account for only one factor of difference (eg, age or weight), and lack integration of the effect of growth and development on drug pharmacokinetics and pharmacodynamics in this population. For off-label medication dosing, when no alternative treatment is available and limited dosage guidelines have been published, clinicians may estimate a pediatric dose based on body surface area ratio.

$$\text{Approximate pediatric dose} = \text{Adult dose} \times [\text{BSA (in m}^2) \div 1.73\ \text{m}^2]$$

Limitations for this dose-estimating approach include the need for the patient to be of normal height and weight for age, and lack of incorporation of exact pharmacokinetic differences regarding each medication.[16]

Absorption

LO 3

Oral absorption may be different in premature infants and neonates due to differences in gastric acid secretion and pancreatic and biliary function. Neonates and infants have increased gastric pH (eg, pH 6–8)

Table 3–2

Normal Ranges of Vital Signs (Heart Rate, Respiratory Rate, Blood Pressure) by Age Group[7–9]

Age Group	Heart Rate (Sleep)[a]	Heart Rate (Awake)[a]	Respiratory Rate[b]	Systolic Blood Pressure[c,d]	Diastolic Blood Pressure[c,d]
Neonate (< 28 days)	90–160	100–205	30–60	67–84	31–45
Infant (1–12 months)	90–160	100–190	30–53	72–104	37–56
Toddler (1–2 years)	80–120	98–140	22–37	86–106	42–63
Preschool (3–5 years)	65–100	80–120	20–28	89–112	46–72
School–age (6–11 years)	58–90	75–118	18–25	97–115	57–76
Adolescent (12–15 years)	50–90	60–100	12–20	102–131	61–83

Note: Prematurity can affect values. Values listed are average ranges.

[a]Beats per minute

[b]Breaths per minute

[c]mm Hg

[d]Exact normal values will vary based on age, height, and sex.

due to lower gastric acid output by body weight, reaching adult values by approximately 2 years of age.[17] Low gastric acid secretion can result in increased serum concentrations of weak bases and acid-labile medications, such as penicillin, and decreased serum concentrations of weak acid medications, such as phenobarbital, due to increased ionization. Additionally, gastric emptying time and intestinal transit time are delayed in premature infants, increasing drug contact time with the GI mucosa and drug absorption.[17,18] Diseases such as gastroesophageal reflux, respiratory distress syndrome, and congenital heart disease may further delay gastric emptying time. Pancreatic exocrine and biliary function are also reduced in newborns, with about 50% less secretion of amylase and lipase than adults, reaching adult values as early as the end of the first year and as late as 5 years of age. Deficiency in pancreatic secretions and bile salts in newborns can decrease bioavailability of prodrug esters, such as erythromycin, which requires solubilization or intraluminal hydrolysis.[18] Due to limited data on oral bioavailability of medications in infants and children for newer agents, some drug dosing recommendations may be extrapolated from adult safety and efficacy studies and case reports.

LO 3 Topical or percutaneous absorption in neonates and infants is increased due to a thinner stratum corneum, increased cutaneous perfusion, and greater body surface-to-weight ratio. Hence, application of topical medications, such as corticosteroids, should be limited to the smallest amount possible. Limiting exposure can help minimize serum concentrations of active drug as well as inactive, yet potentially harmful additives such as propylene glycol.

LO 3 Intramuscular absorption in premature and full-term infants can be erratic due to variable perfusion, poor muscle contraction, and decreased muscle mass compared with older patients.[17] Intramuscular administration may be appropriate for some medications; however, use of this route of administration can be painful and is usually reserved when other routes are not accessible, eg, initial IV doses of ampicillin and gentamicin for neonatal sepsis.

Table 3–3

Maintenance Fluid Calculations by Body Weight[15]

Patient Body Weight	Maintenance Fluid Requirement
< 10 kg	100 mL/kg/day
11–20 kg	1000 mL + 50 mL/kg over 10 kg
> 20 kg	1500 mL + 20 mL/kg over 20 kg

LO 3 Intrapulmonary absorption and distribution is largely due to anatomical size of the lungs and drug delivery. The smaller airways of neonates and lower inspiratory volume can result in greater drug concentrations in the upper and central airways. Particle size, breathing pattern, and route (eg, oral vs nasal) can impact the amount of drug absorbed and should be considered when utilizing pulmonary drug delivery devices such as nebulizers or inhalers.[19]

LO 3 Rectal absorption can also be erratic due to increased peristalsis causing early expulsion of the dosage form in younger patients (ie, infants and young children).[20] Thus it is not commonly recommended if other routes are available. This route is useful in cases of severe nausea and vomiting or seizure activity. For medications that undergo extensive first-pass metabolism, bioavailability increases as the blood supply bypasses the liver from the lower rectum directly to the inferior vena cava. Availability of rectal dosage forms varies and use of oral medications or other dosage forms rectally is based on limited studies and case reports. High osmolality and large volume form may present as limitations to using an oral liquid formulation for rectal use.

Volume of Distribution

LO 3 In pediatric patients, apparent volume of distribution (V_d) is normalized based on body weight and expressed as L/kg. Extracellular fluid and total body water per kilogram of body weight are increased in neonates and infants, resulting in higher V_d for water-soluble drugs, such as aminoglycosides, and decreases with age. Therefore, neonates and infants often require higher doses by weight (mg/kg) than older children and adolescents to achieve the same therapeutic serum concentrations.[17,20] Fluid overload and diuresis can affect V_d and should be assessed for when evaluating drug dosing and pharmacokinetics. The use of extracorporeal membrane oxygenation (ECMO) can further effect V_d of medications in patients due to the added volume from the circuit and potential fluid changes (eg, edema) while on the circuit. Thus, the use of additional clinical and, when available, therapeutic drug monitoring is recommended for those patients requiring ECMO.[21] Neonates and infants have a lower normal range for serum albumin (2–4 g/dL, 20–40 g/L), reaching adult levels after 1 year of age. Highly protein–bound drugs, such as sulfamethoxazole-trimethoprim and ceftriaxone, are not typically used in neonates due to theoretical concern for bilirubin displacement. This displacement may result in a complication known as kernicterus, from bilirubin encephalopathy.[22]

Although neonates have lower body adipose composition compared with older children and adults, their overall V_d for many lipid-soluble drugs (eg, lorazepam) is similar to that of infants and adults. Some medications (eg, vancomycin, phenobarbital) may also reach higher concentrations in the CNS of neonates due to an immature blood–brain barrier.[20]

Metabolism

LO 3

Hepatic drug metabolism is slower at birth in full-term infants compared with adolescents and adults, with further delay in premature neonates. Phase 1 reactions and enzymes, such as oxidation and alcohol dehydrogenase, are impaired in premature neonates and infants and do not fully develop until later childhood or adolescence. Accordingly, the use of products containing ethanol or propylene glycol can result in increased toxicities, including respiratory depression, hypoglycemia, hyperosmolarity, metabolic acidosis, and seizures, and thus should be avoided in neonates and infants. Age at which cytochrome P450 isoenzymes (eg, CYP3A4, CYP2C19) activity reaches adult values varies, depending on the isoenzyme, with delayed development in premature infants. Increased dose requirements by body weight (eg, mg/kg) for some hepatically metabolized medications (eg, phenytoin, valproic acid) in young children (ie, ages 2–4 years of age) are theorized due to an increased liver mass to body mass ratio.[23] This increase in metabolism slows to adult levels as the child goes through puberty into adulthood.[17,23]

Among phase 2 reactions, sulfate conjugation by sulfotransferases is well developed at birth in term infants. Glucuronidation by the uridine diphosphate glucuronosyltransferases, in contrast, is immature in neonates and infants, reaching adult values at 2 to 4 years of age.[18,24] In neonates, this deficiency results in adverse effects including cyanosis, ash gray color of the skin, limp body tone, and hypotension, also known as "gray baby syndrome" with use of chloramphenicol.[24] Products containing benzyl alcohol or benzoic acid should be avoided in neonates due to immature glycine conjugation, resulting in accumulation of benzoic acid. This accumulation can lead to "gasping syndrome," which includes respiratory depression, metabolic acidosis, hypotension, seizures or convulsions, and gasping respirations.[25] Acetylation via *N*-acetyltransferase reaches adult maturation at around 1 year of life; however, overall activity is dependent on genotypic variability.[17]

Elimination

LO 3

Nephrogenesis completes at approximately 36 weeks gestation; thus, premature neonates and infants have compromised glomerular and tubular function that may correlate with a glomerular filtration rate (GFR). This reduction in GFR affects renal drug clearance, thereby necessitating longer dosing intervals for renally cleared medications, such as vancomycin, to prevent accumulation. GFR increases with age and exceeds adult values in early childhood, after which there is a gradual decline to approximate adult value during adolescence. For example, vancomycin is often given every 18 to 24 hours in a low birth weight (LBW) premature neonate, every 6 hours in children with normal renal function, and every 8 to 12 hours in adult patients with normal renal function. Children with cystic fibrosis also present with greater renal clearance of drugs such as aminoglycosides, compared with children without the disease, requiring higher doses by weight and more frequent dosing intervals.[26]

Creatinine clearance (CrCl) is used as a surrogate marker for GFR; however, there are equations available to estimate GFR in the pediatric population. Pediatric GFR is often calculated to mL/min/1.73 m^2. The Cockroft-Gault, Jelliffe, or Modification of Diet in Renal Disease (MDRD) equations for estimating CrCl or GFR in adults should not be used for evaluating patients younger than 18 years, due to lack of validation of these equations in pediatric age ranges, even adolescents.[27,28] Past attempts for proposed application of equations, such as Cockroft-Gault, demonstrated that lack of agreement with measured GFR (via renal scan) in adolescents as young as 13 years of age.[29] Schwartz equation was the previously used method of estimating pediatric GFR from infancy up to 21 years of age (Figure 3–3). This equation uses patient length (cm), serum creatinine (mg/dL) (or μmol/L × 0.0113), and a constant, *k*, which depends on age (including LBW status for infants) for all patients and also gender for those older than 12 years.[30] This "original" Schwartz equation is no longer used by many clinicians due to the change in measurement of serum creatinine methods with calibration traceable to isotope dilution mass spectrometry (IDMS), which invalidates the equation's clinical application.[29,31] Currently the best method, according to the National Kidney Foundation, is the "bedside" Schwartz equation (Figure 3-4).[31]

$$\text{GFR} = \frac{k\text{L}}{\text{SCr}}$$

Age	*k*
Low birth weight < 1 year	0.33
Full term < 1 year	0.45
1–12 years	0.55
13–21 years (female)	0.55
13–21 years (male)	0.70

k = Proportionality constant

L = Length in cm

SCr = Serum creatinine in mg/dL

GFR = estimated glomerular filtration rate (ie, creatinine clearance) in mL/min/1.73 m^2

FIGURE 3–3. "Original" Schwartz equation for estimation of glomerular filtration rate (GFR) in pediatric patients up to 21 years of age. (From Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34(3):571–590.)

$$\textbf{Estimated GFR} = [0.413 \times \text{h}] \div \text{SCr}$$

h = height (in cm)

SCr = serum creatinine (in mg/dL)

Glomerular filtration rate (GFR) in mL/min/1.73 m^2

FIGURE 3–4. Bedside Schwartz equation for estimation of glomerular filtration rate (GFR) in pediatric patients ages 1–18 years old. (Data from Staples A, LeBlong R, Watkins CW, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol. 2010;25:2321–2326.)

Patient Encounter Part 2

JJ is a 3-week-old (weight 4 kg, length 55 cm, no known drug or food allergies), full-term male who presents to the emergency department with lethargy, poor oral intake, and fever. JJ is admitted to the general pediatric ward for further assessment including a neonatal sepsis and meningitis rule-out. Blood samples, cerebral spinal fluid, and urine were collected for Gram stain and culture, still pending results. Given his poor oral intake on admission, the team requests the consultation regarding antibiotic selection.

JJ's Laboratory Values	Normal Ranges
WBC 19 × 10^3/mm^3 (19 × 10^9/L)	6–17.5 × 10^3/mm^3 (6–17.5 × 10^9/L)
Bands 8% (0.08)	4–12% (0.04–0.12)
Segs 38% (0.38)	13–33% (0.13–0.33)
Lymphs 60% (0.6)	41–71% (0.41–0.71)
Monocytes 5% (0.05)	4–7% (0.04–0.07)
SCr 0.3 mg/dL (27 µmol/L)	≤ 0.6 mg/dL (53 µmol/L)

The medical resident asks you whether ceftriaxone (highly protein binding) or cefotaxime (low protein binding) should be used as part of the antibiotic regimen to treat JJ. Which is the most appropriate and why?

Because serum creatinine is a crude marker of GFR, the Schwartz equation, as with other estimation calculations, carries limitations including the potential for overestimating GFR in patients with moderate to severe renal insufficiency. As a result, for example, the original Schwartz using the *k* factor of 0.55 can overestimate GFR by up to 40%.[32,33] Urine output is also a parameter used to help assess renal function in pediatric patients, with a urine output more than 1 to 2 mL/kg/h considered normal.

SPECIFIC CONSIDERATIONS IN DRUG THERAPY

LO 2 In addition to differences in pharmacokinetics and pharmacodynamic parameters, other factors, including dosage formulations, medication administration techniques, and parent/caregiver education, should be considered when selecting drug therapy.

Off-Label Medication Use

Currently, there is a lack of pediatric dosing, safety, and efficacy information for more than 75% of drugs approved in adults.[34] Off-label use of medications occurs in both outpatient and inpatient settings. Off-label use of medication is the use of a drug outside of its approved labeled indication. This includes the use of a medication in the treatment of illnesses not listed on the manufacturer's package insert, use outside the licensed age range, dosing outside those recommended, or use of a different route of administration.[35,36] KEY CONCEPT It is appropriate to use a drug off-label when no alternatives are available; however, clinicians should refer to published studies and case reports for available safety, efficacy, and dosing information. FDA regulatory changes provide incentives for a pharmaceutical manufacturer to study and market new drugs for pediatric patients. However, such incentives are not available for generic drugs.

Routes of Administration and Drug Formulations

LO 4 Depending on age, disease, and disease severity, different routes of administration may be considered. The rectal route of administration is reserved for cases where oral administration is not possible and IV route is not necessary. Topical administration is often used for treatment of dermatologic ailments. Transdermal routes are not often used due to limited product availability. The injectable route of administration is used in patients with severe illnesses or when other routes of administration are not possible. As done with adult patients, IV compatibility and access should be evaluated when giving parenteral medications. Dilution of parenteral medications may be necessary to measure smaller doses for neonates. However, a higher concentration of parenteral medications may be necessary for patients with fluid restrictions, such as premature infants and patients with cardiac anomalies and/or renal disease. Appropriate stability and diluent selection data should be obtained from the literature.

When oral drug therapy is needed, one must also consider the dosage form availability and child's ability to swallow a solid dosage form. Children younger than 6 years are often not able to swallow oral tablets or capsules and may require oral liquid formulations. Not all oral medications, especially those unapproved for use in infants and children, have a commercially available liquid dosage form. Use of a liquid formulation compounded from a solid oral dosage form is an option when compounding and stability data are available. Factors such as drug stability, suspendability, dose uniformity, and palatability should be considered when compounding a liquid formulation.[37] Commonly used **suspending agents** include methylcellulose and carboxymethylcellulose (eg, Ora-Plus). Palatability of a liquid formulation can be enhanced by using simple syrup or OraSweet. If no dietary contraindications or interactions exist, doses can be mixed with food items such as pudding, fruit-flavored gelatin, chocolate syrup, applesauce, or other fruit puree immediately before administration of individual doses. Honey, although capable of masking unpleasant taste of medication, may contain spores of *Clostridium botulinum* and should not be given to infants younger than 1 year due to increased risk for developing botulism. Most hospitals caring for pediatric patients compound formulations in their inpatient pharmacy. Limited accessibility to compounded oral liquids in community pharmacies poses a greater challenge. A list of community pharmacies with compounding capabilities should be maintained and provided to the parents and caregivers before discharge from the hospital.

Common Errors in Pediatric Drug Therapy

Prevention of errors in pediatric drug therapy begins with identification of possible sources. The error rate for medications is as high as 1 in 6.4 orders among hospitalized pediatric patients.[38] Off-label use of medications increases risk of medication error and has been attributed to difference in frequency of errors compared with adults. One of the most common reasons for medication errors in this specialized population is incorrect dosing such as calculation error.[39,40] KEY CONCEPT Medication errors among pediatric patients are possible due to differences in dose calculation and preparation; it is important to identify potential errors through careful review of orders, calculations, dispensing, and administration of drug therapy to infants and children. It is crucial to verify accurate weight, height, and age for dosing calculations and dispensing of prescriptions because pediatric patients are a vulnerable population for medication error. Consistent units of measurements in reporting patient variables, such as weight (kg) and height (cm), should be used. Dosing units such as mg/kg, mcg/kg, mEq/kg, mmol/kg, or units/kg should also be used accurately. Given the age-related differences in metabolism of additives, such as propylene glycol

LO 2

and benzyl alcohol, careful consideration should be given to the active and inactive ingredients when selecting a formulation.

Decimal errors, including trailing zeroes (eg, 1.0 mg misread as 10 mg) and missing leading zeroes (eg, .5 mg misread as 5 mg), in drug dosing or body weight documentation are possible, resulting in several-fold overdosing. Strength or concentration of drug should also be clearly communicated by the clinician in prescription orders. Similarly, labels that look alike may lead to drug therapy errors (eg, mistaking a vial of heparin for insulin). Dosing errors of combination drug products can be prevented by using the right component for dose calculation (eg, dose of sulfamethoxazole/trimethoprim is calculated based on the trimethoprim component).

Use of standardized concentrations and programmable infusion pumps, such as smart pumps with built-in libraries, is encouraged to minimize errors with parenteral medications, especially those for continuous infusions such as inotropes. Electronic health records (EMR) with clinical decision support systems and barcoding technology, with ability for dose range checks by weight for pediatric medication orders and accurate matching of correct ordered medication to patient, respectively, have decreased medication errors.[40]

Prevention of medication errors is a joint effort between health care professionals, patients, and parents/caregivers. Obtaining a complete medication history, including over-the-counter (OTC) and complementary and alternative medicines (CAMs), simplification of medication regimen, clinician awareness for potential errors, and appropriate patient/parent/caregiver education on measurement and administration of medications are essential in preventing medication errors.

Complementary/Alternative and Over-the-Counter Medication Use

Between 30% and 70% of children with a chronic illness (eg, asthma, attention deficit hyperactivity disorder, autism, cancer) or disability use CAMs.[41] CAMs can include mind-body therapy (eg, imagery, hypnosis), energy field therapies (eg, acupuncture, acupressure), massage, antioxidants (eg, vitamins C and E), herbs (eg, St. John's wort, kava, ginger, valerian), prayer, immune modulators (eg, echinacea), or other folk/home remedies. It is important to encourage communication about CAM use, including interdisciplinary discussion between CAM providers and pediatric health care providers.[41] It is critical to appreciate that there are limited data establishing efficacy of various CAM therapies in children. For example, colic is a condition of unclear etiology in which an infant cries inconsolably for over a few hours in a 24-hour period, usually during the same time of day. Symptoms of excessive crying usually improve by the third month of life and often resolve by 9 months of age. No medication has been approved by the FDA for this condition. Some parents are advised by family and friends to use alternative treatments, such as gripe water, to treat colic. Gripe water is an oral solution containing a combination of ingredients, such as chamomile and sodium bicarbonate, not regulated by the FDA. In addition, some gripe water products may contain alcohol, which is not recommended for infants due to their limited metabolism ability (ie, alcohol dehydrogenase). Further, some CAM products (eg, St. John's wort) can interact with prescription drugs and produce undesired outcomes. It is important to assess OTC product use in pediatric patients. For example, treatment of the common cold in children is similar to adults, including symptom control with adequate fluid intake, rest, use of saline nasal spray, and acetaminophen (10–15 mg/kg/dose every 6–8 hours) or ibuprofen (4–10 mg/kg/dose every 8 hours) for relief of discomfort and fever. Other products, such as a topical vapor rub or oral honey, have demonstrated some potential for alleviation of symptoms, such as cough, based on survey studies of parents for children of 2 years and older.[42,43] Unlike adults, symptomatic relief through the use of pharmacologic agents, such as OTC combination cold remedies, is not recommended for pediatric patients younger than 4 years. Currently, the FDA does not recommend the use of OTC cough and cold medications (eg, diphenhydramine and dextromethorphan) in children younger than 2 years; however, the Consumer Healthcare Products Association, with the support of the FDA, has voluntarily changed product labeling of OTC cough and cold medications to state "do not use in children under 4 years of age." This is due to increased risk for adverse effects (eg, excessive sedation, respiratory depression) and no documented benefit in relieving symptoms. It has also been noted that these medications may be less effective in children younger than 6 years compared with older children and adults.[44,45] Also noteworthy is the potential for medication error with use of OTC products in older children, such as cold medications containing diphenhydramine and acetaminophen. A parent/caregiver may inadvertently overdose a child on one active ingredient, such as acetaminophen, by administering acetaminophen suspension for fever and an acetaminophen-containing combination product for cold symptoms. The use of aspirin as an antipyretic or analgesic (eg, for a "cold") in patients younger than 18 years with viral infections is not recommended due to the risk of Reye syndrome. Signs or symptoms of Reye syndrome, usually appearing several days after start of a viral infection, are relatively nonspecific, including diarrhea, persistent vomiting, increased respiratory rate, increasing lethargy, and seizure. While making an appropriate recommendation for an OTC product for a pediatric patient, the parent/caregiver should always be referred to their pediatrician for further advice and evaluation when severity of illness is a concern.

Clinicians should respect parents'/caregivers' beliefs in the use of CAM and OTC products and encourage open discussion with the intention of providing information regarding their risks and benefits to achieve desired health outcomes as well as optimize medication safety.

Medication Administration to Pediatric Patients and Caregiver Education

Considering the challenges in cooperation from infants and younger children, medication administration can become a difficult task for any parent or caregiver. One should also consider factors that may affect adherence to prescribed therapy including caregiver and/or patient's personal beliefs, socioeconomic limitation(s), and fear of adverse drug effects. One common factor to consider is ease of measurement and administration when selecting and dosing pediatric drug therapy. LO 2 Clinicians should check concentrations of available products and round doses to a measurable amount. For example, if a patient were to receive an oral formulation, such as amoxicillin 400 mg/5 mL suspension, and the dose was calculated to be 4.9 mL, the dose should be rounded to 5 mL for ease of administration. Rounding the dose by 10% to the closest easily measurable amount is commonly practiced for most medications (eg, antibiotics); however, drugs with narrow therapeutic indices (eg, anticoagulants) are exceptions to this guideline.

LO 2 The means or devices for measuring and administering medications should also be closely considered. Special measuring devices as well as clear and complete education about their use are essential. Oral syringes are accurate and offered at most community pharmacies for the measurement of oral liquid medications. Studies have demonstrated less error in dose measurement using an oral syringe compared to other devices

Table 3–4

Helpful Tips for Medication Administration for Selected Dosage Forms[48]

Dosage Form	Recommendations
Ophthalmic drops or ointment	• Wash hands thoroughly prior to administration • Position child laying down in supine position • Avoid contact of applicator tip to surfaces, including the eye • Drops should be placed in the pocket of the lower eyelid • Ointment strip should be placed along the pocket of the lower eyelid

Otic drops	• Wash hands thoroughly prior to administration
	• Position child laying down in prone position
	• Tilt head to expose treated ear, gently pull outer ear outward, then due to age-dependent change in angle of Eustachian tube:
	  • If child < 3 years of age, gently pull downward and back; apply drops
	  • If child > 3 years of age, gently pull upward and back; apply drops

Nasal drops	• Wash hands thoroughly prior to administration • Position child laying down in supine position • Slightly tilt head back; place drops in nostril(s) • Remain in position for appropriate distribution of medication
Rectal suppository	• Similar to adult administration; challenging route for administration • For younger patients (ie, < 3 years), a smaller finger (eg, pinky finger) should be used to insert suppository
Metered-dose inhalers	• Use a spacer • For younger children, use one with a mask, be sure the mask is secured/placed closely up against the child's face, avoiding gaps between face and mask and creating a seal to ensure medication delivery • Child should take slow breaths in with each dose • Wait at least 1 minute between doses

(eg, dosing cup, dropper, dosing spoon) and that in addition to appropriate device caregiver health literacy contributes to potential for medication dose measurement error.[46] Due to inconsistencies and risk for possible inaccuracy of measuring smaller doses, dosing or measuring spoons, oral droppers, and medicine cups are not recommended for measuring doses for infants and young children. Household dining or measuring spoons are not accurate or consistent and should not be used for the administration of oral liquids. Additionally, consistency in dosing units used for liquid formulation (eg, milliliters instead of teaspoons or ounces) is necessary to minimize further medication dosing errors.[47]

KEY CONCEPT Comprehensive and clear parent/caregiver education improves medication adherence, safety, and therapeutic outcomes and is essential in care of infants and young children. Information about the drug, including appropriate and safe storage away from children, possible drug interactions, duration of therapy, importance of adherence, possible adverse effects, and expected therapeutic outcomes should be provided. Parent/caregiver education is important in both inpatient and outpatient care settings and should be reviewed at each point of care.

LO 5

LO 5

Because parents/caregivers are often sole providers of home care for ill children, it is important to demonstrate appropriate dose preparation and administration techniques to the caregivers before medication dispensing. First, a child should be calm for successful dose administration. Yet, calming a child is often a challenge during many methods of administration (eg, otic, ophthalmic, rectal). Parents/caregivers should explain the process in a simple and understandable form to the child because this may decrease the child's potential anxiety. In addition, it is also recommended to distract younger children using a favorite item such as toy or to reward cooperative or "good" behavior during medication administration. Helpful tips regarding administration of selected dosage forms in pediatric patients are listed in Table 3–4.[48]

Patient Encounter Part 3

MM is an 18-month-old female who is brought to the clinic with a 5-day history of bilateral ear pain, excessive crying, decreased appetite, and difficulty sleeping. The child's temperature last night was 39°C (102.2°F) by electronic axial thermometer. MM also presents with some nasal congestion and occasional cough. Mom reports to have given the child several doses of ibuprofen, but the pain or temperature did not improve and none was given this morning. No other significant past medical history. The pediatrician diagnoses MM with acute otitis media requiring antibiotic treatment and asks you to develop a treatment care plan for MM including use of amoxicillin at 90 mg/kg/day divided twice a day.

What additional information would you need to develop an appropriate treatment care plan for MM?

Mom asks you if ibuprofen was the right choice for MM's fever and pain and if other options such as acetaminophen or aspirin could be used instead. What would you recommend for pain and fever for MM? Why?

The nurse provides you MM's weight as 25 pounds (11.4 kg). What is MM's calculated dose of amoxicillin based on the dosage form you need to use?

Mom asks you if there are any complementary/alternative OTC cough/cold medications that she can give MM for her nasal congestion and cough. What recommendations would you make to mom?

What items should mom be educated on with regard to the new prescription of amoxicillin?

Patient Care Process

Collect Information:

- For patients up to 2 years of age, review birth history, including gestational age (GA), birth weight, medical complications, postnatal age, and corrected age.
- Review patient's past medical history, comorbidities.
- Review patient's available laboratory data (eg, serum creatinine, liver function tests).
- Review all current medication therapy, including CAM and OTC.
- Review patient's medication allergies and/or intolerances.

Assess the Information:

- Assess appropriateness of therapy. Is patient on appropriate drug therapy for current diagnoses? Are current medication doses appropriate (ie, for age, weight, etc.)? Any medications without indication?
- Evaluate patient's organ function (renal and hepatic), including use of appropriate equations (eg, bedside Schwartz).
- Assess current therapy for safety and efficacy. Is the medication effective for this patient? Is the patient experiencing any adverse effects?
- Consider available data regarding safe and effective dosing of selected drug.
- Assess patient's (or patient's caregiver) history of medication adherence and health care beliefs.

Develop a Care Plan:

- Consider available routes of administration. What is the most appropriate route? If IV medication is needed, what types of IV accesses are available? For example, does the patient have a central or peripheral line? Determine if IV medication needs to be further diluted or concentrated based on patient's comorbidities and fluid status.
- Consider ease of administration for the patient and/or caregiver. Is the dose easily measurable? Is the dosing frequency reasonable for their family schedule?
- Verify accuracy of dose calculations. Verify current weight and dosing units (eg, mg/kg/day, mg/kg/dose). Is the dosing interval appropriate?
- Determine what drug–drug/drug–food interactions are possible with this new therapy. How can they be managed?

Implement the Care Plan:

- Communicate plan for care with patient care team.
- Educate parent/caregiver/patient regarding selected drug therapy including purpose, dose, administration, duration therapy, possible side effects, etc.

Follow-up: Monitor and Evaluate:

- Monitor signs and symptoms of clinical outcomes (improvement and decline). Measure drug serum concentrations when appropriate. Monitor for possible adverse drug events.
- Reinforce patient/caregiver education.

Accidental Ingestion in Pediatric Patients

Pediatric accidental ingestions most often occur in the home.[49] Various factors account for incidence of accidental ingestions in young children, including hand-to-mouth behaviors as well as new and increased mobility resulting in easier access areas where harmful substances are stored (eg, medication cabinets). Indeed, caregivers are encouraged to use "child-safe" devices to lock closets and cabinets to reduce risk of accidental ingestions; however, this is not a substitute for appropriate caregiver supervision.

Ingested substances can vary, from household cleaning solutions to prescription and nonprescription medications. The most common exposures in children age less than 5 years were cosmetics/personal care products, analgesics, household cleaning substances, foreign bodies (eg, small toys), and topical preparations.[49] Management of accidental ingestions varies depending on the ingested substance, the amount, and the age and size of the child. The American Academy of Clinical Toxicology and the AAP do not recommend the use of ipecac syrup for treatment of accidental ingestion; thus, inducing emesis is not a recommended approach for any type of ingestion.[50] Clinicians receiving calls regarding management of accidental ingestions, depending on severity of case, should direct them to the emergency department for evaluation and/or the local or regional poison control center for specific recommendations, which can be reached via a universal contact number (1-800-222-1222), with additional information located through the American Association of Poison Control Centers (www.aapcc.org).[51]

Abbreviations Introduced in This Chapter

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
bpm	Beats per minute
CAM	Complementary and alternative medicine
CDC	Centers for Disease Control and Prevention
CPOE	Computer physician order entry
CrCl	Creatinine clearance
ELBW	Extremely low birth weight
GA	Gestational age
GFR	Glomerular filtration rate
LBW	Low birth weight
MDI	Metered-dose inhaler
OTC	Over-the-counter
V_d	Volume of distribution (apparent)
VLBW	Very low birth weight

REFERENCES

1. American Academy of Pediatrics, Committee on Fetus and Newborn. Age terminology during the perinatal period. Pediatrics. 2004;114:1362–1364.
2. Chen R, Wax Y, Toppelberg G, Barell V. A criterion for a standardized definition of low birthweight. Int J Epidemiol. 1991;20(1):180–186.
3. Oken E, Kleiman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr. 2003;3:6.
4. WHO growth standards are recommended for use in the U.S. for infants and children 0 to 2 years of age. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/growthcharts/who_charts.htm. Accessed August 1, 2017.

5. Centers for Disease Control Growth Charts, 2000. National Center for Health Statistics and National Center for Chronic Disease Prevention and Health Promotion. Available from: http://www.cdc.gov/growthcharts. Accessed August 1, 2017.
6. Barlow SE and the Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120(suppl):S164–S192.
7. de Caen AR, Berg MD, Chameides L, et al. Part 12: pediatric advanced life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(suppl 2): S526–S542.
8. Flynn JT, Kaelber DC, Baker-Smith CM, et al; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3). pii: e20171904.
9. American Heart Association. Pediatric advanced life support provider manual. Dallas, TX: American Heart Association; 2006. p. 273.
10. Schmidt BD. How to take a child's temperature. American Academy of Pediatrics. Available from: https://www.healthychildren.org/English/health-issues/conditions/fever/Pages/How-to-Take-a-Childs-Temperature.aspx. Accessed August 27, 2017.
11. Section on Clinical Pharmacology and Therapeutics; Committee on Drugs, Sullivan JE, Farrar HC. Fever and antipyretic use in children. Pediatrics. 2011;127(3):580–587.
12. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw. 1993;12(6):59–66.
13. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs. 1988;14(1):9–17.
14. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurs. 1997;23(3):293–297.
15. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics. 1957;19(5):823–832.
16. Shirkey HC. Drug dosage for infants and children. JAMA. 1965;193:443–446.
17. Anderson GD, Lynn AM. Optimizing pediatric dosing: a developmental pharmacologic approach. Pharmacotherapy. 2009;29(6):680–690.
18. Ramirez A, Wong WW, Shulman RJ. Factors regulating gastric emptying in preterm infants. J Pediatr. 2006;149(4):475–479.
19. Everard ML. Inhalation therapy for infants. Adv Drug Deliv Rev. 2003;55:869–878.
20. Sage DP, Kulczar C, Roth W, Liu W, Knipp GT. Persistent pharmacokinetic challenges to pediatric drug development. Front Genet. 2014;5:281. Published online 2014 August 27.
21. Buck ML. Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. Clin Pharmacokinet. 2003;42(5):403–417.
22. Thyagarajan B, Deshpande SS. Cotrimoxazole and neonatal kernicterus: a review. Drug Chem Toxicol. 2014;37(2):121–129. Epub 2013 Oct 7.
23. de Wildt SN, Tibboel D, Leeder JS. Drug metabolism for the paediatrician. Arch Dis Child. 2014;99(12):1137–1142. Epub 2014 Sep 3.
24. Mulhall A, de Louvois J, Hurley R. Chloramphenicol toxicity in neonates: its incidence and prevention. Br Med J (Clin Res Ed). 1983;287(6403):1424–1427.
25. Menon PA, Thach BT, Smith CH, Landt JL, Hillman RE, Hillman LS. Benzyl alcohol toxicity in a neonatal intensive care unit. Incidence, symptomatology, and mortality. Am J Perinatol. 1984;1(4):288–292.
26. Prestidge C, Chilvers MA, Davidson AG, Cho E, McMahon V, White CT. Renal function in pediatric cystic fibrosis patients in the first decade of life. Pediatr Nephrol. 2011;26(4): 605–612.
27. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
28. Jelliffe RW. Creatinine clearance: bedside estimate. Ann Intern Med. 1973;79(4):604–605.
29. Filler G, Foster J, Acker A, Lepage N, Akbari A, Ehrich JH. The Cockcroft-Gault formula should not be used in children. Kidney Int. 2005;67(6):2321–2324.
30. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34(3):571–590.
31. Staples A, LeBlong R, Watkins CW, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol. 2010;25:2321–2326.
32. Seikaly MG, Browne R, Bajaj G, Arant BS Jr. Limitations to body length/serum creatinine ratio as an estimate of glomerular filtration in children. Pediatr Nephrol. 1996;10(6):709–711.
33. Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? Pediatr Nephrol. 2003;18(10):981–985.
34. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med. 2007;161(3):282–290.
35. American Academy of Pediatrics, Committee on Drugs. Uses of drugs not described in the package insert (off-label uses). Pediatrics. 2002;110:181–183.
36. Conroy S. Unlicensed and off-label drug use: issues and recommendations. Pediatr Drugs. 2002;4:363–369.
37. Nahata MC, Pai VB. Pediatric Drug Formulations, 6th ed. Cincinnati, OH: Harvey Whitney Books; 2011. p. 385.
38. Marino BL, Reinhardt K, Eichelberger WJ, Steingard R. Prevalence of errors in a pediatric hospital medication system: implications for error proofing. Outcomes Manag Nurs Pract. 2000;4:129–135.
39. Stucky ER, American Academy of Pediatrics, Committee on Drugs and Committee on Hospital Care. Prevention of medication errors in the pediatric inpatient setting. Policy Statement. Pediatrics. 2003;112(2):431–436.
40. Conroy S, Sweis D, Planner C, Yeung V, Collier J, Haines L, Wong IC. Interventions to reduce dosing errors in children: a systematic review of the literature. Drug Saf. 2007;30(12):1111–1125.
41. Kemper KJ, Vohra S, Walls R; Task Force on Complementary and Alternative Medicine; Provisional Section on Complementary, Holistic, and Integrative Medicine, American Academy of Pediatrics. The use of complementary and alternative medicine in pediatrics. Pediatrics. 2008;122(6):1374–1386.
42. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin CM Jr. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med. 2007;161(12):1140–1146.
43. Paul IM, Beiler JS, King TS, Clapp ER, Vallati J, Berlin CM Jr. Vapor rub, petrolatum, and no treatment for children with nocturnal cough and cold symptoms. Pediatrics. 2010;126(6):1092–1099.
44. Use caution when giving cough and cold products to kids. U.S. Food and Drug Administration. Available from: https://www.fda.gov/drugs/resourcesforyou/specialfeatures/ucm263948.htm. Accessed August 1, 2017.
45. Public health advisory: FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children. U.S. Food and Drug Administration. Available from: https://www.fda.gov/NewsEvents/Newsroom/

PressAnnouncements/2008/ucm051137.htm. Accessed August 1, 2017.
46. Yin HS, Mendelsohn AL, Wolf MS, et al. Parents' medication administration errors: role of dosing instruments and health literacy. Arch Pediatr Adolesc Med. 2010;164(2):181–186.
47. Yin HS, Dreyer BP, Ugoaja DC, et al. Unit of measurement used and parent medication dosing errors. Pediatrics. 2014;134(2): e354–e361.
48. Buck ML, Hendrick AE. Pediatric Medication Education Text, 5th ed. American College of Clinical Pharmacy, 2009; Sec1: xvii–xxvii.
49. Mowry JB, Spyker DA, Brooks DE, Zimmerman A, Schauben JL. 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report. Clin Toxicol (Phila). 2016;54(10):924–1109.
50. Höjer J, Troutman WG, Hoppu K, et al. Position paper update: ipecac syrup for gastrointestinal decontamination. Clin Toxicol (Phila). 2013;51(3):134–139.
51. American Association of Poison Control Centers. Available from: www.aapcc.org. Accessed August 1, 2017.

4 Palliative Care

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LEARNING OBJECTIVES

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

1. Describe the philosophy of palliative care including hospice care and its impact on medication therapy management.
2. Discuss the therapeutic management of palliative care patients and how it differs from and is similar to traditional patient care at the end of life.
3. List the most common symptoms experienced by the terminally ill patient.
4. Explain the pathophysiology of the common symptoms experienced in the terminally ill patient.
5. Describe the pharmacologic rationale of medication therapy used for symptom management in the terminally ill patient.
6. Recommend nonpharmacologic and pharmacologic management of symptoms in a terminally ill patient.
7. Develop a patient-specific palliative care management plan.
8. Educate patients and caregivers regarding palliative care management plan, including rationale of treatment, importance of medication adherence, and assessment and monitoring of desired outcomes.

INTRODUCTION

LO1 KEY CONCEPT According to the World Health Organization (WHO), "Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." The goal of palliative care is to achieve the best quality of life for patients and their families.[1] "Palliate" literally means "to cloak." The WHO goal of achieving high quality of life depends on a team approach to manage disease-related symptoms while honoring the patient's goals for care.[2] Palliative care focuses on patients and their families and the challenges associated with life-threatening illness.[3] The goal is to prevent and relieve suffering by means of early identification, assessment, and treatment of pain and other physical symptoms, including associated psychosocial, emotional, and spiritual concerns.[1] Palliative medicine is rapidly becoming a well-recognized medical specialty[4] and is much needed due to the increased number of patients with chronic, slowly debilitating diseases.[2]

LO1

The term *palliative care* is frequently used synonymously with hospice, and although hospice programs provide palliative care, palliative care has a much broader application. In the United States, hospice is defined by Medicare and other third-party payers as a benefit available to individuals who have less than or equal to 6 months life expectancy if the disease runs its typical course.[2] Hospice care guidelines and regulations are primarily defined by federal regulations. Palliative care outside of the umbrella of hospice care, in contrast, is not currently regulated nor has the same reimbursement structure. Palliative care services may be provided at any point during the disease process and are not limited to the last 6 months of life; therefore, patients and families may receive palliative care services beginning at the time of diagnosis of life-limiting illness. Palliative care may be delivered in all care settings.[5] The foundation for providing quality palliative care centers around active participation of an interdisciplinary team working closely to meet patient and family goals.[6] Palliative care team members include representatives from medicine, nursing, social work, pastoral or related counseling, pharmacy, nutrition, rehabilitation, and other professional disciplines providing a holistic approach to the patient's care.

LO2

LO2

KEY CONCEPT The goals of palliative care include enhancing quality of life while maintaining or improving functionality.[6,7] Palliative care should most logically be delivered to patients from the onset of any chronic, life-altering disease. Before many of our modern medical and therapeutic advancements were developed, curative treatments were not normally available.[8] Provision of comfort was considered the mainstay for patient care. Advances in medical care, nutrition, public health, and trauma care resulted in fewer patient deaths and medical management shifted focus from comfort to a death-denying approach, with prolonging life as the primary goal. With this shift, palliative care became less emphasized until 1967 when the first modern hospice was established in London, England. Today the palliative care philosophy attempts to combine enhanced quality of life, compassionate care, and patient and family support with modern medical advances.

LO1

LO1

EPIDEMIOLOGY AND ETIOLOGY

The first hospice in the United States was founded in 1974. Since then, hospice acceptance and utilization has increased; currently, approximately 6100 hospice agencies care for patients across the United States.[9] In 2013, approximately 59% of hospice patients were cared for in the home, and 84% of hospice patients were older than 65 years.[9]

In a 2007 study, hospice patients lived 29 days longer than nonhospice patients, with the largest difference noted in chronic heart failure (CHF) patients.[10] Lung cancer patients receiving early palliative care survived 23% longer than those with delayed palliative care, according to a 2010 study.[11] Early referrals to hospice appear to improve overall care of the patient and offer prolonged survival in some patients. The integration of palliative care prior to the patient's eligibility for hospice care may prove to even further improve survival and quality of life and care of patients.

Because health care providers have an increasing recognition of the benefit of palliative care for patients with all life-limiting illness, increased integration of this model of care has extended to other disease states beyond cancer.

PATHOPHYSIOLOGY

LO 2 Understanding the pathophysiology of multiple end-stage disease states is daunting, yet in palliative care, the emphasis is not so much on the disease state management as it is on the assessment and appropriate treatment of associated physical, psychological, social, and spiritual symptoms. Palliative care focuses on symptom management for patients with progressive life-limiting illnesses from diagnosis through death where the pathophysiological impact of disease on a patient's symptoms may vary greatly depending on the stage of a patient's illness. KEY CONCEPT Palliative care is appropriate for all life-limiting diseases including cancer, chronic obstructive pulmonary disease (COPD), dementia (including Alzheimer disease), Parkinson disease, chronic cardiac disease, stroke, renal failure, hepatic failure, multiorgan failure, diabetes mellitus, and so on.

LO 2 For the purpose of this chapter, pathophysiology is not a primary focus. Rather, the philosophy of managing physical, psychological, social, and spiritual symptoms to maintain quality of life and prevent suffering is discussed within the context of progressively incurable illnesses. Although palliative may coexist with aggressive disease state management to extend life, as the patient approaches the end of life, philosophy and management generally move away from those principles related to the disease state management of patients where prolonging life is the goal.

CLINICAL PRESENTATION AND DIAGNOSIS

Cancer

LO 3 LO 4 Palliative care is most commonly associated with cancer patients. Regardless of whether or not the cancer is curable, most patients have various degrees of physical, psychological, social, and spiritual symptoms that arise once a diagnosis is confirmed. Once a cancer patient has failed curative and life-prolonging therapy, prognosis and disease trajectory is easier to determine than in patients with other life-limiting diseases. The change in focus from cure to symptom control becomes apparent and therefore more acceptable. Symptoms associated with cancer depend on both the primary tumor site and the location of metastatic spread. Symptoms may also result from the effects of cancer treatments such as chemotherapy and radiation. (See Chapters 88 to 99 for specific cancers and their treatments.)

End-Stage Heart Failure

LO 4 LO 3 Many forms of heart disease result in sudden death; however, the disease progression of heart failure is protracted yet unpredictable. Advanced heart failure (class III to IV or stage C or D) is characterized by persistent symptoms that limit activities of daily living despite optimal drug therapy. Common symptoms include fatigue, breathlessness, anxiety, fluid retention, and pain. In heart failure, standard medication management is intended to reduce progression of cardiac remodeling and is considered disease modifying. However, as patients approach the final months of life, with the exception of cholesterol-lowering agents, these same cardiac medications are also palliative and should not be discontinued prematurely without cause (Figure 4–1). Exacerbations of heart failure

	Mortality Benefit	Functional Benefit	Renal Dosing Adjustments	Risk vs Benefit Considerations
Diuretics *(eg, furosemide, torsemide, bumetanide)*	–	✓	✓	Continue for symptom management (edema, dyspnea) **Caution:** Dehydration, hypokalemia
ACEI *(eg, lisinopril, enalapril)*	✓	✓	✓	**Caution:** Dehydration, sepsis, concurrent NSAID use and renal artery stenosis can increase renal toxicity
Aldosterone antagonists *(eg, spironolactone)*	✓	–/✓	✓	Primary benefit for reducing mortality **Caution:** Hyperkalemia risk with renal insufficiency
β-Blockers *(eg, carvedilol, metoprolol)*	✓	✓	–	Taper doses prior to discontinuation **Caution:** May cause hypotension and bradycardia
Inotrope PO *(eg, digoxin)*	–	✓	✓	**Caution:** Digoxin toxicity (N/V, anorexia, confusion, arrhythmia)

FIGURE 4–1. Drugs, their use in Class III–IV heart failure, and their effects on mortality, hospital admissions, and functional status. Checkmark, indicating a positive impact on specified parameter, and—indicating no significant impact on specified parameter.[7,31]

symptoms should be aggressively treated as long as the patient is responsive to therapy and wishes to receive treatment. In hospice, this can often be accomplished through medication manipulation in the patient's home without the need for hospitalization (see Chapter 6).

Chronic Obstructive Pulmonary Disease

COPD has a prolonged and variable course. Patients with COPD have a high number of physician visits and hospital admissions. Palliative care treatment is directed at reducing symptoms, reducing the rate of decline in lung function, preventing and treating exacerbations, and maintaining quality of life. In end-stage COPD, bronchodilators and anti-inflammatory agents become less effective. As patients decline, their ability to use inhalers appropriately becomes more difficult. Utilizing a nebulizer to administer bronchodilators allows for more reliable drug delivery to the site of action. Symptoms of late-stage disease include wheezing, chronic sputum production, cough, frequent respiratory infections, **dyspnea** with exertion progressing to dyspnea at rest, fatigue, pain, hypoxia, and weight loss. Pulmonary hypertension may also occur and can lead to cor pulmonale or right-sided heart failure (see Chapter 15).

End-Stage Kidney Disease

Chronic kidney disease is progressive and leads to renal failure. In end-stage kidney disease, the only life-sustaining treatments are dialysis or renal transplant. Without treatment, kidney failure causes uremia, oliguria, hyperkalemia and other electrolyte disorders, fluid overload and hypertension unresponsive to treatment, anemia, hepatorenal syndrome, and uremic pericarditis. Symptoms associated with chronic kidney disease (stage 5) include fatigue, pruritus, nausea, vomiting, constipation, dysgeusia, muscle pain, agitation, and bleeding abnormalities. Palliative care in these patients includes the minimization of these symptoms; however, because many options for drug therapy will be cleared through the kidneys, agents should be chosen cautiously to avoid other complications (see Chapter 26).

End-Stage Liver Disease

Like kidney disease, the only treatment to prolong life in advanced liver disease is transplant. Patients with end-stage liver disease typically present with ascites, jaundice, pruritus, or encephalopathy, and frequently all four symptoms. Additionally, bleeding disorders are common, and associated esophageal or gastric varices bleeds are the cause of death in about one-third of those who die from liver disease. Palliative care in these patients focuses on the symptom management of end-stage liver disease complications.

Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS)

Pharmacologic advances have changed prognosis and progression of HIV/AIDS. Palliative care is predominantly directed toward patients without access to drug therapy in the early stages of disease. Patients with progressed HIV/AIDS are susceptible to acquire opportunistic infections and cancer that may hasten their death. Common symptoms observed in individuals with HIV/AIDS at the end of their life include fatigue, profound weight loss, breathlessness, nausea, GI disturbances, and pain. The goal of palliative care in these patients is to minimize common AIDS-related symptoms (see Chapter 87).

Stroke/Cerebral Vascular Accident

Stroke results from hemorrhage or ischemia. The prognosis of cerebral vascular accident (CVA) patients is unpredictable and may be extended, resulting in caregiver fatigue. Approximately one-third of patients who have a stroke will die within 2 years. Patients with stroke deal with loss of physical and cognitive function, poststroke pain, and frequent depression. Incontinence, aphasia, **dysphagia**, and seizures are also common. Patients who have dysphagia have a high incidence of aspiration pneumonia, which often is the cause of death (see Chapter 11).

Parkinson Disease

Parkinson disease is a degenerative neurologic disease with a long chronic, progressive course evidenced by akinesia, rigidity, and tremor. The goal of therapy is to reduce symptoms and maintain or improve quality of life. Palliative care provides support to both the patient and caregiving system as patients become more disabled and as neuropsychiatric problems arise. Frequent symptoms are skin infections and breakdown, constipation, pain, depression, hallucinations, and confusion. Individuals with Parkinson disease often die from bronchial pneumonia due to dysphagia or complication from falls (see Chapter 33).

Amyotrophic Lateral Sclerosis (Lou Gehrig Disease)

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disorder characterized by progressive loss of motor neurons. The median survival is approximately 3 years from the symptom onset with less than 15% of patients surviving 10 years. Initially, symptoms of ALS present as limb weakness, with other symptoms developing in no particular order including cramps, spasticity, pain, dysarthria, sialorrhea, fatigue, insomnia, depression, fear and anxiety, involuntary emotional expression disorder, constipation, aspiration, and laryngospasm. Many patients do not have cognitive impairment; however, one-fourth to one-half of patients with ALS may have associated frontal lobe dementia. Disease progression eventually involves all systems except sphincter control and eye movement. Unless the individual has long-term mechanical ventilation, the cause of death is typically respiratory failure.

Alzheimer Disease and Other Dementia

Dementia is a progressive, nonreversible deterioration in cognitive function with associated behavioral dysfunction. Alzheimer disease accounts for most dementia cases; vascular, Parkinson disease, dementia with Lewy body, and frontotemporal dementias are less prevalent. Drug therapy targets slowing progression of cognitive symptoms and preserving patient function. As patients progress toward end-stage dementia, in addition to memory loss and personality and behavioral changes, they require assistance in basic activities of daily living such as feeding, dressing, and toileting. At this point they may not respond to their surroundings, may not communicate, or have impaired movements and dysphagia. Depression, agitation, delusions, compulsions, confusion, hallucinations, incontinence, and disruption of sleep/wake cycles are all common symptoms in end-stage dementias. Symptom assessment is challenging due to the cognitive impairment and frequent aphasia. Palliative care is not only directed toward the patient, but also emotional support for those close to them (see Chapter 29).

TREATMENT

LO 7 KEY CONCEPT Following a complete assessment of the patient, developing a comprehensive therapeutic plan that utilizes the fewest number of medications to achieve the highest quality of life is essential. Many times, one drug may relieve multiple symptoms, resulting in better patient care, lower costs, and decreased medications. Cost-effective drug recommendations are essential to control costs. Avoiding polypharmacy will reduce adverse drug events related to drug interactions, excessive side effects, and therapy duplication. The following list of symptoms includes common symptoms observed in palliative and end-of-life care; however, it is not comprehensive. LO 3 KEY CONCEPT Palliative care is more than just pain management. It includes the treatment of symptoms resulting in the discomfort for the patient, which may include nausea and vomiting, agitation, anxiety, depression, delirium, dyspnea, anorexia and cachexia, constipation, diarrhea, pressure ulcers, and edema.

Note that many drugs used to treat symptoms in palliative and end-of-life care are often prescribed for unapproved uses, administered by unapproved routes or in dosages higher than that recommended by the package insert. This "off-label" use of medication is not unique to palliative care. Conducting large-scale, rigorous drug studies that supply necessary information for an approved drug indication possesses ethical difficulty due to the delicate nature of patient's receiving palliative and/or hospice care.

Anxiety

A comprehensive review of anxiety disorders may be found in Chapter 40.

▶ *Palliative Care Considerations*

- Anxiety is "characterized by apprehensive anticipation of future danger or misfortune accompanied by psychological symptoms such as worrying, vigilance, and rumination as well as by physical feelings such as tension, jitters, dyspnea, chest discomfort, or abdominal stress."[7]
- Anxiety is closely related to fear, but fear has an identified cause or source of worry (eg, fear of death). Fear may be more responsive to counseling than anxiety that the patient cannot attribute to a particular fearful stimulus. Anxiety disorders are the most prevalent class of mental disorders, so it is not surprising that anxiety is a common cause of distress at life's end.

LO 3 In addition to anxiety disorders, a variety of conditions can cause, mimic, or exacerbate anxiety.[12,13] Delirium, particularly in its early stages, can easily be confused with anxiety. Physical complications of illness, especially dyspnea and undertreated pain, are common precipitants. Significant anxiety is present in most patients with advanced lung disease and is closely related to periods of oxygen desaturation. Medication side effects, especially akathisia from older antipsychotics and antiemetics (including metoclopramide), can present as anxiety. Interpersonal, spiritual, or existential concerns can mimic and exacerbate anxiety. Patients with an anxious or dependent coping style are at high risk of anxiety as a complication of advanced illness. Short of making a diagnosis of a formal anxiety disorder, differentiating normal worry and apprehension from pathologic anxiety requires clinical judgment.

LO 3 Behaviors indicative of pathological anxiety include intense worry or dread, physical distress (eg, tension, jitteriness, or restlessness), maladaptive behaviors and diminished coping, and inability to relax.[12]

Pathological anxiety may be complicated by insomnia, depression, fatigue, GI upset, dyspnea, or dysphagia.[14] Anxiety can also worsen these conditions, if they are already present. Untreated anxiety may lead to numerous complications, including withdrawal from social support, poor coping, limited participation in palliative care treatment goals, and family distress. Reassess the patient for anxiety with any change in behavior or any change in the underlying medical condition. Assessment for formal anxiety disorders or other contributing factors is key to management. A comprehensive review of insomnia may be found in Chapter 41.

▶ *Nonpharmacologic Treatment*

LO 7 LO 8 Regardless of treatment approach chosen, the following principles apply. Ask questions and listen to patients' concerns and fears. Offer emotional support and reassurance when appropriate. Err on the side of treatment—be willing to palliate anxiety. Assess treatment response and side effects frequently. Aim to provide maximum resolution of anxiety and educate patients and families about anxiety and its treatments.

LO 6 Psychotherapies can help manage anxiety, although availability of trained therapists willing to make home visits, and limited stamina and attention span of seriously ill patients, typically make such therapies impractical in the hospice setting. Cognitive and behavioral therapies can be beneficial, including simple relaxation exercises or distraction strategies (ie, focusing on something pleasurable or at least emotionally neutral). Encourage pastoral care visits, especially if spiritual and existential concerns predominate.

LO 8 When an underlying cause of anxiety can be identified, treatment is initially aimed at the precipitating problem, with monitoring to see if anxiety improves or resolves as the underlying cause is addressed.[14]

▶ *Pharmacotherapy*

LO 5 In most cases, management of pathological anxiety in the hospice setting involves pharmacologic therapies. Benzodiazepines are standard treatment; however, selective serotonin reuptake inhibitors (SSRIs), typical and atypical antipsychotics, may be appropriate based on the patient's life expectancy.[14] The primary LO 6 goal of therapy for anxiety in hospice is patient comfort. Aim to prevent anxiety, not just treat it with as needed medications. Think of pain management as an analogy. As with all medications LO 5 that act in the CNS, anxiolytics, such as benzodiazepines, should be dosed at the lower end of the dose range to prevent unnecessary sedation, particularly in the frail and elderly. However, recognize that standard or higher doses may be required. Avoid use of bupropion and psychostimulants for anxiety. Although effective for depression, they are ineffective for anxiety and may make anxiety worse. Many patients have difficulty swallowing as they approach the end of life. Lorazepam, alprazolam, and diazepam tablets are commonly crushed and placed under the tongue with a few drops of water if the liquid formulations are not readily available. Low-dose haloperidol is also used to treat anxiety in palliative care, particularly if delirium is present.[15] Chapter 40 provides more detailed information on appropriate use of anxiolytic agents.

Delirium

▶ *Palliative Care Considerations*

Delirium is very common in hospice, occurring in more than 80% of terminally ill patients, most often in the last few days of life.[11] Potential causes of delirium in the hospice setting include, but are not limited to, medical illness, dehydration, hypoxia, sleep deprivation, metabolic disturbances, sepsis, side effects of drugs

(particularly anticholinergic agents, benzodiazepines, opioids, corticosteroids, tricyclic antidepressants), urinary retention, urinary tract infection, constipation or impaction, uncontrolled pain, or alcohol or drug withdrawal.[7,15]

LO 3 A classic symptom of delirium is clouding of consciousness. This can be manifested by an inability to either maintain or shift attention. Patients also have impaired cognitive functioning, which may or may not include memory disturbances. "Sundowning" is a very common phenomenon at the end of life, especially in the presence of delirium. It presents as daytime sleepiness and nighttime agitation and restlessness. Another common characteristic is fluctuation in severity of delirium symptoms during the course of the day. This can even occur within the course of a single hour or also from day to day. Patients exhibiting agitation from their delirium are easy to identify, but those who present as withdrawn and with diminished responsiveness ("quiet" delirium) are more difficult to diagnose. It is not uncommon for patients to exhibit both quiet and agitated delirium. Treatment is the same for both types of delirium. Delirium is difficult to distinguish from dementia. Delirium more commonly presents as a sudden onset (eg, hours to days), with an altered level of consciousness and a clouded sensorium. However, dementia more commonly presents gradually and with an unimpaired level of consciousness.[15]

LO 4

► *Nonpharmacologic Treatment*

LO 6 Establishing a safe, soothing environment including familiar objects such as photographs and familiar music can be helpful to calm the patient. Minimizing risk of injury is important when the patient is agitated. Providing education to families and caregivers about the causes of delirium, signs and symptoms, and how to best manage it will help reduce their anxiety and distress when it occurs.

► *Pharmacotherapy*

LO 5 The most important initial step is to determine the goal of care. If possible, reverse the underlying cause of delirium to restore the patient to a meaningful cognitive status.[7,11] If the precipitating factors cannot be reversed, initiate to treat the symptoms. If the patient is irreversibly delirious and agitated, drug therapy is generally indicated.

Antipsychotic (neuroleptic) drugs (conventional or atypical antipsychotics) are the drugs most commonly used to treat confusion and agitation associated with delirium. However, treatment of delirium with these drugs is an "off-label" indication. Atypical antipsychotics including risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, and aripiprazole are also an option for management of delirium.[16]

Haloperidol, when given in doses less than 2 mg/day, is well tolerated and nonsedating. Doses greater than 4.5 mg/day are associated with increased incidence of extrapyramidal symptoms.[17] Cumulative doses of 35 mg or single IV doses greater than 20 mg have been associated with QTc prolongation.[18] When sedation is beneficial for terminal aggressive, agitated delirium, chlorpromazine provides more sedation as compared with low-dose haloperidol. When patients are bedbound and in the final stages of life, orthostatic hypotension common with chlorpromazine is not a concern. Haloperidol and chlorpromazine are commonly given sublingually or rectally if swallowing becomes difficult, although these are not approved routes of administration. Haloperidol, but not chlorpromazine, can be given subcutaneously.[19]

LO 5 Administering benzodiazepines alone in a patient with delirium can actually make the delirium and confusion worse. While addition of benzodiazepines with antipsychotics is not routinely used, delirium induced by withdrawal or untreated anxiety may benefit from addition of a benzodiazepine.[13]

Patient Encounter 1

LM is a 67-year-old man diagnosed with prostate cancer with metastases to the left anterior iliac crest and left femoral neck and greater trochanter. He is being seen by the inpatient palliative care team. Past medical history: coronary artery disease, hypertension, benign prostatic hyperplasia, hyperlipidemia, hypothyroidism, depression. No known allergies. LM reports left hip pain rating 7/10 (visual analog pain scale, 0–10). Pain is: deep, constant, aching pain causing limitation in mobility. Pain also radiates down the back of his left leg. Radiating pain is a 6/10 (visual analog pain scale, 0–10), episodic, exacerbated by movement and is a "lightning bolt" down his leg. LM reports worsening of urinary symptoms, constipation, and dizziness upon standing. LM reports bruising to his right elbow and knee after a recent fall.

VS: BP 101/60 mm Hg, RR 20 breaths/min, P 60, wt 60 kg (132 lbs), ht 5'7" (170 cm)

Medications: amlodipine 10 mg by mouth daily, fluoxetine 20 mg by mouth daily, simvastatin 40 mg by mouth daily, tamsulosin 0.4 mg by mouth daily, finasteride 5 mg by mouth daily, levothyroxine 200 mcg by mouth once daily, multivitamin by mouth once daily, hydrocodone/acetaminophen 5-325 1 tablet by mouth every 4 hours as needed, docusate 100 mg by mouth twice daily as needed.

What two types of pain is LM experiencing?

What may be contributing to the worsening of LM's urinary symptoms?

What other urinary symptoms and/or urinary related complications should be monitored for if LM's cancer progresses?

What potential drug–drug interactions may exist, and how would you monitor the patient for these drug interactions?

What medications should be added, changed, or discontinued?

List nonpharmacologic interventions that the practitioner could make to improve the care of LM.

Dyspnea

► *Palliative Care Considerations*

LO 3 Dyspnea is described as an uncomfortable awareness of breathing. It is a subjective sensation, and patient self-report is the only reliable indicator. Respiratory rate or Po_1 may not correlate with the feeling of breathlessness.[20] Respiratory effort and dyspnea are not the same. While opioids do not address bronchoconstriction or bronchospasm, patients may report substantial relief of dyspnea from opioids with no change in respiratory rate. The prevalence of dyspnea varies from 12% to 74%, worsening during the last week of life in terminally ill cancer patients to between 50% and 70%. History and physical examination should be taken and reversible causes of dyspnea should be identified and treated, if present.[21]

► *Nonpharmacologic Treatment*

LO 6 Provide information, anticipate and proactively prepare the patient and family for worsening symptoms. Identify and attempt to minimize triggers that cause episodes of dyspnea. Educate the patient and family regarding treatment of dyspnea, including the use of opioids and benzodiazepines for dyspnea-associated anxiety. Prevent isolation and address spiritual issues that can worsen symptoms. Encourage relaxation and minimize the need for exertion.

Reposition to comfort, usually to a more upright position or with the compromised lung down. Avoid strong odors, perfumes, and smoking in the patient's presence or in close proximity. Improve air circulation/quality: provide a draft, use fans, or open windows and adjust temperature/humidity with air conditioner or humidifier.

► *Pharmacotherapy*

LO 5 If no treatable causes can be identified or when treatments do not completely alleviate distressing symptoms, opioids are first-line agents for treating dyspnea.[21] Opioids suppress respiratory awareness, decrease response to hypoxia and hypercapnia, vasodilate, and have sedative properties. Low-dose opioids (eg, starting oral dose of morphine ~5 mg) have been shown to be safe and effective in the treatment of dyspnea. Opioid doses should be titrated judiciously. Once an effective dose of an opioid has been established, converting to an extended-release preparation may simplify dosing. When using opioids, anticipate side effects and prevent constipation by initiating a stimulant laxative/stool softener combination.

Nebulized opioids for treatment of dyspnea are controversial. Study results have been inconsistent.[22,23] Nonrandomized studies, case reports, and chart reviews describe anecdotal improvement in dyspnea using nebulized opioids; however, several controlled studies using nebulized opioids have provided inconclusive or negative results. Nebulized opioids may be an alternative in patients who are not able or willing to take an oral agent or cannot tolerate adverse effects of systemic administration.

LO 5 Nebulized furosemide appears effective for dyspnea refractive to other conventional therapies.[24] The hypothesized mechanism of action of nebulized furosemide is its ability to enhance pulmonary stretch receptor activity, inhibition of chloride movement through the membrane of the epithelial cell, and its ability to increase the synthesis of bronchodilating prostaglandins.[24]

LO 5 Because anxiety can exacerbate dyspnea, benzodiazepines and antidepressants that have anxiolytic properties are frequently beneficial. Not all dyspnea is caused by low oxygen saturation. However, oxygen therapy is useful and beneficial for dyspnea if hypoxia is present.

For known etiologies of dyspnea, consider the following:

Bronchospasm or COPD exacerbation: Albuterol, ipratropium, and/or oral steroids are effective for symptoms management. Nebulized bronchodilators are more effective than handheld inhalers in patients who are weak and have difficulty controlling breathing.

LO 5 **Thick secretions:** If cough reflex is strong, loosen secretions by increasing fluid intake. Guaifenesin may thin secretions; however, its efficacy in the absence of hydration is controversial. Nebulized saline may also help loosen secretions. If the patient is unable to cough, hyoscyamine, glycopyrrolate, or scopolamine patch can effectively dry secretions.[21] Oral glycopyrrolate is preferred since it has less propensity to cause the anticholinergic side effect of confusion.

Anxiety associated with dyspnea: Consider benzodiazepines (eg, lorazepam, diazepam).

Effusions: Thoracentesis may be necessary.

Low hemoglobin: Red blood cell transfusion (controversial) or erythropoietin (rarely used in hospice but might have larger role in palliative care).

LO 5 **Infections:** Antibiotic therapy as appropriate.

LO 5 **Pulmonary emboli:** Anticoagulants for prevention and treatment or vena cava filter placement (rarely used in hospice but might have a larger role in palliative care).

Patient Encounter 2

KP is a 74-year-old man admitted to hospice with a diagnosis of chronic obstructive pulmonary disease (COPD). Comorbidities include type 2 diabetes mellitus, hyperlipidemia, and hypothyroidism. KP continues to smoke cigarettes (1 ppd) and admits to consuming 2 to 4 beers per day. No known drug allergies. Pulmonary symptoms include moderate to severe dyspnea upon exertion with moderate dyspnea at rest, excessive secretions, chronic productive cough; he is oxygen dependent and has recurrent pneumonias requiring hospitalizations. KP reports poor appetite, uncontrolled anxiety, and insomnia.

VS: BP 145/50 mm Hg, RR 45 breaths/min, P 88, Wt 54.5 kg (120 lb), Ht 5'8" (173 cm)

Medications: Metformin 1000 mg by mouth twice daily, glipizide 5 mg by mouth once daily, atorvastatin 10 mg by mouth daily, levothyroxine 250 mcg daily, tiotropium handihaler inhale the contents of one capsule once daily, fluticasone/salmeterol dry powder inhaler, one inhalation by mouth twice daily, albuterol inhaler two puffs every 6 hours as needed for shortness of breath.

What parameters should be assessed prior to making changes to or adding additional interventions for KP's current situation?

What medications could be added, changed, or discontinued?

What are some nonpharmacologic interventions for treating KP's shortness of breath?

LO 5 **Rales due to volume overload:** Reduction of fluid intake or diuretic therapy as appropriate.

Nausea and Vomiting

A comprehensive review of nausea and vomiting may be found in Chapter 20.

► *Palliative Care Considerations*

Up to 71% of palliative care patients will develop nausea and vomiting with ~40% experiencing these symptoms in the last 6 weeks of life. Chronic nausea can be defined as lasting longer than a week and without a well-identified or self-limiting cause, such as chemotherapy, radiation, or infection.[3] Four major mechanisms are correlated with the stimulation of the vomiting center (Figure 4–2). Potentially reversible causes of nausea and vomiting should not be overlooked. Causes of chronic nausea in end-of-life patients may include autonomic dysfunction, constipation, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), other drugs, infection, bowel obstruction, metabolic abnormalities (eg, renal or hepatic failure, hypercalcemia), increased intracranial pressure, anxiety, radiation therapy, chemotherapy, or untreated pain.[23,25,26]

LO 3 LO 4

LO 4

► *Nonpharmacologic Treatment*

LO 6 Relaxation techniques may prove beneficial. Strong foods or odors should be avoided and eliminate offending medications.

► *Pharmacotherapy*

LO 5 Clinical features of nausea and vomiting should guide the choice of antiemetics used (for a more comprehensive review, see Chapter 20).

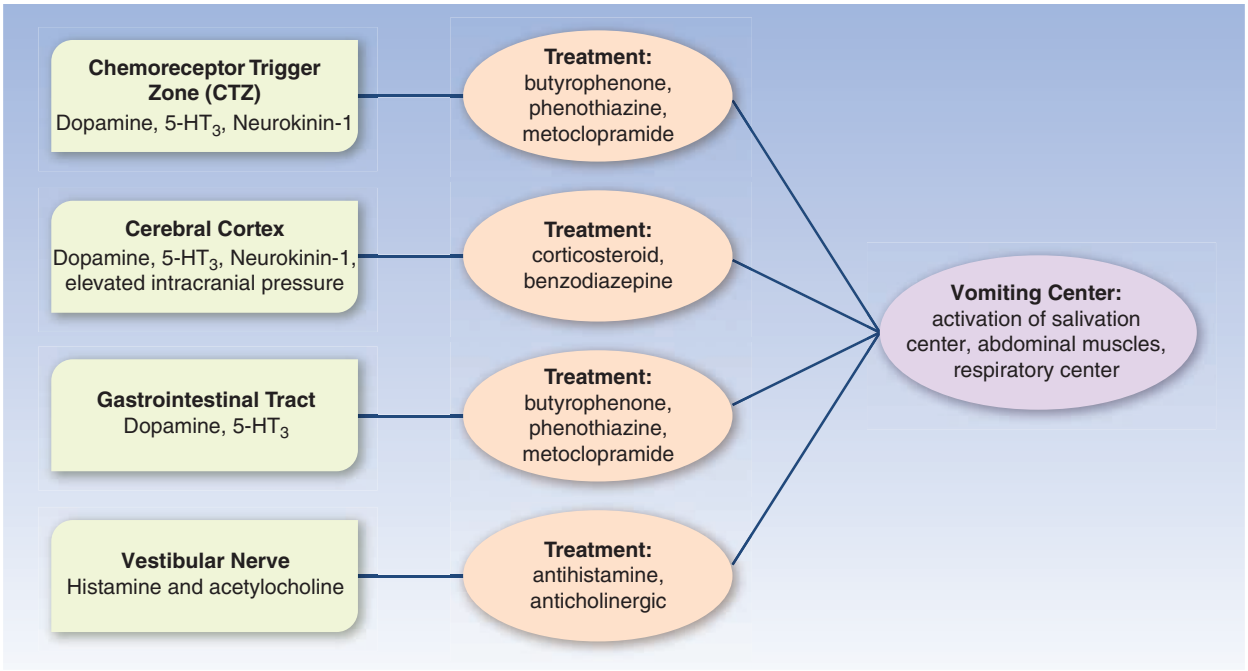

FIGURE 4–2. Mechanisms and associated neurotransmitters involved in nausea and vomiting.[7,28,25]

LO 5 Chemoreceptor trigger zone (CTZ)-induced nausea and vomiting are caused by chemotherapeutic agents, bacterial toxins, metabolic products (eg, uremia), and opioids. Dopamine (D_2), serotonin (5-Hydroxytryptamine [5-HT]), and neurokinin-1 are the primary neurotransmitters involved in this process. Therapy is based on blocking D_2 with D_2-antagonists including butyrophenones (eg, haloperidol), phenothiazines, and metoclopramide.

Due to receptor specificity, serotonin$_3$ (5-HT$_3$) antagonists such as ondansetron, granisetron, dolasetron, and palonosetron have limited usefulness in nausea and vomiting at the end of life.[7,25] They are typically indicated with emetogenic chemotherapy and up to 10 to 14 days posttreatment. Aprepitant is a neurokinin-1 antagonist indicated for the treatment of nausea due to highly emetogenic chemotherapy in combination with a 5-HT$_3$ antagonist and corticosteroid. Aprepitant should not be used as monotherapy.[23]

LO 4 LO 5 **Cerebral cortex**–induced nausea and vomiting can be caused by anxiety, taste, and smell, and also secondary to increased intracranial pressure. Corticosteroids decrease intracranial pressure due to tumor involvement. Corticosteroids have been found to be effective in nonspecific nausea and vomiting. The mechanism of this action is unknown. Anxiolytics such as benzodiazepines are used to treat anxiety and "anticipatory" gustatory and olfactory stimulation.[23]

Vestibular nausea and vomiting is triggered by motion. Opioids can sensitize the vestibular center resulting in movement-induced nausea. Since histamine and acetylcholine are the predominant neurotransmitters, antihistamines and anticholinergics are the drugs of choice in movement-induced nausea and vomiting.

LO 4 **GI tract** stimulation occurs through vagal and sympathetic pathways. These pathways are triggered by stimulation of mechanoreceptors or chemoreceptors located in the gut. Gastric stasis, GI obstruction, drugs, metastatic disease, bacterial toxins, chemotherapeutic agents, and irradiation may cause nausea and vomiting. Glossopharyngeal or vagus nerve stimulation in the pharynx by sputum, mucosal lesions, or infection (eg, *Candida*) can also evoke nausea. The major neurotransmitters in the upper GI tract are D_2, acetylcholine, and 5-HT. Metoclopramide is a 5-HT$_4$ agonist and increases gastric motility above the jejunum, whereas anticholinergics decrease GI spasticity and motility in nausea induced by gut hyperactivity. In high doses, metoclopramide also acts as a 5-HT$_3$ antagonist.[7,23]

Autonomic failure causes gastroparesis resulting in anorexia, nausea, early satiety, and constipation. Delayed gastric emptying occurs in patients with diabetes mellitus, chronic renal failure, and neurological disorders. Malnutrition, cachexia, lung and pancreatic cancers, HIV, radiotherapy, and drugs such as opioids, anticholinergics, antidepressants, and vasodilators have been associated with autonomic failure and resulting chronic nausea, poor performance, tachycardia, and malnutrition. Evaluate underlying causes, including multiple drugs that may cause gastroparesis. If drug therapy is indicated, metoclopramide is effective in improving gastric emptying.[7]

LO 4 LO 5 **GI irritation** can cause nausea and vomiting due to generalized gastritis, gastroesophageal reflux disease (GERD), or peptic ulcer disease. Histamine$_2$ (H_2) antagonists or proton pump inhibitors (PPIs) are considered the drugs of choice for ongoing gastritis.

Refractory cases of nausea and vomiting often require judiciously selected combinations of medications from different classes (eg, various combinations of haloperidol, metoclopramide, lorazepam, and dexamethasone).

Pain

A comprehensive review of pain management may be found in Chapter 34.

▶ *Palliative Care Considerations*

LO 7 According to the SUPPORT study, 74% to 95% of very ill or dying patients still experience uncontrolled pain.[26] Conducting a comprehensive pain assessment is key to choosing appropriate therapeutic interventions. Palliative care patients must be evaluated for anxiety, depression, delirium, and other neurological influences that may heighten a patient's awareness or response to pain.

▶ *Nonpharmacologic Treatment*

LO6 Nonpharmacologic treatment is essential. Physical, complementary, and cognitive behavioral interventions reduce the perception of pain and decrease the dose requirements of medications. Examples of such strategies may include providing education, massage, ice, heat, physical therapy, music therapy, imagery, pet therapy, and psychotherapy.

▶ *Pharmacotherapy*

LO7 LO5 Pain should be assessed thoroughly and frequently, especially at the onset of treatment. The WHO approach to pain management addresses nociceptive pain (see Chapter 34). Although opioid analgesics are not always necessary or appropriate for all types of pain, most patients with cancer-related pain require opioids. For chronic, constant pain, around-the-clock dosing of analgesics (preferably long-acting agents) is usually necessary and preferred.[27] When titrating opioid doses, increase daily maintenance doses by 25% to 50% if patients are routinely requiring three or more breakthrough doses per 24 hours as a result of around-the-clock maintenance dose failure. The around-the-clock maintenance doses should not be increased if breakthrough doses are used only for incident pain such as increased activity or dressing changes.

Fentanyl transdermal patches may be appropriate in some patients; however, many patients at the end of life experience fat and muscle wasting and dehydration, resulting in reduced and variable absorption. Fentanyl transdermal patches have a slow onset of action, contributing to difficulty in dose titration.[7]

LO5 Only short-acting opioids should be used for breakthrough pain (eg, immediate-release morphine, oxycodone, and hydromorphone are common examples). The dose of short-acting opioids for the treatment of breakthrough pain should be equal to 5% to 20% of the total daily maintenance dose. Frequencies for breakthrough dosing should not exceed the following:

- **Oral:** Every 1 to 2 hours
- **Subcutaneous:** Every 20 to 30 minutes
- **IV:** Every 8 to 20 minutes

LO8 Monitor for and appropriately treat common side effects of opioids. Common side effects of opioids include constipation, nausea and vomiting, itching, and transient sedation. Because constipation occurs with all chronic opioid therapy, prevention is imperative. Stimulant laxatives (senna or bisacodyl) with or without a stool softener (docusate) are the drugs of choice for opioid-induced constipation.[7] Myoclonus, delirium, hallucinations, and hyperalgesia are possible signs of opioid-induced neurotoxicity and require rotation to another opioid or dose reduction. Respiratory depression is uncommon with the appropriate opioid dose titration. However, if dangerous opioid-induced respiratory depression does occur, small doses (0.1 mg) of the μ receptor antagonist naloxone are appropriate and can be repeated as necessary. The goal is to increase respirations to a safe level while preventing the patient from experiencing a loss of pain control.

LO5 Different types of pain may require specific types of analgesics or adjuvant medications. Identification and treatment of these separate pain types will help avoid unnecessary opioid dose escalations and opioid side effects. Examples of pain types commonly seen in patients with advanced illness are as follows. See Figure 4–3 for medication options.

LO4 **Visceral pain** (nociceptive pain induced by stretching or spasms of visceral organs including the GI tract, liver, and pancreas) should be treated with an adjuvant such as an anticholinergic agents or, if inflammation is associated with the pain, corticosteroids.

Bone pain (metastatic site of cancer) is best treated with NSAIDs or corticosteroids in addition to standard opioid therapy.

Neuropathic pain (pain caused by damage to the afferent nociceptive fibers) can be managed with tricyclic antidepressants, antiepileptic drugs, tramadol, tapentadol or *N*-methyl-D-aspartate antagonists, such as ketamine. Methadone is an opioid μ-agonist that has a role in neuropathic pain given its added *N*-methyl-D-aspartate antagonist activity. Methadone has a very long half-life as compared to most other opioids, except buprenorphine. It should be used with caution and under the close supervision of clinicians experienced in the use of this drug for pain management.

Terminal Secretions

▶ *Palliative Care Considerations*

Terminal secretions, or death rattle, is the noise produced by the oscillatory movements of secretions in the upper airways in association with the inspiratory and expiratory phases of respiration.[28,29] LO4 As patients lose their ability to swallow and clear oral secretions, accumulation of mucus results in a rattling or gurgling sound produced by air passing through mucus in the lungs and air passages. The sound does not represent any discomfort for the patient. However, the sound is sometimes so distressing to the family that it should be treated. LO4 Terminal secretions are typically seen only in patients who are obtunded or are too weak to expectorate. LO5 Drugs that decrease secretions are best initiated at the first sign of death rattle because they do not affect existing respiratory secretions. These agents have limited or no impact when the secretions are secondary to pneumonia, pulmonary congestion, or edema.[30]

▶ *Nonpharmacologic Treatment*

LO6 Position the patient on their side or in a semiprone position to facilitate drainage of secretions. If necessary, place the patient in the Trendelenburg position (lowering the head of the bed); this allows fluids to move into the oropharynx, facilitating an easy removal. Do not maintain this position for long due to the risk of aspiration. Oropharyngeal suctioning is another option but may be disturbing to the patient and visitors. LO6 Fluid intake can also be decreased, as appropriate.[30]

▶ *Pharmacotherapy*

LO5 LO6 Anticholinergic drugs remain the standard of therapy for prevention and treatment of terminal secretions due to their ability to effectively reduce the future production of secretions.[28-30] Drugs used for this indication are similar pharmacologically, and one can be selected by anticholinergic potency, onset of action, route of administration, alertness of patient, and cost. LO6 The most commonly used anticholinergic agents are atropine, hyoscyamine, scopolamine, and glycopyrrolate.

Anticholinergic side effects include blurred vision, constipation, urinary retention, confusion, delirium, restlessness, hallucinations, dry mouth, and heart palpitations. Unlike the other anticholinergics, glycopyrrolate does not cross the blood–brain barrier and is associated with fewer CNS side effects, and is often preferred, if the use of anticholinergic intervention is prolonged for more than 7 to 10 days. Glycopyrrolate is a potent drying agent when compared with other agents and has the potential to cause excessive dryness.[30]

Pharmacologic Adjuvants: Nociceptive Pain	
Bone Pain *(inflammatory)*	
Nonsteroidal anti-inflammatory drug (NSAID)	
Ibuprofen (Motrin)[a] Naproxen (Naprosyn)[a] Celecoxib (Celebrex)[b] Meloxicam (Mobic)[b]	• Often first-line for untreated diffuse bone pain • Similar efficacy among NSAIDs; however, the risks of GI bleeding, GI ulcers, renal toxicity, and cardiovascular concerns are higher among the nonselective NSAIDs • Selective NSAIDs have less GI effects, but retain risk of renal toxicity
Bisphosphonates	
Zolendronic acid (Zometa) Pamidronate (Aredia) Ibandronate (Boniva)	• Role in treating diffuse bone pain • Intravenous administration with renal monitoring • Monitor: osteonecrosis of the jaw, follow-up with dental evaluation
Steroids	
Dexamethasone (Decadron) Methylprednisolone (Medrol) Prednisone (Deltasone)	• May be preferred over NSAIDs for diffuse bone pain in patients experiencing anorexia and fatigue • Burst and taper recommended for rapid pain control • Monitor: edema, glucose, insomnia, GI upset • Less edema with mineralcorticosteroid • Administer doses earlier in the day with food to avoid insomnia and GI upset
Visceral Pain	
Anticholinergic/Antispasmodics	
Dicyclomine (Bentyl) Glycopyrolate (Robinul IV) Hyoscyamine (Levsin) Scopolamine (Transderm Scop)	• Monitor: *(especially in elderly)* constipation, dry mouth, confusion, dizziness, urinary retention • Steroids may also be used concurrently for visceral pain with associated inflammatory processes (ie, pleuritic pain, capsular organ pain, diffuse intestinal cancer) • Often used short term for treatment of terminal secretions "death rattle"
[a]Nonselective NSAID [b]COX-II selective NSAID	

FIGURE 4–3. Pharmacologic adjuvants for the treatment of bone pain and inflammatory pain.[7,23,26]

Advanced Heart Failure

▶ *Palliative Care Considerations*

LO 3 Heart failure symptoms at the end of life may include hypotension, volume overload, edema, and fatigue. Patients should be assessed to confirm symptoms are related to heart failure rather than other disease states to ensure appropriate treatment.[31]

LO 5 Goals for advanced heart failure treatment differ from traditional heart failure management. Drug therapy focuses on symptom management rather than improving mortality. Prevention of cardiovascular disease through cholesterol reduction is no longer necessary at this point.

▶ *Nonpharmacologic Treatment*

LO 6 Patients should be maintained in a comfortable position with feet elevated to minimize lower leg fluid accumulation. Minimizing high-salt foods and limiting fluid intake can help reduce fluid accumulation. At this stage in heart failure, comfort becomes the primary initiative.

▶ *Pharmacotherapy*

LO 7 As patients approach the end of life, it is difficult to determine when certain medications for heart failure should be dose reduced or discontinued. The following general principles may help serve as a guide. However, each individual's history, prognosis, and current condition should be evaluated to determine appropriateness.

LO 5 LO 6 If a patient becomes symptomatic due to hypotension, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and/or β-adrenergic blocker doses should be reduced or discontinued. For β-adrenergic blockers, in particular, this should be done gradually to avoid significant clinical deterioration. If volume overload occurs or persists while taking β-adrenergic blocker therapy, consider tapering off the medication. Likewise, for patients experiencing fatigue while taking a β-adrenergic blocking agent, consider tapering down the dose *only if* their heart rate does not increase with exertion. Consider discontinuing the ACE inhibitor (or the angiotensin receptor blocker) if the patient's renal function deteriorates (eg, cardiorenal syndrome).

In patients with excessive fluid overload where sodium and water intake restrictions are not effective or not possible, consider increasing the dose of diuretic. However, vascular dehydration can occur in some patients with end-stage heart failure if the dose of diuretic is excessive.

Patient Encounter 3

JM is a 45-year-old man recently diagnosed with pancreatic cancer. He received several rounds of palliative chemotherapy with localized radiation over the past few months with the last chemotherapy and radiation administered 4 weeks ago. The interventions were unsuccessful in limiting tumor growth, which has now metastasized to liver, brain, and right intercostal bones. JM has jaundice with mild ascites with no reported pruritus. JM's chief complaint today is uncontrolled nausea and vomiting which worsens with meals and has been going on for a week. The oncologist prescribed ondansetron 8 mg by mouth every 8 hours as needed. JM has the prescription at home and has taken two doses without benefit or improvement in his nausea. Comorbidities include hypertension and depression with recent uncontrolled anxiety. Allergy: Codeine (reaction unknown). Medications include: hydrocodone/acetaminophen 5-325 1–2 tablets by mouth every 4–6 hours as needed for pain, ibuprofen 200 mg 1–2 tablets by mouth every 4–6 hours as needed for pain and acetaminophen 500 mg 1–2 tablets by mouth every 6 hours as needed, ondansetron 8 mg by mouth every 8 hours as needed for nausea, dexamethasone 4 mg by mouth twice daily (give after breakfast and after lunch).

What are potential causes of JM's nausea and vomiting? Based on this differential list, what questions would you ask JM during your assessment of his nausea and vomiting?

What potential drug–drug interactions and side effects exist in this patient?

What medications could be added, changed, and/or discontinued?

How does the patient's reported allergy to codeine impact potential treatment options?

LO 7 LO 8 Digoxin toxicity is common; therefore, patients should be carefully monitored and therapy adjusted or discontinued as appropriate. The symptoms of digoxin toxicity including complaints of anorexia, nausea and vomiting, visual disturbances, disorientation, confusion, or cardiac arrhythmias.[31]

LO 7 Hydroxymethylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors (and other cholesterol-lowering medications) are likely to have a long-term effect rather than a palliative effect.

Figure 4–1 provides a list of agents that improve functional status in advanced heart failure patients.

OUTCOME EVALUATION

KEY CONCEPT Involving the patient, family, and caregivers in the development of the therapeutic plan demonstrates responsible palliative care. Before the implementation of drug therapy, LO 8 the patient, family, and caregiver should be involved with the decision-making process. The practitioner should provide information about all reasonable options for care so that the patient, family, and caregivers can collaborate with the health care team to meet their combined goals. KEY CONCEPT Positive therapeutic outcomes include resolution of symptoms while minimizing adverse drug events. When treating symptoms pharmacologically, adverse drug events must be avoided or minimized to prevent negative outcomes.

Patient Care Process

Collect Information:

- Evaluate physical examination, review of systems and relevant laboratory findings and assess for symptoms related to, or worsened by their current hospice diagnosis.
- Perform medication reconciliation (prescription, OTC medications, herbal).
- Determine the goal as they relate to the hospice plan of care.
- Identify cultural, spiritual, or ethnic traditions that impact patient care and incorporate those aspects into the plan of care.

Assess the Information:

- Ensure that medications confer benefit for functional status rather than only survival (see Figure 4–1) and that this approach supports the patient's goals.
- Establish realistic medication outcomes prior to initiating or titrating a medication for palliative care.
- Verify prescription coverage or institutional formulary when adding medications.
- Provide preventative care recommendations (ie, immunization, annual health screening, etc.), and discuss their health benefits.

Develop a Care Plan:

- Based on prognosis of a health condition, determine if continuing medication for preventative or long-term management is appropriate.
- If laboratory monitoring is discontinued, medications with a narrow therapeutic index may be discontinued.
- Ensure that medications are appropriate for the patient's functional status.
- Evaluate adherence strategies and monitor for side effects.
- Before adding a medication to treat symptoms, ensure that the symptom is not attributable to current medications.

Implement the Care Plan:

- Involve the patient, family, and caregivers in development of pharmacologic/nonpharmacologic strategies based on patient's goals.
- Share patient preferences, priorities, and goals with health care providers.
- Communicate resuscitation preferences with caregivers and health care providers.

Follow-up: Monitor and Evaluate:

- Monitor results following initiation of drug therapy, and discuss findings in context to symptom prioritization, goals, and outcomes.
- Continuous evaluation of therapy as functional status (ie, ambulation, swallowing, continence) changes, and ensure safe and effective medication use.
- Encourage the patient, family, and caregivers to contact the hospice or palliative team with questions.
- Bimonthly reviews of the patient's medical condition, medications, and goals occur during hospice interdisciplinary meetings.

LO 7 Patients with life-limiting diseases have emotional and spiritual issues that deserve attention by trained professionals. Addressing these concerns and providing support and coping skills can dramatically reduce the medication requirements for symptom control. Psychosocial and spiritual support is not only directed toward the patient in palliative care but also supports the family during the time of the illness and after the death of their loved one.

LO 8 KEY CONCEPT Patient and caregiver education is vital to ensuring positive outcomes. If the patient and caregiver are unaware of the purpose and goals for interventions used in palliative medicine, adherence to regimens will be hindered and outcomes will be compromised. Education regarding the role and value of the palliative care team will allow the patient and family to understand why palliative care is important to their overall quality of life. Patients will achieve the best possible outcomes when practitioners incorporate the interdisciplinary palliative care approach to care early in the disease progression of patients with life limiting illnesses.

Abbreviations Introduced in This Chapter

5-HT	5-Hydroxytryptamine (serotonin)
ACE	Angiotensin-converting enzyme
ALS	Amyotrophic lateral sclerosis
ARB	Angiotensin receptor blocker
CHF	Chronic heart failure
COPD	Chronic obstructive pulmonary disease
CTZ	Chemoreceptor trigger zone
CVA	Cerebral vascular accident
GERD	Gastroesophageal reflux disease
HMG-CoA	Hydroxymethylglutaryl coenzyme-A
NSAID	Nonsteroidal anti-inflammatory drug
PPI	Proton pump inhibitor
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization

REFERENCES

1. WHO definition of palliative care. World Health Organization. Available from: http://www.who.int/cancer/palliative/definition/en. Accessed June 28, 2017.
2. Medicare hospice benefits. Centers for Medicare and Medicaid Services. Available from: https://www.medicare.gov/Pubs/pdf/02154-Medicare-Hospice-Benefits.PDF. Accessed June 28, 2017.
3. Clinical practice guidelines for quality palliative care, 3rd ed. National Consensus Project for Quality Palliative Care. Available from: https://www.hpna.org/multimedia/NCP_Clinical_Practice_Guidelines_3rd_Edition.pdf. Accessed August 1, 2017.
4. Lupu D, Salsberg E, Quigley L, Wu X. The 2015 class of hospice and palliative medicine fellows-from training to practice: implications for HPM workforce supply. J Pain Symptom Manage. 2017;53:944–951.
5. Edwards SJ, Abbott R, Edwards J, et al. Outcomes assessment of a pharmacist-directed seamless care program in an ambulatory oncology clinic. J Pharm Pract. 2014;27:46–52.
6. Sandsdalen T, Grondal VA, Hov R, Høye S, Rystedt I, Wilde-Larsson B. Patients' perceptions of palliative care quality in hospice inpatient care, hospice day care, palliative units in nursing homes, and home care: a cross-sectional study. BMC Palliative Care. 2016;15:79.
7. Protus BM, Kimbrel J, Grauer P. Palliative Care Consultant: A Reference Guide for Palliative Care, 4th ed. Hospiscript Services, a Catamaran Company, 2015.
8. History of Hospice Care, Hospice: A Historical Perspective. National Hospice and Palliative Care Organization, 2016.
9. NHPCO's Facts and Figures on Hospice Care in America, 2015 Ed. National Hospice and Palliative Care Organization, 2015.
10. Connor SR, Pyenson B, Fitch K, Spence C, Iwasaki K. Comparing hospice and nonhospice patient survival among patients who die within a three year window. J Pain Symptom Manage. 2007;33(3):238–246.
11. Temel JS, Greer JA, Muzinkansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med. 2010;363(8):733–742.
12. Desplenter F, Bond C, Watson M, et al. Incidence and drug treatment of emotional distress after cancer diagnosis: a matched primary care case—control study. Br J Cancer. 2012;107:1644–1651.
13. Bush SH, Kanji S, Pereira JL, et al. Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. J Pain Symptom Manage. 2014;48(2):231–248.
14. Kolva E, Rosenfeld B, Pessin H, Breitbart W, Brescia R. Anxiety in terminally ill patients. J Pain Symptom Manage. 2011;42:691–701.
15. Bush SH, Leonard MM, Agar M, et al. End-of-life delirium: issues regarding recognition, optimal management, and the role of sedation in the dying phase. J Pain Symptom Manage. 2014;48(2):215–230.
16. Gareri P, De Fazio P, Manfredi VG, De Sarro G. Use and safety of antipsychotics in behavioral disorders in elderly people with dementia. J Clinical Psychopharmacol. 2014;34(1):109–123.
17. Lonergan E, Britton AM, Luxenberg J. Antipsychotics for delirium. Cochrane Database of Syst Rev. 2009;2:CD005594.
18. Haloperidol Monograph. Lexicomp Online. Hudson (OH): Lexi-Comp Inc. Available from: http://www.crlonline.com/crlsql/servlet/crlonline. Accessed August 3, 2017.
19. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996;153:231–237.
20. Storey P, Knight CF. UNIPAC Four: Management of Selected Non-Pain Symptoms in the Terminally Ill, 2nd ed. New York, NY: Mary Ann Liebert; 2003. pp. 29–35.
21. Brennan CW, Mazanec P. Dyspnea management across the palliative care continuum. J Hosp Palliat Nurs. 2011;13(3):130–139.
22. Afolabi TM, Nahata MC, Pai V. Nebulized opioids for the palliation of dyspnea in terminally ill patients. Am J Health Syst Pharm. 2017;74:1053–1061.
23. Palliative Care. National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology. 2017.
24. Kamal AH, Maguire JM, Wheeler JL, Currow DC, Abernethy AP. Dyspnea review for the palliative care professional: treatment goals and therapeutic options. J Palliat Med. 2012;15(1):106–114.
25. Prommer E. Role of haloperidol in palliative medicine: an update. Am J Hosp Palliat Care. 2012;29:295–301.
26. Adult Cancer Pain. National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology. 2017.
27. McCaffery M, Pasero C. Pain: Clinical Manual, 2nd ed. St. Louis, MO: Elsevier Mosby; 1999.
28. Lokker ME, van Zuylen L, van der Rijt C. Prevalence, impact, and treatment of death rattle: a systematic review. J Pain Symptom Manage. 2014;47(1):105–122.

29. Gavazzi A, DeMaria R, Manzoli L, et al. Palliative needs for heart failure or chronic obstructive pulmonary disease: results of a multicenter observational registry. Int J Cardiol. 2015;184:552–558.
30. Protus BM, Grauer PA, Kimbrel JM. Evaluation of atropine 1% ophthalmic solution administered sublingually for the management of terminal respiratory secretions. Am J Hosp Palliat Care. 2012;30(4):388–392.
31. Whellan DJ, Goodlin SJ, Dickinson MG, et al. End-of-life care in patients with heart failure. Consensus statement. J Card Fail. 2014;20(2):121–134.

Part II

Disorders of Organ Systems

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5 Hypertension

Augustus Hough, Ya-Feng Wen, Brandon Cave, David Parra, and Robert J. Straka

LEARNING OBJECTIVES

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

1. Identify guideline-based treatment goals for patients with hypertension.
2. Recognize underlying causes and contributing factors in the development of hypertension.
3. Describe the appropriate measurement of blood pressure (BP).
4. Classify BP levels after appropriate measurement.
5. Recommend appropriate lifestyle modifications.
6. Determine patient-centered pharmacotherapy for individuals with hypertension.
7. Identify specific conditions and populations requiring special consideration when designing a treatment plan for hypertension.
8. Construct an appropriate monitoring plan to assess hypertension treatment.

INTRODUCTION

It is well established that reducing elevated blood pressure (BP) in patients at sufficient risk provides significant cardiovascular benefit. However, despite efforts to promote awareness, treatment, and management of high BP, control remains suboptimal. Worldwide, approximately one-third of adults have controlled BP, and in the United States, slightly over one-half of adults experience control.[1] Based on clinical evidence, national and international organizations continually refine recommendations on the management of patients with high BP. The purpose of this chapter is to: (a) provide a summary of key issues associated with the management of hypertension; (b) discuss the basic approach to treating hypertension and provide a functional summary of the prevailing themes of contemporary guidelines; and (c) summarize pharmacotherapeutic issues essential for clinicians to consider when treating hypertension.

Various algorithms recommend nonpharmacologic and pharmacologic management, with the underlying premise that lowering elevated BP reduces target organ damage leading to reductions in stroke, myocardial infarction (MI), end-stage renal disease, and heart failure (HF). BP targets and treatment recommendations for a particular patient may vary based on different guidelines and/or position statements, depending on their interpretation of the clinical evidence available at the time of development. This chapter primarily focuses on the most recent comprehensive, evidence-based 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, put forth by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Clinical Practice Guidelines and hereafter referred to as the 2017 ACC/AHA guidelines.[2]

KEY CONCEPT The 2017 ACC/AHA guidelines classify BP and provide guidance on accurate assessment of BP as well as the nonpharmacologic and pharmacologic approaches to managing hypertension. Various guidelines recognize that the lowest risk of adverse cardiovascular or renal outcomes is at a BP around 115/75 mm Hg, with risk rising as BP increases. For each increase by 20 mm Hg in systolic BP (SBP), or approximate 10 mm Hg increase in diastolic BP (DBP), the risk of death from ischemic heart disease, stroke, and other vascular diseases increases by twofold in individuals aged 40 to 69 years. The risk is even greater in older individuals.

KEY CONCEPT The 2017 ACC/AHA guidelines classify elevations in BP beyond specific thresholds as elevated BP, stage 1 hypertension, and stage 2 hypertension (Table 5–1) to imply different levels of risk and the need for varying intensities of intervention with drug therapy.[2] Specific BP thresholds for treatment and BP goals of therapy are established based on cardiovascular risk assessment or the presence of specific comorbid conditions (Figure 5–1 and Table 5–2).[2] Recommendations for BP-lowering medications typically begin with one or two (in the case of stage 2 hypertension and average BP of 20/10 mm Hg above the BP target) antihypertensive drugs. In addition, recommendations

Table 5–1

Classification of Hypertension in Adults[a,2]

BP Classification	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
Normal	< 120	AND	< 80
Elevated	120–129	AND	< 80
Stage 1 hypertension	130–139	OR	80–89
Stage 2 hypertension	≥ 140	OR	≥ 90

[a]Adults with SBP and DBP in two categories should be assigned to the higher BP classification.

BP, blood pressure.

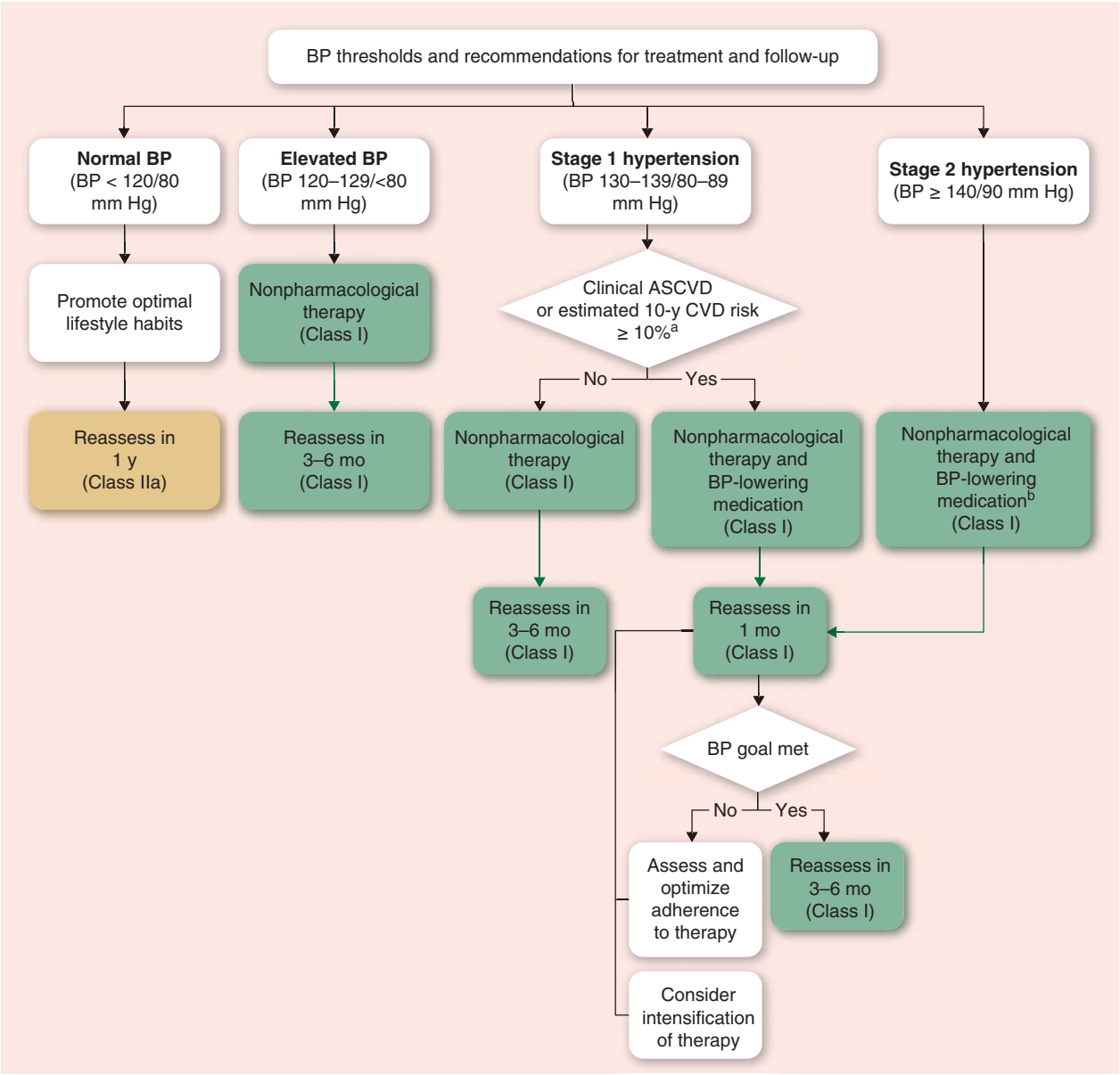

FIGURE 5–1. General recommendations for blood pressure (BP) threshold and recommendations for treatment and follow-up. Patients with elevated BPs should incorporate nonpharmacologic therapies to promote BP lowering. As BP reaches stage 1 hypertension thresholds for therapy are guided based on a patient's level of risk as determined by baseline presence of cardiovascular disease, chronic kidney disease (CKD) or diabetes mellitus (DM) (all placing patient at higher risk) and cardiovascular disease risk as calculated with the American College of Cardiology/American Heart Association (ACC/AHA) Pooled Cohort Equations (values ≥ 10% defining higher risk). Lower risk patients are reasonable for an initial trial of nonpharmacologic therapies while those with higher risk or stage 2 hypertension are initially begun on BP-lowering medications. Consideration may be given in patients with stage 2 to the initiation of combination therapy at treatment onset. "Class" indicates the strength of the recommendation, with Class I considered the strongest. [a]Using the ACC/AHA Pooled Cohort Equations. Note that patients with DM or CKD are automatically placed in the high-risk category. For initiation of renin–angiotensin system (RAS) inhibitor or diuretic therapy, assess blood tests for electrolytes and renal function 2 to 4 weeks after initiating therapy. [b]Consider initiation of pharmacological therapy for stage 2 hypertension with 2 antihypertensive agents of different classes. Patients with stage 2 hypertension and BP greater than or equal to 160/100 mm Hg should be promptly treated, carefully monitored, and subject to upward medication dose adjustment as necessary to control BP. Reassessment includes BP measurement, detection of orthostatic hypotension in selected patients (eg, older or with postural symptoms), identification of white coat hypertension or a white coat effect, documentation of adherence, monitoring of the response to therapy, reinforcement of the importance of adherence, reinforcement of the importance of treatment, and assistance with treatment to achieve BP target. (ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; mo, month; y, year.) (Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertens. 2017.)

Table 5–2

Blood Pressure Thresholds and Goals of Pharmacologic Therapy in Patients with Hypertension According to Clinical Conditions[2]

Clinical Condition(s)	BP Threshold for Antihypertensive Therapy Initiation (mm Hg)	BP Goal (mm Hg)
General		
Clinical CVD or 10-year ASCVD risk ≥ 10%	≥ 130/80	< 130/80
No Clinical CVD and 10-year ASCVD risk < 10%	≥ 140/90	< 130/80
Older persons (≥ 65 years of age; noninstitutionalized ambulatory, community-living adults)	≥ 130 (SBP)	< 130 (SBP)
Specific Conditions		
Diabetes mellitus	≥ 130/80	< 130/80
Chronic kidney disease	≥ 130/80	< 130/80
Chronic kidney disease postrenal transplantation	≥ 130/80	< 130/80
Heart failure	≥ 130/80	< 130/80
Stable ischemic heart disease	≥ 130/80	< 130/80
Secondary stroke prevention	≥ 140/90	< 130/80
Secondary stroke prevention (lacunar)	≥ 130/80	< 130/80
Peripheral arterial disease	≥ 130/80	< 130/80

ASCVD, atherosclerotic cardiovascular disease (calculator available online at http://tools.acc.org/ascvd-risk-estimator/); BP, blood pressure; CVD, cardiovascular disease; SBP, systolic blood pressure.

Adapted from Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertens. 2017, with permission.

for specific medications are provided by race and/or the presence of compelling indications (Table 5–3) for which explicit evidence in the literature exists to document the utility of a particular agent or class of agents.[2,3] Selection of subsequent drug therapy involves an iterative process of adding antihypertensive drugs as needed to achieve target BP, otherwise known as a stepped approach. Although calls for greater personalization in selecting drug therapy have been advocated, including plasma renin

Table 5–3

Compelling Indications for Individual Drug Classes[2,3]

	Recommended Drug Class						
Compelling Indication	**Diuretic**	**Ald Ant**	**BB**	**CCB**	**ACE-I**	**ARB**	**Dir Vaso**
Heart failure with reduced ejection fraction	X	X	X		X	X	X
Heart failure with preserved ejection fraction	X		X		X	X	
Stable ischemic heart disease[a]	X	X	X	X	X	X	
Chronic kidney disease[b]					X	X	
Post renal transplantation				X	X[c]		
Diabetes	X			X	X[d]	X[d]	
Secondary stroke prevention	X				X	X	
Atrial fibrillation						X	
Peripheral arterial disease	X			X	X	X	
Thoracic aortic disease			X				
Black race[e]	X			X			

[a]Recommended β-blockers for BP control or angina relief include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid β-blockers with intrinsic sympathomimetic activity. Atenolol should not be used as it is less effective than placebo for reducing cardiovascular events. CCBs recommended (class I) if blood pressure goal not met with BB, ACE-I or ARBs, and angina pectoris present.

[b]Recommendations stronger (class IIa) for patients with chronic kidney disease (CKD) and albuminuria (≥ 300 mg/day or ≥ 300 mg/g creatinine) and weaker (class IIb) for CKD stage 3 or higher without albuminuria or stage 1 or 2 with albuminuria (≥ 300 mg/day or ≥ 300 mg/g creatinine).

[c]ACE-I may be reserved in the development of albuminuria or heart failure after transplantation.

[d]ACE-I or ARB may be considered in the presence of albuminuria.

[e]Black adults with or without diabetes mellitus but without heart failure or CKD.

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

Data from Whelton PK CR, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2017; and Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206–1252.

activity (PRA) testing or noninvasive hemodynamic monitoring, these approaches are not widely used.[4,5] In contrast, the roles of 24-hour ambulatory BP monitoring (ABPM), home BP (HBP) monitoring, and ambulatory office-based BP (AOBP) monitoring have been increasingly clarified in the context of select patient groups.[6,7] Regardless of the guideline and strategy implemented in practice, it is imperative that clinicians consider patient-specific characteristics and preferences among other considerations when establishing BP targets and drug selection.

EPIDEMIOLOGY

KEY CONCEPT Hypertension is widely prevalent and significantly contributes to cardiovascular-related morbidity, mortality, and associated health care costs. Worldwide in 2014, around 22% of adults aged 18 years and over had hypertension.[8] In the United States, the prevalence of hypertension was estimated to include nearly 86 million individuals (one in three adults 20 years of age or older), with an estimated $51.2 billion spent annually in direct and indirect costs.[1] When applying the definition of hypertension in the 2017 ACC/AHA guidelines, the estimated prevalence of American adults with hypertension increases to nearly half (46%) of the US adult population.[2] The prevalence of hypertension differs based on age, sex, and ethnicity. As individuals age, risk of systolic hypertension increases. Hypertension is slightly more prevalent in men than women before the age of 35, similar between the ages of 35 and 64 years, and more prevalent in women than men 65 years and older. Age-adjusted prevalence of hypertension is highest in non-Hispanic blacks (40.3%–42.9%) when compared with non-Hispanic whites (30.4%–27.6%) and Mexican Americans (26.5%–27.2%).[1]

ETIOLOGY

KEY CONCEPT The cause of hypertension is usually unknown and referred to as primary hypertension in more than 90% of patients. However, in some patients there is an identifiable cause of hypertension, referred to as secondary hypertension. Causes of secondary hypertension include:[9]

LO 2

- Chronic kidney disease (CKD) (renal parenchymal disease)
- Coarctation of the aorta
- Cushing syndrome and other glucocorticoid excess states
- Drug induced/related (Table 5–4)
- Pheochromocytoma/paraganglioma
- Primary aldosteronism and other mineralocorticoid excess states
- Renovascular hypertension
- Obstructive sleep apnea
- Thyroid or parathyroid disease

The 2017 ACC/AHA guidelines recommend screening for secondary causes of hypertension for uncontrolled drug-resistant hypertension (three or more drugs), abrupt onset, age less than 30 years, excessive target organ damage, onset of diastolic hypertension in older adults or in the presence of unprovoked or excessive hypokalemia.[2] In addition to primary and secondary hypertension, the clinician may encounter what is referred to as resistant hypertension. KEY CONCEPT Patients failing to achieve goal BP despite adherence to optimal doses of three antihypertensive agents of different classes (ideally, one being a diuretic) have resistant hypertension and should be evaluated for secondary causes of hypertension.[10] Several causes of resistant hypertension are listed in Table 5–4 and should be carefully considered in such patients.[11] Additional consideration should be given to the clinical scenario of pseudohypertension, or elevated BP resulting from a myriad of potentiating factors including therapy adherence, white coat hypertension, or poor BP measurement technique.[10]

LO 2

Table 5–4

Causes of Resistant Hypertension[11]

Apparent Resistance
Improper blood pressure measurement
Failure to receive or take antihypertensive medication appropriately (nonadherence)
Inadequate doses (subtherapeutic)
Improper antihypertensive selection or combination
White coat hypertension

True Resistance
Secondary hypertension
Drug effects and interactions
- Adrenal steroid hormones
- Amphotericin B
- Cocaine, amphetamines, and other illicit drugs
- Cyclosporine and tacrolimus
- Erythropoietin
- Fluid retention from kidney disease or potent vasodilators (eg, minoxidil)
- Herbal products (ma huang, guarana, bitter orange, blue cohosh)
- Highly active antiretroviral therapy (HAART)
- Inadequate diuretic therapy
- Natural licorice (including some chewing tobacco)
- Neurologic and psychiatric agents (eg, venlafaxine, lithium, thioridazine hydrochloride)
- Nonsteroidal anti-inflammatory medications
- Oral contraceptive hormones
- Recent caffeine or nicotine intake
- Sympathomimetics (decongestants, anorectics, and stimulants)
- Vascular endothelial growth factor inhibitors (bevacizumab, sorafenib, sunitinib)

Volume overload
Excess sodium intake
Comorbidities
- Obesity
- Excess alcohol intake
- Chronic pain syndromes
- Intense vasoconstriction (arteritis)
- Anxiety-induced hyperventilation/panic attacks

Genetic variation
- Genetic differences in drug efficacy or metabolism

PATHOPHYSIOLOGY

KEY CONCEPT The pathophysiology of primary hypertension is heterogeneous but ultimately exerts its effects through two primary determinants of BP: cardiac output (CO) and peripheral vascular resistance (PVR). The processes influencing these two determinants are numerous and complex, and although the underlying cause of primary hypertension remains unknown, it is most likely multifactorial. As a review of these mechanisms is beyond the scope of this text, readers are referred to other sources.[9]

Patient Encounter 1

A 72-year-old white man comes into your clinic for an annual appointment. Seated BP measured in the left arm is 153/96 mm Hg and 157/89 mm Hg in the right arm. You request that the patient return in 1 week for a follow-up BP. His seated BPs in the right arm at follow-up are 156/92 mm Hg and 150/87 mm Hg. The patient's physical examination was unremarkable, but his electrocardiogram revealed evidence of left ventricular hypertrophy. His past medical history is significant for dyslipidemia. He does not smoke tobacco or drink alcohol and he walks daily for 30 minutes; however, he struggles with a heart healthy diet. He is currently taking aspirin 81 mg daily. His cholesterol panel revealed a high-density lipoprotein (HDL) cholesterol level of 40 mg/dL (1.03 mmol/L), triglyceride level of 140 mg/dL (1.58 mmol/L), and total cholesterol of 198 mg/dL (5.12 mmol/L). Calculated low-density lipoprotein cholesterol level is 130 mg/dL (3.36 mmol/L). All other laboratory values were within normal limits.

Based on the information above, what stage of hypertension does this patient have?

What is the patient's BP target?

What steps are involved in assuring that the patient's BP measurements are accurate?

The development of primary hypertension involves interplay between genetic and environmental factors interacting with multiple physiological systems including neural, renal, hormonal, and vascular. Further complicating this is that an individual's phenotype of primary hypertension (eg, diastolic hypertension in middle-aged individuals, isolated systolic hypertension in the elderly, and obesity-related hypertension) may have different contributing mechanisms.[9] Because of these complexities, no final common pathway has been identified and a single target for the treatment of primary hypertension remains elusive. Therefore, guidelines for the selection of specific therapeutic agents allow the clinician some flexibility in choices.

Genetic Factors

Although multiple genetic polymorphisms have been associated with relatively small effects on SBP, DBP, and response to antihypertensive medications, replications of these findings in large populations are elusive. Consequently, with very few exceptions, the information available to date is far from sufficient to provide any practical guidance for clinicians.[12] Nevertheless, genetic-based sources of variability in response to drug therapy continue.

Environmental Factors

Environmental factors contributing to hypertension are well-characterized. Nicotine use (including cigars and smokeless tobacco) and caffeine cause transient increases in BP via norepinephrine release and, in the case of caffeine, by its antagonism of vasodilatory adenosine receptors. Acute alcohol ingestion may have a transient variable effect (increased due to sympathetic nerve activity or lowering due to vasodilation), whereas chronic heavy consumption of alcohol and binge drinking raises the risk of hypertension.[9] Many other environmental factors have been implicated in the development of hypertension. These include obesity, physical inactivity, fetal environment, postnatal weight gain, premature birth and low birth weight, potassium and magnesium depletion, vitamin D deficiency, and environmental toxins (eg, lead).[9]

Neural Mechanisms

Over-activity of the sympathetic nervous system (SNS) in the early stages of primary hypertension manifests as increased heart rate, CO, and peripheral vasoconstriction. Despite this, outcome trials of agents targeting the SNS (α- and β-adrenergic blockers) have not performed as well as other drug classes. Nevertheless, strategies aimed at targeting the SNS continue with specific interest in invasive strategies aimed at resistant hypertension.[9]

Renal Mechanisms

The contribution of sodium to the development of primary hypertension is related to excess sodium intake and/or abnormal sodium excretion by the kidneys.[9] However, it is generally accepted that dietary salt is associated with increases in BP that can be lowered with reduction of sodium intake,[13] particularly in the approximately 30% of individuals deemed salt sensitive.[14]

Hormonal Mechanisms

Renin is produced and stored in the juxtaglomerular cells of the kidney, and its release is stimulated by impaired renal perfusion, salt depletion, and β_1-adrenergic stimulation. The release of renin is the rate-limiting step in the eventual formation of angiotensin II, which is a potent vasoconstrictor (Figure 5–2).[9] The role of

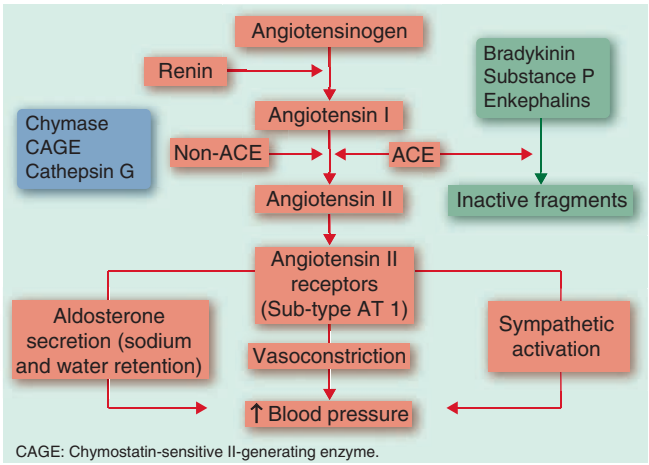

FIGURE 5–2. Diagram of the renin-angiotensin-aldosterone system (RAAS), a key system involved in the modulation of blood pressure. The diagram depicts the pathways involved in the action of various antihypertensive agents including angiotensin-converting enzyme (ACE) inhibitors, ARBs, diuretics, and aldosterone antagonists. By inhibiting the action of ACE, ACE inhibitors reduce both the formation of the vasoconstrictors angiotensin II and the degradation of vasodilating substances including bradykinin. ARBs primarily act through inhibition of the action of angiotensin II on the angiotensin-I receptors that modulate vasoconstriction. Aldosterone antagonists directly inhibit the action of aldosterone; diuretics affect sodium and water retention at a renal level. (ARB, angiotensin receptor blockers; AT1, angiotensin-1.) (From Victor RG, Kaplan NM. Kaplan's Clinical Hypertension, 10th ed. Philadelphia, PA: Wolters Kluwer Lippincott Williams & Wilkins Health; 2010, with permission.)

the renin-angiotensin-aldosterone system (RAAS) in primary hypertension is supported by the presence of high levels of renin, suggesting the system is inappropriately activated. Proposed mechanisms include increased sympathetic drive, defective regulation of the RAAS (nonmodulation), and the existence of a subpopulation of ischemic nephrons that release excess renin.[9] However, there are also patients with primary hypertension and low levels of renin which suggests alternative mechanisms, unrelated to renin levels or activity, may be in play. Thus, although uncommon in general practice, PRA measurements may be utilized to guide antihypertensive therapy selection. In fact, it has been demonstrated that patients with low PRA (< 0.65 ng/mL/hour [0.18 ng/L/s]) respond preferentially to diuretics, aldosterone antagonists, and calcium channel blockers (CCBs), whereas those with higher PRA levels respond preferentially to renin-mediated therapies such as β-blockers, angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), and direct renin inhibitors.[5] However, use of PRA measurements to guide therapy is not without controversy and the reader is referred to other sources for more information.[12]

Vascular Mechanisms

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

Contributing Comorbidities

Several comorbidities have a high concurrence with the presence of hypertension leading to a higher risk of target organ damage, cardiovascular morbidity and mortality, and overall health care costs. Specifically, these include diabetes mellitus (DM), dyslipidemia, obesity, and CKD. As such, the assessment of atherosclerotic cardiovascular disease (ASCVD) risk in all patients with hypertension should be part of the management plan while pursuing target BPs through nonpharmacologic and pharmacologic means.[15]

MEASUREMENT OF BLOOD PRESSURE

KEY CONCEPT Appropriate technique in measuring BP is a vital component to the diagnosis and management of hypertension.

LO 3

Accurate measurement of a patient's BP requires control of factors that may influence variability in the measure. Failure to consider these factors, including body position, cuff size, device selection, auscultatory technique, and dietary intake prior to the visit, may lead to misclassification and thus inaccurate assessments of risk. Clinicians should instruct patients to avoid exercise, alcohol, caffeine, or nicotine 30 minutes before BP measurement. Patients should be sitting comfortably with their back supported and arm free of constrictive clothing with legs uncrossed and feet flat on the floor for a minimum of 5 minutes before the first reading. Systolic and diastolic BP tend to increase when the cuff size is too small. Ideally, the cuff bladder should encircle at least 80% of the arm's circumference to ensure a more accurate measurement of BP.[3]

To reduce deviations in BP measurement in the clinic, the patient and clinician should not talk during measurement. The measurement arm should be supported and positioned at heart level. If a mercury or aneroid device is used, then the palpatory method (inflate the cuff to approximately 80 mm Hg rapidly while palpating the radial pulse, then increase pressure slowly by 10 mm Hg increment every 2 to 3 seconds until the radial pulse is no longer felt [estimated SBP]; the cuff is then inflated further until the pressure is about 30 mm Hg higher) must be used first to estimate the SBP.[6] If an automated device is used, this is not necessary. After the patient's cuff is inflated above the systolic pressure, the pressure indicator should drop at a rate of 2 to 3 mm Hg/s. A stethoscope placed over the brachial artery in the antecubital fossa identifies the first and disappearance of audible **Korotkoff sounds**, which should be taken as systolic and diastolic pressure, respectively. A minimum of two readings at least 1 minute apart are then averaged. If measurements vary by more than 5 mm Hg between the two readings, then one or two additional BP measurements are collected (at least 1 minute apart from each measurement) and the multiple readings averaged. BP classification is based on the average of two or more properly measured BP readings on each of two or more office visits. Details and further recommendations for accurate measurement of BP in special populations can be found elsewhere.[3,15] Finally, the measurement of clinic or office BPs is often poorly correlated with assessments of BP in other settings. Consequently, under select circumstances, clinicians are increasingly using 24-hour ABPM, AOBP monitoring, and HBP monitoring. Corresponding values of systolic and diastolic BP for clinic, 24-hour ABPM, AOBP, and HBP measurements are provided in **Table 5–5**.[2] These methods of BP measurement are useful in identifying patients with white coat hypertension or in the case of 24-hour ABPM, elevations of BP during the

Table 5–5

Corresponding Values (mm Hg) of Systolic BP/Diastolic BP for Various Methods of BP Measurement[2]

Clinic	HBPM[a]	Daytime ABPM[a]	Nighttime ABPM[a]	24-Hour (Overall) ABPM[a]
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/90	145/90	140/85	145/90

[a]Average of recorded values.

ABPM, ambulatory BP measurement; BP, blood pressure; HBPM, home BP measurement.

Adapted from Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertens. 2017, with permission.

Clinical Presentation and Diagnosis of Primary Hypertension

General

Prevalence of hypertension is likely to be highest with middle-aged or older patients
Gender: In the United States, hypertension is slightly more prevalent in men than women before the age of 35 years, similar between the ages of 35 and 64 years, and higher in women than men thereafter

Symptoms

The patient with primary hypertension may be asymptomatic yet still have major cardiovascular disease (CVD) risk factors

Signs

Adult patients have an average of two or more BP readings (SBP and DBP) on two or more occasions.
Classification of an individual's hypertension (Table 5–1) can be made based on the higher classification from either the SBP or DBP readings; for example, an individual whose readings are consistently 136/94 mm Hg would be classified as having stage 2 hypertension.

LO 4

Basic Testing (facilitates CVD risk factor profiling, establishes a baseline for monitoring medication use, and facilitates screening for select secondary causes of hypertension)

- Fasting lipid panel (to determine ASCVD risk and those who may benefit from statin therapy as described in Chapter 12, "Dyslipidemias")
- Hemoglobin A_{1C} or fasting plasma glucose (to identify patients with impaired fasting glucose or diabetes as described in Chapter 43, "Diabetes Mellitus")
- Complete blood count
- Serum sodium, potassium, calcium, creatinine with estimated glomerular filtration rate (GFR; may all be included as part of a comprehensive metabolic panel)
- Thyroid-stimulating hormone (simple test and hypo- or hyperthyroidism are remedial causes of hypertension)
- Urinalysis
- Electrocardiogram (ECG)

Optional Testing (may provide information on target organ damage)

- Echocardiogram
- Uric acid
- Urinary albumin to creatinine ratio

The following abnormal tests may indicate hypertension-related damage:

- Serum creatinine elevated (> 1.2 mg/dL [106 µmol/L])
- Microalbuminuria, which is diagnosed either from a 24-hour urine collection (20–200 mcg/min) or from elevated concentrations (30–300 mg/L) on at least two occasions. Use of the albumin-to-creatinine ratio (ACR) in a spot urine sample is becoming more common, and microalbuminuria is defined by this measure as 30 to 300 mg/g creatinine (3.4–34 mg/mmol creatinine)

Common Comorbidities and Factors Contributing to Cardiovascular Risk

- DM
- Metabolic syndrome
- Insulin resistance
- Dyslipidemia
- Microalbuminuria/CKD
- Family history
- Central obesity
- Physical inactivity
- Tobacco use

Cardiovascular Risk Assessment

Calculate with risk assessment tools, such as the ACC/AHA ASCVD Risk Estimator (http://tools.acc.org/ascvd-risk-estimator/)

Target Organ Damage

- Cerebrovascular disease (eg, stroke or transient ischemic attack)
- Ocular (hypertensive retinopathy)
- Cardiac (left ventricular hypertrophy, left ventricular dysfunction, coronary artery disease [CAD], HF)
- CKD (eg, albuminuria, nephrosclerosis)
- Peripheral arterial disease

night and masked hypertension, or hypertension not identified through traditional office measurement. They may also aid in the management of patients with refractory hypertension with minor target organ damage, suspected autonomic neuropathy, hypotensive symptoms, and patients with large differences between home and office BP measurements. Benefits derived from these additional methods of BP monitoring may be of greater prognostic significance than traditional office-based measurements.[7,16] Consequently, the 2017 ACC/AHA guidelines recommend utilizing out-of-office self-monitoring of BP to confirm hypertension diagnosis, and for titration of BP-lowering medications in conjunction with clinic and telehealth counseling.[2]

TREATMENT

Desired Outcomes

The goal of BP management is to reduce the risk of CVD-related morbidity and mortality manifested as target organ damage such as CAD, stroke, and kidney disease.

General Approach to Treatment

KEY CONCEPT Drug therapy for the management of patients with hypertension should be considered as adjunctive to nonpharmacologic approaches for BP lowering. Ultimately, the attainment of target BP in many cases may be more important

than the antihypertensive agent selected. Previous research has established the value of using individual antihypertensive drugs versus placebo to achieve reduction in morbidity and mortality by lowering BP. According to the 2017 ACC/AHA guidelines, the recommended BP target for the vast majority of patients is less than 130/80 mm Hg.[2] The BP threshold for treatment varies according to the patient's baseline cardiovascular risk. BP-lowering medications are recommended in patients with clinical CVD (defined as coronary heart disease, HF, or stroke) and an average SBP of 130 mm Hg or higher or an average DPB of 80 mm Hg or higher. In addition, BP-lowering medications are recommended for primary prevention in adults with an estimated 10-year ASCVD risk of 10% or higher and whose SBP/DBP exceeds 130/80 mm Hg. The recommended tool for calculating ASCVD risk is the ACC/AHA ASCVD Risk Estimator (http://tools.acc.org/ascvd-risk-estimator/). BP thresholds and goals for pharmacologic therapy in these patients and those with other clinical conditions are summarized in Table 5–2. Although these guidelines clearly recommend treatment thresholds for most individuals with or without CVD or select comorbidities, the benefits of aggressive BP control using pharmacotherapy remain debatable for certain patients. Examples where conflicting data require reconciliation include controlled studies, such as the SPRINT (Systolic Blood Pressure Intervention Trial),[17] ACCORD (Action to Control Cardiovascular Risk in Diabetes),[18] and SPS3 (Secondary Prevention of Small Subcortical Strokes; blood-pressure targets in patients with recent lacunar stroke)[19] trials, where improved outcomes across all major endpoints for patients achieving a more intensive BP-lowering goal were not consistently observed. Although these inconsistencies underscore the need for additional high-quality research with the aim of determining the most appropriate BP targets for specific patient groups, the 2017 ACC/AHA guidelines were generated by inclusion of many associations and groups representing a wide array of specialty populations.[2]

Evidence supports the position that the main benefits of pharmacologic therapy are related to achievement of BP lowering and are generally independent of the selection of an individual drug regimen. Inherent in this position is the realization that lifestyle changes or nonpharmacologic approaches alone are rarely successful in attaining target BPs, and multidrug therapy (sometimes as many as three or more agents) is necessary for most patients.[6,20] Given the need for multiple medications to control hypertension, clinicians should work to minimize pill burden, frequency of administration, and cost. When possible and appropriate, selecting fixed-combination drug therapies, longer acting formulations and generic or formulary-based medications may optimize adherence. The 2017 ACC/AHA guidelines state that it is reasonable to initiate pharmacologic therapy with a single agent in patients with stage 1 hypertension.[2] In those with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target, it is recommended to start therapy simultaneously with two agents from different classes.[2] Furthermore, this guideline identifies black adults as a cohort who may be considered for two or more drugs to control hypertension. Both circumstances acknowledge the urgency to control hypertension with a high likelihood of needing multiple medications.

Another general consideration for antihypertensive therapy planning includes incorporation of chronotherapeutic principles. The timing of administration of antihypertensive medications may have relevance to the manifestations of adverse effects and/or optimizing therapeutic outcomes. A study of patients with CKD and diabetes demonstrated that moving the administration time of one antihypertensive agent to bedtime dosing significantly reduced composite cardiovascular events compared to administering all antihypertensive agents at one time in the morning.[21]

Nonpharmacologic Treatment: Lifestyle Modifications

Therapeutic lifestyle modifications consisting of nonpharmacologic approaches to BP reduction should be part of all treatment plans. The most widely studied interventions demonstrating effectiveness include:

- Dietary sodium restriction
- Increasing dietary potassium intake
- Low-fat diet, high in vegetables and fruits
- Weight reduction in overweight or obese individuals
- Regular physical activity
- Moderation of alcohol consumption

KEY CONCEPT Implementation of these lifestyle modifications successfully lowers BP, often with results similar to those of therapy with a single antihypertensive agent.[6,15] Combining multiple lifestyle modifications can have even greater BP-lowering effects. Sodium restriction to 2.4 g (100 mmol) of elemental sodium (6 g of sodium chloride or one teaspoon of table salt) per day lowers BP and has been recommended for the general population, especially individuals with hypertension.[22] Although controversy surrounds the optimal level of sodium intake and its cardiovascular benefits and risks,[23] adoption of an optimal dietary pattern that includes consuming fewer processed foods is expected to afford overall cardiovascular benefits.

Compared to the general population, BP lowering through sodium restriction is more pronounced in salt-sensitive individuals (low PRA), persons with diabetes, metabolic syndrome, or CKD, as well as older individuals and black people.[5,15] Simple dietary advice and instructions on reading nutrition labels should be introduced to patients initially and assessed and reinforced at subsequent visits. A diet high in fruits, vegetables, and low-fat dairy products, along with a reduced intake of total and saturated fat, can significantly reduce BP in as little as 8 weeks.[24] See Table 5–6.[3,22]

Smoking cessation should be encouraged for overall cardiovascular health despite its lack of chronic effects on BP.[15] Although BP-lowering lifestyle modifications have never been documented to reduce cardiovascular morbidity and mortality in patients with hypertension, they do effectively lower BP in most hypertensive patients and exhibit a favorable effect on other risk factors including dyslipidemia and insulin resistance. This may obviate the need for drug therapy in those with mild elevations in BP or minimize the doses or number of antihypertensive agents required in those on therapy.[15]

Pharmacologic Treatment

KEY CONCEPT An approach to selection of drugs for the treatment of patients with hypertension should be evidence-based with considerations regarding the individual's comorbidities, co-prescribed medications, and practical patient-specific issues including cost. The evidence-based 2017 ACC/AHA guidelines recommend drug therapy that is largely grounded in the best available evidence for superiority in outcomes—specifically morbidity and mortality.[2] The approach is often tempered

Table 5–6

Lifestyle Modifications to Manage Hypertension[a,3]

Modification	Recommendation	Approximate Systolic BP Reduction (Range)
Weight reduction	Maintain normal body weight (body mass index: 18.5–24.9 kg/m^2)	5–20 mm Hg/10 kg
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Dietary sodium restriction	Reduce dietary sodium intake to no more than 100 mmol/day (2.4 g sodium or 6 g sodium chloride). If these targets cannot be achieved, an absolute reduction in 1 g sodium/day is recommended	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day, most days of the week)	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than two standard drinks per day in most men and to no more than one standard drink per day in women and lighter weight persons[b]	2–4 mm Hg

[a]For overall cardiovascular risk reduction, stop smoking. The effects of implementing these modifications are dose and time dependent and could be greater for some individuals.

[b]One standard drink is defined as 12 oz (355 mL) beer, 5 oz (148 mL) wine, or 1.5 oz (44 mL) 80-proof whiskey.

BP, blood pressure; DASH, dietary approaches to stop hypertension.

with practical considerations related to competing options for specific comorbidities and issues regarding a patient's experience or tolerance for side effects and, in some cases, the cost of medications.

Landmark trials such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have provided some objective basis for comparisons between initiating antihypertensive drug therapy with one class of antihypertensives versus another; however, there is room for criticism of these studies.[20,25,26] Consequently, practical interpretations of their conclusions must leave room for individualization based on clinical judgment. Overall, current clinical guidelines provide a reasonable basis for guiding the selection of drug classes for individuals based on their stage of hypertension, comorbidities, and special circumstances. The following sections summarize key features of specific drug classes and guideline-based recommendations. An overview of specific oral antihypertensive drug classes in common use is summarized in Table 5–7.[3,6,27,28]

Diuretics

Diuretics have been advocated as initial therapy for uncomplicated patients with hypertension based on their practical attributes including cost, availability as combination agents and overall years of experience, as well as favorable outcomes in clinical trials for select populations. For example, patients randomized to chlorthalidone, a thiazide-type diuretic, as initial antihypertensive therapy had similar outcomes to those randomized to receive initial therapy with either amlodipine or lisinopril.[20] However, differences in outcomes for select secondary endpoints or special populations demonstrated superiority of chlorthalidone-based therapy over either ACE-I or CCB-based regimens. Criticism of the different BPs achieved in the various treatment groups, the artificial construct guiding the use of add-on drugs to base therapy, and the overrepresentation of African-Americans exhibiting select endpoints have weakened the interpretability of this trial.[20] Furthermore, other studies have challenged the status of diuretics as an ideal baseline choice for initial antihypertensive drug therapy for all patients[25,26] and even the choice of diuretic used,[29] supporting the debate over whether the means by which BP is lowered (specific drug selected) is more or less important than the extent and/or time taken to lower BP. Nonetheless, diuretics remain supported by many as acceptable baseline initial therapy for hypertensive patients without compelling indications to the contrary.

Key differences in the features of various subtypes of diuretics may also play a role in selection. The four subtypes include thiazides, loop diuretics, potassium-sparing agents, and aldosterone antagonists. The latter will be discussed separately. Each diuretic subtype has clinically-based properties that distinguish their roles in select patient populations. Thiazide diuretics are by far the most commonly prescribed with the greatest number of outcome-based studies supporting their use. This type of diuretic inhibits the sodium-chloride symporter in the renal distal convoluted tubule thus increasing sodium and chloride excretion. In the United States, hydrochlorothiazide and chlorthalidone represent the most commonly prescribed thiazide-type diuretics and have been the subject of large outcome-based studies. Although subtle differences in pharmacokinetics between these agents exist, practical differences are limited to their relative diuretic potency, with chlorthalidone being considered approximately 1.5 to 2 times more potent than hydrochlorothiazide for BP reduction.[29] Several recent analyses have demonstrated superiority of chlorthalidone over hydrochlorothiazide,[29] leading the 2017 ACC/AHA guidelines to specifically recommend chlorthalidone over other diuretics.[2,30]

Because the relationship between antihypertensive efficacy and metabolic/electrolyte-related side effects of thiazide diuretics is dose-related, attention to the differential in potency may be important. Specifically, select metabolic effects (hyperlipidemia and hyperglycemia) and electrolyte-related effects (hypokalemia, hypomagnesemia, hyperuricemia, and hypercalcemia) increase with higher doses. These effects may complicate the management of higher risk patients with common comorbidities such as dyslipidemia or diabetes, or even those likely to be sensitive to complications from hyperuricemia and the potassium- or magnesium-wasting effects of diuretics such as patients with dysrhythmias or those taking digoxin. Thiazide diuretic-induced development of new-onset diabetes remains debatable since the ALLHAT and Systolic Hypertension in the Elderly Program (SHEP) demonstrated no significant adverse cardiovascular

Table 5–7

Commonly Used Oral Antihypertensive Drugs by Pharmacologic Class[3,6,27,28]

Class	Brand	Dosage (mg/day) Low	Usual	Frequency	Select Adverse Events	Comments[a]
Diuretics						
Thiazides and thiazide-like	Chlorthalidone (Hygroton)	12.5	12.5–25	QDay	Hypokalemia and other electrolyte imbalances Negative effect on glucose and lipids	Thiazide diuretics are generally more effective antihypertensive agents than loop diuretics Ineffective in patients with estimated CrCL < 30 mL/min (0.5 mL/s), except metolazone Not first-line agents in pregnancy, but may be used with close monitoring for hypokalemia Monitor electrolytes (ie, decreased serum potassium) and metabolic abnormalities (ie, dyslipidemia, hyperglycemia) Use caution in patients with gout and severe renal impairment Contraindications include hypersensitivity and anuria
	Hydrochlorothiazide (Esidrix, HydroDiuril, Microzide, Oretic)	12.5	12.5–50	QDay		
	Indapamide (Lozol)	1.25	2.5	QDay		
	Metolazone (Zaroxolyn)	0.5	2.5–10	QDay		
Loops	Bumetanide (Bumex)	0.5	1	QDay or BID	Hypokalemia and other electrolyte imbalances	Preferred diuretic class in patients with estimated CrCL < 30 mL/min (0.5 mL/s) Monitor electrolytes (ie, decreased potassium) and metabolic abnormalities (ie, dyslipidemia, hyperglycemia) Use with caution in patients with gout Contraindications include hypersensitivity, anuria, acute renal insufficiency
	Furosemide (Lasix)	20	40	BID		
	Torsemide (Demadex)	5	10	QDay		
Potassium-sparing	Amiloride (Midamor)	5	20	QDay or BID	Potassium-sparing diuretics may enhance hyperkalemic effects of drug therapies (eg, ACE inhibitor, aldosterone antagonist)	Reserved for patients with diuretic-induced hypokalemia Monitor electrolytes (ie, potassium) Contraindications include hypersensitivity, acute renal insufficiency, hyperkalemia Avoid in patients with estimated CrCL < 30 mL/min (0.5 mL/s)
	Triamterene (Dyrenium)	100	100	QDay or BID		
Aldosterone antagonists	Eplerenone (Inspra)	25	50–100	QDay or BID	Hyperkalemia	Eplerenone contraindicated as an antihypertensive in patients with estimated CrCL < 50 mL/min (0.83 mL/s) or serum creatinine > 1.8 mg/dL (159 µmol/L) for women or 2 mg/dL (177 µmol/L) in men as well as type 2 diabetes mellitus with microalbuminuria. Also contraindicated in patients concomitantly receiving strong CYP3A4 inhibitors or a serum potassium > 5.0 mEq/L (mmol/L) at initiation
	Spironolactone (Aldactone)	12.5	25–50	QDay or BID	Gynecomastia (spironolactone)	
β-Blocker						
Cardioselective	Atenolol (Tenormin)	25	100	QDay or BID	Bradycardia Heart block Heart failure Dyspnea, bronchospasm Fatigue, dizziness, lethargy, depression	Caution with heart rate < 60 and respiratory disease Selectivity of β_1 agents is diminished at higher doses Abrupt discontinuation may cause rebound hypertension May mask signs/symptoms of hypoglycemia in diabetic patients
	Bisoprolol (Zebeta)	5	5–10	QDay		
	Metoprolol tartrate (Lopressor)	25	50–100	BID		
	Metoprolol succinate (Toprol XL)	25	50–100	QDay		

Nonselective	Nadolol (Corgard)	20	40–80	QDay	Hyper/hypoglycemia, hyperkalemia, hyperlipidemia	Contraindicated in hypersensitivity, sinus node dysfunction or severe sinus bradycardia (in the absence of a pacemaker), heart block (greater than first-degree), cardiogenic shock, acute decompensated heart failure
	Nebivolol (Bystolic)	2.5	5–10	QDay		
	Propranolol (Inderal)	40	40–160	BID		
	Propranolol long-acting (Inderal LA, InnoPran XL)	80	80–320	QDay		
	Timolol (Blocadren)	10	10–40	QDay		
Mixed α- and β-blocker	Carvedilol (Coreg)	3.125	6.52–25	BID		
	Carvedilol CR (Coreg CR)	10	20–80	QDay		
	Labetalol (Trandate)	100	100–300	BID		
CCB						
Nondihydropyridines	Diltiazem long-acting (Cardizem SR, Cardizem CD, others)	120	240–360	QDay	Bradycardia, heart block (nondihydropyridines) Constipation (nondihydropyridines) Peripheral edema, headache, flushing	Caution with heart rate < 60 (verapamil, diltiazem) Use caution in concomitant use with β-blocker; may potentiate heart block Extended-release formulations are preferred for once- or twice-daily medication administration
	Verapamil sustained-release (Calan SR, Isoptin SR, Verelan)	120	240–480	QDay		
Dihydropyridines	Amlodipine (Norvasc)	2.5	5–10	QDay	Gingival hyperplasia (dihydropyridines) Reflex tachycardia (dihydropyridines)	Contraindicated in hypersensitivity, sinus node dysfunction, or severe sinus bradycardia (in the absence of a pacemaker) (nondihydropyridines), heart block (greater than first degree) in the absence of a pacemaker (nondihydropyridines), atrial fibrillation/flutter associated with accessory bypass tract (nondihydropyridines), reduced ejection fraction (most CCBs except amlodipine)
	Felodipine (Plendil)	2.5	5–10	QDay		
	Isradipine SR (DynaCirc SR)	2.5	5–10	BID		
	Nicardipine SR (Cardene SR)	30	60–120	BID		
	Nifedipine long-acting (Adalat CC, Procardia XL)	30	30–90	QDay		
	Nisoldipine (Sular)	8.5	17–34	QDay		
ACE inhibitors	Benazepril (Lotensin)	5	10–40	QDay or BID	Cough Hyperkalemia Renal insufficiency Angioedema	Monitor electrolytes (ie, serum potassium) Monitor renal function Initial dose may be reduced in renal impairment, the elderly, patients who are volume depleted or maintained on diuretic therapy Use with caution in patients with baseline hyperkalemia Contraindicated in pregnancy and hypersensitivity, bilateral renal artery stenosis or unilateral renal artery stenosis in a solitary functional kidney
	Captopril (Capoten)	12.5	50–100	BID or TID		
	Enalapril (Vasotec)	5	10–40	QDay or BID		
	Fosinopril (Monopril)	10	10–40	QDay		
	Lisinopril (Prinivil, Zestril)	5	10–40	QDay		
	Moexipril (Univasc)	7.5	7.5–30	QDay or BID		
	Perindopril (Aceon)	4	4–8	QDay		
	Quinapril (Accupril)	5	10–40	QDay or BID		
	Ramipril (Altace)	2.5	5–10	QDay or BID		
	Trandolapril (Mavik)	1–2	2–8	QDay		

(*Continued*)

Table 5–7

Commonly Used Oral Antihypertensive Drugs by Pharmacologic Class[3,6,27,28] (*Continued*)

Class	Brand	Dosage (mg/day) Low	Usual	Frequency	Select Adverse Events	Comments[a]
ARBs	Azilsartan (Edarbi)	40	80	QDay	Hyperkalemia	Above comments to ACE inhibitors also apply to ARBs
	Candesartan (Atacand)	4	8–32	QDay or BID	Renal function deterioration	
	Eprosartan (Teveten)	400	600–800	QDay or BID	Angioedema	
	Irbesartan (Avapro)	150	150–300	QDay	Hypotension/syncope	
	Losartan (Cozaar)	50	50–100	QDay or BID		
	Olmesartan (Benicar)	10	20–40	QDay		
	Telmisartan (Micardis)	40	40–80	QDay		
	Valsartan (Diovan)	80	80–320	QDay		
Direct renin inhibitors	Aliskiren (Tekturna)	75	150–300	QDay	Hyperkalemia Hypotension	Use caution in patients with severe renal impairment and in patients with deteriorating renal function or renal artery stenosis, both bi- and unilateral Contraindicated in combination with ACE-Is or ARBs in patients with diabetes
Central α_2 agonists	Methyldopa (Aldomet)	125	250–500	BID	Transient sedation initially	First-line agent in pregnancy (methyldopa)
	Clonidine oral (Catapres)	0.1	0.1–0.2	BID	Hepatotoxicity, hemolytic anemia, peripheral edema (methyldopa)	Tolerance may occur 2–3 months after initiation of methyldopa; increase dose or add thiazide
	Clonidine patch (Catapres TTS)	0.1	0.1–0.3	Once weekly		Contraindications include hypersensitivity, concurrent use of MAO inhibitor (methyldopa), hepatic disease [methyldopa], pheochromocytoma (methyldopa)
	Guanfacine (Intuniv)	1	1–2	QDay	Orthostatic hypotension (methyldopa, clonidine) Dry mouth, muscle weakness (clonidine)	
α_1 Blockers	Doxazosin (Cardura)	1	1–8	QDay	Syncope, dizziness, palpitations, orthostatic hypotension	Contraindicated in hypersensitivity
	Prazosin (Minipress)	1	2–20	BID or TID		
	Terazosin (Hytrin)	1	1–20	QDay or BID		
Direct vasodilator	Isosorbide dinitrate 20 mg and hydralazine 37.5 (BiDil)	20/37.5	20–40/37.5–75	TID	Edema, hypertrichosis (minoxidil) Tachycardia	Give minoxidil with diuretic and β-blocker to mitigate side effects Contraindicated in hypersensitivity, pheochromocytoma (minoxidil), increased intracranial pressure [isosorbide dinitrate + hydralazine]
	Hydralazine (Apresoline)	10	25–100	BID	Lupus-like syndrome (hydralazine)	
	Minoxidil (Loniten)	2.5	5–100	QDay or BID		
Peripheral sympathetic inhibitors	Reserpine (generic only)	0.1	0.1–0.25	QDay	Mental depression Orthostatic hypotension Nasal congestion, fluid retention, peripheral edema Diarrhea, increased gastric secretion	Contraindications include hypersensitivity, peptic ulcer disease or ulcerative colitis, history of mental depression or electroconvulsive therapy

[a]Comments listed are not intended to be inclusive of all adverse effects, monitoring parameters, cautions, or contraindications, and may vary by source.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CYP, cytochrome P450; BID, twice daily; CCB, calcium channel blocker; CrCL, creatinine clearance; MAO, monoamine oxidase; QDay, once daily; TID, three times daily. Modified from Reference 6 and Saseen JJ, Maclaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:57–58, with permission.

events from new diuretic-associated diabetes versus other trials contradicting this observation.[31] Nonetheless, clinicians should generally not exceed 25 to 50 mg/day of hydrochlorothiazide or 25 mg/day of chlorthalidone.[32] In addition, regardless of the dose used, careful assessment of the potential for metabolic- or electrolyte-based effects is essential.

Additionally, it is important to recognize that when estimated creatinine clearance approaches or is less than 30 mL/min (0.50 mL/s), thiazide diuretics have limited efficacy, rendering loop diuretics to be preferred. Clinicians are advised to reevaluate the use of thiazide diuretics prescribed to individuals whose renal function has been declining with age and whose risk for the consequences of metabolic effects may be more significant.[33] Loop diuretics, such as furosemide, bumetanide, torsemide, and ethacrynic acid, have a common site of action in the thick ascending limb of the loop of Henle. As this region reabsorbs over 35% to 45% of filtered sodium, their diuretic efficacy is superior to that of thiazides, potassium-sparing diuretics, and aldosterone antagonists. With the exception of torsemide, which has a longer half-life, the loop diuretics should be administered twice daily (BID) when utilized primarily for their antihypertensive (vs diuretic) effect. The most significant adverse effect of loop diuretic use is excessive diuresis leading to hyponatremia or hypotension. Additionally, hypokalemia, hypomagnesemia, and hypocalcemia may develop over time and contribute to the potential for cardiac arrhythmias. Overall, relevance of drug–drug interactions and potential for aggravating select conditions (hyperglycemia, dyslipidemias, and hyperuricemia) should be routinely monitored.[9]

Potassium-sparing diuretics that do not act through mineralocorticoid receptors include triamterene and amiloride. These agents are often prescribed in combination with potassium-wasting diuretics to mitigate potassium loss. When administered alone or as a combination product, these agents result in modest diuresis given that their site of action on the distal tubule and collecting ducts has minimal impact on blocking sodium reabsorption. Their most significant risk is the potential for hyperkalemia. This is especially relevant in the context of those patients with moderate to severe renal impairment or those receiving nonsteroidal anti-inflammatory drugs (NSAIDs), potassium supplements, or other agents with potassium-sparing properties, such as ACE-Is or ARBs.[9]

Aldosterone Antagonists

Aldosterone antagonists such as spironolactone and eplerenone modulate vascular tone through a variety of mechanisms besides diuresis (Figure 5–2). Their potassium-sparing effects mediated through aldosterone antagonism counteract the potassium-wasting effects of other diuretics such as thiazide or loop diuretics. Patients with resistant hypertension (with or without primary aldosteronism) experience significant BP reductions with the addition of low-dose spironolactone (12.5–50 mg/day) to diuretics, ACE-Is, and ARBs.[34] Although a positive attribute, it is important to recognize the risk for hyperkalemia in patients with impaired or fluctuating renal function, or those who are receiving ACE-Is, ARBs, direct renin inhibitors, potassium supplements, potassium-containing salt substitutes, or NSAIDs. In addition, spironolactone is associated with **gynecomastia**, whereas eplerenone rarely causes this complication, presumably because of its greater aldosterone blocking specificity than spironolactone and minimal effects on androgens and progesterone.[6,9]

β-Blockers

Most contemporary guidelines refrain from supporting the use of β-blockers as first-line antihypertensive agents.[6,15,32] The basis of this position varies but often cites studies indicating inferior outcomes[35] and a lack of positive outcomes in elderly patients when compared to other antihypertensives. These analyses were conducted with a limited number of β-blockers (usually atenolol), and thus their findings may or may not apply to newer formulations of existing agents (eg, metoprolol succinate) or agents with unique properties such as carvedilol or nebivolol.[35] However, the role of β-blockers in patients with specific select comorbidities is well-established (Table 5–3).[3] Specific studies conducted in patients with comorbidities such as CAD, HF with reduced ejection fraction (HFrEF), or recent MI have clearly demonstrated morbidity and mortality benefits from β-blocker use.[36] Their hemodynamic effects and antiarrhythmic properties make them desirable for hypertensive patients who suffer from ischemic conditions including acute coronary syndromes (ACS). The mechanisms through which β-blockers affect BP are complex but most certainly include their modulation of renin, which appears to result in a reduction in CO and/or reduction in PVR along with their negative inotropic/chronotropic actions (Figure 5–2).

The specific pharmacologic properties of β-blockers are varied and diverse. An understanding of these properties may assist in the selection of one agent over others given a patient's specific condition(s) or comorbidities. One of these properties is cardioselectivity: the property of some β-blockers that preferentially block the β_1-receptor versus β_2-receptor. Some β-blockers exhibit membrane stabilization activity, which relates to the β-blocker's capacity to exhibit certain antiarrhythmic properties. Some β-blockers, as shown in **Figure 5–3**, possess properties referred to as intrinsic sympathomimetic activity (ISA). β-Blockers possessing this property effectively block the β-receptor at higher circulating catecholamine levels, such as during exercise, while having modest β-blocking activity at times of lower catecholamine levels, such as at rest.[37]

Cardioselectivity represents the most clinically relevant property of β-blockers, but β-blockers with ISA are not recommended for use in the post-ACS patient.[37] With regard to cardioselectivity, it is important to consider patients with asthma and/or chronic obstructive pulmonary disease. A β-blocker with relative cardioselectivity to block β_1-receptors may be more desirable in such a patient, whereas a nonselective β-blocker may be potentially disadvantageous. In such a patient, low doses of cardioselective β-blockers may achieve adequate blockade of β_1-receptors in the heart and kidneys while minimizing the undesirable effects of β_2-receptor blockade on the smooth muscle lining the bronchioles. In doing so, hypertension may be managed while avoiding complications of the coexisting reactive airway disease, which is mediated by β_2-receptor stimulation. Similarly, either because of a reduction in the β_2-mediated vascular blood flow or by enhanced unopposed α-agonist–mediated vasoconstriction, a patient with peripheral vascular disease and intermittent claudication may experience a worsening of symptoms with use of a nonselective β-blocker (Figure 5–3). It is important to remember that cardioselectivity depends on dose, with diminished selectivity exhibited with higher doses.

A limited number of β-blockers also possess vasodilatory properties that are either mediated through α_1-receptor blockade (carvedilol, labetalol) or via L-arginine/nitric oxide-induced release from endothelial cells, with subsequent increased nitric

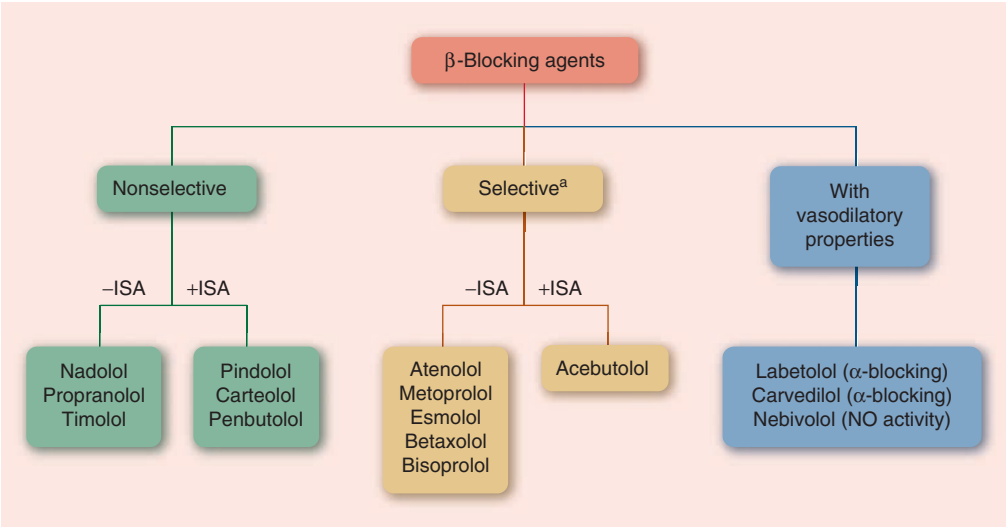

FIGURE 5–3. Flowchart listing various β-blocking agents separated by β-receptor activity and intrinsic sympathomimetic activity. [a]β-1 Cardioselective. (ISA, intrinsic sympathomimetic activity; NO, nitric oxide.)

oxide bioavailability in the endothelium (nebivolol). Although theoretically of benefit, there has been no proven evidence of superior outcomes from use of β-blockers with these vasodilatory properties.

The adverse effects of β-blockers follow their pharmacology. Their potential to precipitate bradycardia, various degrees of heart block, or signs and symptoms of HF may be of concern to those with a subclinical diagnosis of HF, the elderly, or those with reduced left ventricular ejection fraction (LVEF). Conversely, abrupt discontinuation of β-blockers has been cited as a precipitating factor in the development of ischemic syndromes, especially for those patients in whom β-blockers were used for extended periods of time, at higher doses, or who had underlying ischemic heart disease. In such cases, tapering the dose over a period of several days to 1 or even 2 week(s) is recommended. β-Blocker use in diabetics is usually a complex decision requiring consideration of their consequential effects on insulin, glucose availability, and blocking the signs and symptoms of hypoglycemia against their potential for morbidity/mortality benefits for select candidates with comorbidities such as HFrEF. Lastly, β-blockers, particularly first-generation agents (ie, those other than carvedilol, nebivolol), have a greater effect on glucose metabolism as well as other metabolic effects, and they should be used cautiously if at all with diuretics unless compelling indications exist for both.

The FDA-approved drug labeling for metoprolol, carvedilol, nebivolol, and propranolol states that when coadministered with drugs that affect cytochrome P450 (CYP) 2D6 metabolic pathways, their efficacy and/or toxicity may be altered. However, specific recommendations vary by agent. For example, recommendations for metoprolol state that dose titration or an alternative agent should be considered for individuals classified as CYP2D6 poor, intermediate, and ultra-rapid metabolizers. However, similar recommendations are not explicitly suggested for carvedilol, nebivolol, or propranolol.

Calcium Channel Blockers

Exhibiting considerable interclass diversity, CCBs are recognized as effective antihypertensives, particularly in the elderly.[6] Although the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial comparing valsartan-based and amlodipine-based therapy failed to achieve its primary endpoint of cardiac morbidity and mortality, secondary endpoints including stroke and MI were reduced by amlodipine-based therapy.[26] In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), amlodipine-based therapy achieved greater BP-lowering and appeared to provide greater protection against stroke and MI versus atenolol-based therapy.[25]

The variety of pharmacologic properties among the subclasses of CCBs is significant and categorizes their expected effects on the cardiovascular system and potential risk of toxicities. Dihydropyridine CCBs such as nifedipine and amlodipine are commonly associated with edema, especially when used at higher doses. Nondihydropyridine CCBs such as verapamil and diltiazem are recognized for their electrophysiological effects, and negative chronotropic and inotropic effects. These pharmacologic properties may be exploited for their specific clinical utility. Verapamil and diltiazem effectively block cardiac conduction through the atrioventricular node, exhibiting value in the management of patients with atrial fibrillation in addition to hypertension. However, their negative inotropic effects can be detrimental to patients with reduced LVEF and should be avoided. In contrast, the dihydropyridine subclass of agents has no utility for managing patients with atrial dysrhythmias but may be used safely (exception being nifedipine) in patients with reduced ejection fraction. Similarly, all CCBs possess some coronary vasodilating properties and, therefore, may be used in select patients for the management of patients with angina, in addition to their antihypertensive benefits.[9]

ACE Inhibitors

ACE-Is have been extensively studied for the treatment of hypertension, and outcome-based trials generally support their use for a wide array of patients, especially with select comorbidities. These compelling indications include their qualified role in managing patients with hypertension who have a history of type 1 or 2 DM, HF, MI, CKD, or stroke.[15] Comparative trials using either ACE-Is or diuretics as initial drug therapy have demonstrated that diuretics may be superior to ACE-Is in regard to combined incidence of new onset CVD and HF,[20] but indistinguishable in terms of overall outcomes.[38] It is therefore

reasonable to conclude that both diuretics and ACE-Is represent appropriate choices as either first- or second-line hypertensive therapies that effectively achieve a target BP goal for most patients with or without comorbidities.

Although generally well-tolerated, ACE-Is are associated with two hallmark side effects: hyperkalemia and a persistent dry cough. Modest elevations in serum potassium should be anticipated when starting or increasing the dose of an ACE-I, particularly in patients with compromised renal function and those receiving any concurrent NSAIDs, potassium supplements, or potassium-containing salt substitutes. Hyperkalemia is rarely a reason for discontinuation of therapy. Nonetheless, periodic monitoring of serum potassium is prudent for patients receiving ACE-Is. The dry cough associated with ACE-Is is thought to be caused by accumulation of bradykinin resulting from a direct effect of inhibiting angiotensin-converting enzyme. If a cough jeopardizes compliance with the agent, ARBs should be considered as possible alternative agents because there is less incidence of cough.

Less common adverse effects of ACE-Is include acute kidney injury, particularly in patients with hemodynamically significant bilateral renal artery stenosis (or unilateral if one functioning kidney), preexisting kidney dysfunction, blood dyscrasias, or angioedema.

In general, effects of ACE-Is on renal function and potassium can be predicted given an understanding of their pharmacologic actions (Figure 5–2). Inhibition of angiotensin II synthesis through ACE inhibition (or direct blockage of the angiotensin II receptor by ARBs) naturally would reduce the efferent renal artery tone, thereby changing the intraglomerular pressure. Although changes in the afferent renal artery tone also occur, the overall effects usually produce a reduction in GFR with resulting decline in GFR of up to 30%.[9] Such reductions in GFR are not usually indications to discontinue use of the ACE-I; however, continued monitoring for further decreases in GFR and consideration of dose reduction remain prudent. Alternatively, should declines in GFR exceed 30%, dose reduction or discontinuation is warranted until further evaluation can be made.

Angiotensin Receptor Blockers

ARBs are inhibitors of the angiotensin-1 (AT1) receptors (Figure 5–2). AT1 receptor stimulation evokes a pressor response via a host of accompanying effects on catecholamines, aldosterone, and thirst.[9] Consequently, inhibition of AT1 receptors directly prevents this pressor response and results in upregulation of the RAAS. Upregulation of the RAAS results in elevated levels of angiotensin II, which have the added effect of stimulating the angiotensin-2 (AT2) receptors. AT2-receptor stimulation is generally associated with antihypertensive activity; however, long-term effects of AT2-receptor stimulation on cellular growth and repair mechanisms are relatively unknown. While the pharmacologic differences between ARBs and ACE-Is are clear, the therapeutic relevance resulting from these differences remains ambiguous. Previously, the clinical benefits of ARBs were considered less robust as compared to ACE-Is, but the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) has demonstrated that in high-risk patients, telmisartan is noninferior to ramipril for the reduction of death from cardiovascular causes, MI, stroke, or hospitalization for HF.[39] This study also demonstrated that an ACE-I in combination with an ARB reduces proteinuria to a greater extent than either agent as monotherapy but increases the composite of dialysis, doubling of serum creatinine, and death.[40] Although better tolerated than ACE-Is, ARBs have not been shown to demonstrate superiority of outcomes relative to ACE-Is.

At this point, ARBs have emerged as an effective class of antihypertensives whose low incidence of side effects and demonstrated clinical role in patients with specific comorbidities have afforded them an attractive position in the antihypertensive armamentarium. However, as with ACE-Is, patients may develop angioedema. Although estimates of cross-reactivity are reportedly low,[41] one should always exercise caution when considering the use of an ARB in a patient with a known history of angioedema to an ACE-I. Like ACE-Is, the antihypertensive effectiveness of ARBs is greatly enhanced by combining them with diuretics. Combining an ACE-I with an ARB for treating hypertension should almost always be avoided. However, in select situations, the addition of ARBs to ACE-Is for patients with HF has demonstrated additional incremental benefits and may be considered if aldosterone antagonists are not indicated or tolerated.[41] Overall, ARBs have proven their value as reasonable first-line agents for uncomplicated patients with hypertension, well-tolerated alternatives to ACE-Is for patients with select comorbidities (CKD, DM, and prior MI [Table 5–3]) and alternatives when ACE-Is are not well-tolerated.

Renin Inhibitors

Aliskiren is the first agent in the newest class of antihypertensive agents. Although similar to ACE-Is and ARBs in that it acts

Patient Encounter 2

A 52-year-old Hispanic woman returns to your clinic for a follow-up visit. Her seated BP measurements are 160/90 mm Hg and 158/92 mm Hg. Her heart rate is 98 beats/min. She is currently on nebivolol 40 mg daily, hydrochlorothiazide 25 mg daily, amlodipine 10 mg daily, captopril 12.5 mg three times daily, terazosin 5 mg daily, and rosuvastatin 40 mg daily. She states that she has been adherent with all medications, but prescription bottles she brought in reveal she is overdue on refills yet she has at least 2 to 3 weeks worth of medication in each vial. She is not familiar with the names of her medications, smokes one pack of cigarettes per day, and does not consume any alcohol or illicit substances. She is overweight, does not exercise, and consumes mostly processed and/or fast foods. Past medical history is significant for prior MI 18 months ago treated medically, hypertension, obstructive sleep apnea, and osteoarthritis. Physical examination was unremarkable. Laboratory values were significant for serum creatinine of 0.8 mg/dL (71 µmol/L), a potassium level of 3.5 mEq/L (mmol/L), fasting glucose of 120 mg/dL (6.7 mmol/L), total cholesterol of 260 mg/dL (6.72 mmol/L), HDL cholesterol of 45 mg/dL (1.16 mmol/L), triglyceride level of 180 mg/dL (2.03 mmol/L), and calculated low-density lipoprotein (LDL) cholesterol of 179 mg/dL (4.63 mmol/L).

Based on the information provided, does the patient have resistant hypertension?
Based on the information presented, create a care plan for this patient's hypertension. This should include (a) goals of therapy, (b) a patient-specific therapeutic plan, and (c) a plan for appropriate monitoring to achieve goals and avoid adverse effects.

within the RAAS, it is unique in that it directly blocks renin, thereby reducing PRA and subsequently AT1 and AT2 with a resultant reduction in BP. This disruption of the negative feedback loop results in a compensatory increase in pro-renin and renin levels, the significance of which is not well-established. Aliskiren has been shown to be well-tolerated and effective in reducing BP when used as monotherapy and in combination with other antihypertensive agents, including thiazide diuretics, ARBs, and CCBs.[15] However, long-term clinical trials evaluating efficacy and safety have not been completed, and thus the effects of aliskiren on morbidity and mortality are as yet unknown. Additionally, the Aliskiren Trial In Type 2 Diabetes Using Cardio-renal End points (ALTITUDE) comparing ACE-I or ARB monotherapy to that in combination with aliskiren was stopped prematurely as the combination therapy did not reduce cardiovascular endpoints.[42] Therefore, combining two or more RAAS blocking agents (ACE-Is, ARBs, or renin inhibitors) for the treatment of hypertension is not recommended.[40,42] Because of aliskiren's role in the RAAS, recommendations and precautions for monitoring serum potassium and kidney function should be similar to those of ACE-Is and ARBs.

α_1-Blockers

Generally, α_1-blockers are considered inferior agents and should not be used as monotherapy. Further, doxazosin is associated with an increase in cardiovascular and cerebrovascular events.[20] However, α_1-blockers may be considered as add-on therapy to other agents (eg, fourth or fifth line) when hypertension is not adequately controlled. In addition, they may have a specific role in the antihypertensive regimen for elderly men with **prostatism**; however, their use is often curtailed by complaints of transient dizziness, palpitations, or syncope following the first dose and **orthostatic hypotension** with chronic use. Due to their ability to cross blood-brain barrier, α_1-blockers can also cause asthenia, vivid dreams, and depression. In addition, **priapism** may occur. When selected, however, combination therapy with thiazide is recommended to minimize potential edema resulting from the α_1-blocker's tendency to cause sodium and water retention. The roles of doxazosin, terazosin, and prazosin in management of patients with hypertension are limited due to the paucity of outcome data and absence of a unique role for special populations or compelling indications.[15]

Central α_2-Agonists

Limited by their tendency to cause **orthostasis**, sedation, dry mouth, and vision disturbances, clonidine, methyldopa, guanfacine, and guanabenz represent rare choices in contemporary treatment of patients with hypertension. However, adding clonidine to other antihypertensive agents may be used for individuals with resistant hypertension and methyldopa is a viable option for pregnancy. Their central α_2-adrenergic stimulation is thought to reduce sympathetic outflow and enhance parasympathetic activity, thereby reducing heart rate, CO, and total PVR. Occasionally used for cases of resistant hypertension, these agents may have a role when other more conventional therapies appear ineffective. The availability of a transdermal clonidine patch applied once-weekly may offer an alternative to hypertensive patients with adherence problems. Of particular importance is the potential for severe rebound hypertension when clonidine is abruptly discontinued. Rather, clonidine's dose should be gradually reduced when being discontinued. In patients concurrently taking a β-blocker, the β-blocker should be tapered to discontinuation first, ideally several days before initiating the clonidine taper. Because clonidine withdrawal results in an increase in SNS activity, patients withdrawing from clonidine while on a β-blocker could experience unbalanced α-mediated vasoconstriction.[9]

Other Agents

Direct vasodilators such as hydralazine and minoxidil represent alternative agents used for patients with resistant hypertension. They primarily act to relax smooth muscles in arterioles and activate baroreceptors. Because of the reflex tachycardia and fluid retention they cause, their use in the absence of concurrently administered β-blockers and diuretics such as furosemide is uncommon. Other side effects associated with minoxidil include pericardial effusion, nonspecific T-wave change on the ECG, and hypertrichosis (excessive body hair), particularly in women. Rarely, hydralazine-induced lupus-like syndrome can occur in some patients. Although uncommon, females, those receiving doses in excess of 200 mg/day, individuals with slow hepatic acetylation capacity, or having certain immunogenic factors appear to be at greater risk.[43] Because slow acetylation can increase the bioavailability of hydralazine leading to adverse effects, in 2013 the Food and Drug Administration (FDA) listed N-acetyltransferase-1 (NAT-1) and NAT2 genes as biomarkers for the effectiveness and/or toxicity of hydralazine. References describing the appropriate use and monitoring of these infrequently utilized agents should be consulted before use.[9] Finally, reserpine, although slow to act, reduces sympathetic tone and thus PVR by depleting norepinephrine from sympathetic nerve endings. Although included in the SHEP and ALLHAT trials,[20,44] reserpine's numerous side effects, including gastric ulceration, depression, and sexual side effects, have limited its utility. Two additional agents, guanethidine and guanadrel, act as postganglionic sympathetic inhibitors inhibiting the release of norepinephrine as well as depleting norepinephrine from these nerve terminals. However, these agents have little role in the management of hypertension because of significant adverse effects.[9]

Antihypertensive Toxicity and Management

Common adverse reactions and monitoring parameters with each class of antihypertensive agents are discussed in the earlier sections. Overdoses occurring from antihypertensive agents are relatively uncommon but their consequences, especially those involving β-blockers, CCBs, and vasodilators, can be profound.[45] This contrasts with the toxicities observed from diuretics, ACE-Is, ARBs, and direct renin inhibitors, which are generally more limited. Early gastrointestinal decontamination followed by routine supportive care, including intravenous (IV) crystalloid boluses, airway protection, and/or vasopressor administration should be initiated in patients manifesting significant bradycardia, hypotension, and/or seizures. If unresponsive to standard supportive care, glucagon and/or high dose insulin with glucose (if no response to glucagon) may be used when β-blocker toxicity is suspected or confirmed. The early use of high dose insulin and IV calcium can be effective for CCB poisonings. While administering calcium, one should monitor the ECG, avoid rapid infusions, and never infuse calcium in the same line as phosphate-containing solutions to prevent precipitation. Patients who ingest sustained-release formulations may experience delayed responses and prolonged toxicity and require 24-hour observation, even if asymptomatic upon presentation.

Patient Encounter 3

A 62-year-old black man with history of hypertension, gout, and CKD presents to clinic for his annual examination. Upon reviewing his medication history, you see the patient has been taking chlorthalidone 25 mg daily and allopurinol 200 mg daily. Physical examination is unremarkable. Laboratory values are remarkable for potassium 3.6 mEq/L (mmol/L), serum creatinine 1.4 mg/dL (124 µmol/L), serum uric acid 9.2 mg/dL (547 µmol/L), and proteinuria 600 mg/24 hours (0.6 g/day). Patient's average seated BP was 128/76 mm Hg with HR of 76 beats/min.

Based on the 2017 ACC/AHA guidelines, is this patient achieving his blood pressure goal?
Would you consider changes to current antihypertensive therapy given the patient's BP, laboratory values, and medical history?
How would you assess the effectiveness of your therapeutic recommendations for this patient?

SPECIAL PATIENT POPULATIONS

Compelling Indications and Special Considerations

KEY CONCEPT Specific antihypertensive therapy is warranted for certain patients with comorbid conditions that may elevate their level of risk for CVD. Clinical conditions and patient factors for which there is compelling evidence supporting one or more classes of drug therapy include:

LO 7

- Stable ischemic heart disease (SIHD)
- HF
- Diabetes
- CKD
- Valvular heart disease
- Atrial fibrillation
- Cerebrovascular disease
- Elderly
- Race

Compelling indications for specific drug therapies are summarized in Table 5–3.[6] The basis for recommendations for select patient populations may follow pharmacology and, in some cases, evidence of specific target values in select patient populations.

In patients with an ACS or stable angina and hypertension, β-blockers and possibly long-acting CCBs are indicated because of their antihypertensive and antianginal effects.[36] Nitrate therapy should also be considered in patients with persistent angina and hypertension, and in the setting of an ACS. In post-MI patients, especially those with reduced LVEF, β-blockers and ACE-Is or ARBs are indicated due to their proven reduction of cardiovascular morbidity/mortality in this population. Aldosterone antagonists are also indicated for the post-MI patient with reduced LVEF and either diabetes or symptoms of HF.[41] Patients with CAD were included in the SPRINT trial, which showed a reduction in major adverse cardiovascular events, including mortality, with intensive SBP reduction (SBP < 120 mm Hg) versus standard treatment (< 140 mm Hg) as measured via AOBP.[17] However, it should be noted that serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure were more frequent in the intensive therapy arm and must weigh into decisions regarding application of the SPRINT findings. This data was considered by the 2017 ACC/AHA guidelines Committee as part of the evidence and rationale to support a lower BP target (< 130/80 mm Hg) in this patient population.[2]

Patients with HF represent a heterogeneous cohort of patients with specific recommendations for BP therapy depending on their classification. BP targets for patients with HF have been recently updated by the ACC/AHA with a target SBP less than 130 mm Hg recommended for stage A HF patients and those with stage C HF with either reduced or preserved LVEF, but with no clear update for stages B and D.[46] Patients with HFrEF and hypertension should be treated with evidence-based β-blockers (bisoprolol, carvedilol, or metoprolol succinate), ACE-Is or ARBs, and aldosterone antagonists as each has evidence supporting their morbidity/mortality benefits for such patients. In contrast, diuretics are recommended in HF patients with evidence of volume overload for symptom relief. African-Americans with HFrEF are ideal candidates for combination therapy with isosorbide dinitrate and hydralazine based on morbidity and mortality benefits and potential beneficial effects on lowering BP.[41] The dihydropyridine CCBs, amlodipine or felodipine, may be used in patients with HFrEF for uncontrolled BP; however, they offer no beneficial effect on morbidity and mortality and may increase the risk of edema.[41] For patients with HF with preserved ejection fraction (HFpEF), use of non-dihydropiridine CCBs (diltiazem and verapamil) is not discouraged in contrast to patients with HFrEF.[41] Updated HFpEF recommendations highlight the potential role for aldosterone antagonists in decreasing HF hospitalization in this cohort.[46]

Patients with diabetes and hypertension without CKD (regardless of age) represent a target population whose initial drug therapy depends on if they are Black or non-Black. Specifically, Black patients with diabetes and no CKD should be treated initially with thiazide-type diuretics or CCBs alone or in combination. In the presence of albuminuria in a patient with diabetes and hypertension, ACE-Is or ARBs can be considered initially. Non-Black patients with diabetes and no CKD are candidates for the same starting therapies but with expanded options including either ACE-Is or ARBs.[2]

In patients with CKD and hypertension (regardless of age, race, or presence of diabetes), ACE-Is or ARBs alone or in combination with other agents are preferred.[32] ACE-Is in combination with a thiazide diuretic are also preferred in patients with a history of prior stroke or transient ischemic attack. This therapy reduces the risk of recurrent stroke, making it particularly attractive in these patients for BP control.

Hypertension in patients with asymptomatic aortic stenosis can be treated with pharmacologic therapy, but therapy should be initiated with the use of low doses and carefully titrated upward as appropriate. In patients with chronic aortic dissection, β-blockers were associated with improved survival, whereas ACE-Is did not improve survival.[2]

In patients with atrial fibrillation, ARB therapy is suggested for reduction in recurrence of atrial fibrillation.[2] The use of an ARB versus CCBs or β-blockers has clinical superiority and may be an appropriate first-line therapy choice for antihypertensive therapy in patients with atrial fibrillation.[2] Of note, no data on the role of ACE-Is in this situation is available at this point.

LO 7

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

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

Hypertensive crisis includes both hypertensive emergencies and hypertensive urgencies. A hypertensive emergency occurs when severe elevations in BP are accompanied by acute or life-threatening target organ damage such as ACS, unstable angina with dynamic ST changes, encephalopathy, intracerebral hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, rapidly progressive renal failure, accelerated malignant hypertension with papilledema, and eclampsia, among others. BP is generally greater than 180/120 mm Hg, although a hypertensive emergency can occur at lower levels, particularly in individuals without previous hypertension. The goal in most hypertensive emergency cases is to reduce SBP by up to 25% in the first hour; if stable, then lower to 160/100–110 mm Hg over the next 2 to 6 hours; and then carefully to normal over the following 24 to 48 hours. For individuals with compelling conditions, including aortic dissection, severe preeclampsia or eclampsia, or pheochromocytoma crisis, a more aggressive BP-lowering approach (reduce SBP to < 140 mm Hg in the first hour and < 120 mm Hg in aortic dissection) should be taken.[2] IV therapy is generally required and may consist of the agents listed in Table 5–8. A hypertensive urgency is manifested as a severe elevation in SBP greater than 179 mm Hg and DBP greater than 109 mm Hg without evidence of acute or life-threatening target organ damage.[47] In these individuals, BP can usually be managed with orally administered short-acting medications (ie, captopril, clonidine, or labetalol) and observation in the emergency department over several hours, with subsequent discharge on oral medications and follow-up in the outpatient setting within 24 hours.[2]

The target for BP in patients 65 years and older remains uncertain and in part depends on whether the patient is ambulatory, community dwelling, institutionalized, and able to tolerate therapy. A target BP of less than 130 mm Hg systolic is recommend in noninstitutionalized ambulatory community dwelling patients. In addition, if the patient has a high burden of comorbidity and limited life expectancy, a more personalized team-based approach taking into account potential risks and benefits of therapy is warranted.[2] The treatment of patients 60 years of age and older with hypertension should follow the same approach as other populations, with the exception that lower starting doses may be warranted to avoid adverse effects. Special attention should be paid to postural hypotension. This includes an approach that consists of careful assessment of orthostatic symptoms, measurement of BP in the upright position upon standing for 1 to 3 minutes, and caution to avoid volume depletion and rapid titration of antihypertensive therapy as was done in the Hypertension in the Very Elderly Trial (HYVET).[48] It should also be noted that in the HYVET trial, patients were excluded if standing SBP at baseline was less than 140 mm Hg. Newer data from the SPRINT suggests patients 75 years of age and older benefit in a similar fashion from intensive SBP reduction (< 120 mm Hg vs < 140 mm Hg as measured by AOBP) as did patients less than 75 years of age with regard to cardiovascular morbidity and mortality risk reduction.[17] In this situation, while some patients may benefit from pursuing intensive BP-lowering targets, tolerability must not be overlooked and aspects of patient selection and safety considerations are paramount when considering any BP-lowering strategy in the elderly.

In individuals with isolated systolic hypertension, the optimal level of diastolic pressure is not known, and although treated patients who achieve diastolic pressures less than 60 to 70 mm Hg had poorer outcomes in a landmark trial, their cardiovascular event rate was still lower than those receiving placebo.[33]

While the treatment approach of hypertension in minority populations is similar, special consideration should be paid to socioeconomic and lifestyle factors that may be important barriers to BP control. In addition, in patients of African origin, diminished BP responses have been seen with ACE-Is and ARBs compared with diuretics or CCBs.[3]

Hypertension in pregnancy is a major cause of maternal, fetal, and neonatal morbidity and mortality. There are four different categories of hypertension in pregnancy: preexisting chronic hypertension, gestational hypertension, preeclampsia-eclampsia, and preeclampsia superimposed on chronic hypertension. Each category is treated slightly differently. Table 5–9 summarizes oral drug therapy options for pregnant patients with chronic hypertension. Also refer to the American College of Obstetricians and Gynecologists task force on hypertension in pregnancy for detailed therapeutic options for acute severe hypertension in preeclampsia.[49]

In children and adolescents, three or more BP readings are compared with tables listing the 90th, 95th, and 95th + 12 mm Hg for BPs based on age, height, and gender that classify BP as normal, elevated BP, and stage 1 and stage 2 hypertension.[50] The prevalence of hypertension in adolescent populations is increasing. This, along with increases in obesity, sedentary lifestyle, or a positive family history, increases the risk of CVD. The clinician should be aware that secondary causes are common in adolescents with hypertension and the identification and aggressive modification of risk factors with nonpharmacologic and pharmacologic interventions is paramount for risk reduction of target organ damage. The 2017 Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents published by the American Academy of Pediatrics provides specific recommendations to modify and treat risk factors in this population of patients.[50] The *Nelson Textbook of Pediatrics* is also recommended for a comprehensive review of treatment of congenital and pediatric hypertension, which is beyond the scope of this chapter.

OUTCOME EVALUATION

LO 8

Short-term goals are to achieve reduction in BP safely through the iterative process of using pharmacologic therapy, along with nonpharmacologic therapy and lifestyle changes. Key to achieving target BP goals is a comprehensive monitoring plan, which considers the following:

- In patients in whom healthy lifestyle changes alone are recommended (ie, elevated BP or stage 1 hypertension without clinical ASCVD, CKD, DM, and estimated 10-year CVD risk < 10%), BP should be reassessed every 3 to 6 months.
- In patients starting pharmacologic therapy, BP and HR should be measured at monthly intervals, or more frequently in patients with marked elevations or significant comorbidities (eg, HF, CKD) until BP goal is achieved.
- Monitor renal function and electrolytes within 2 to 4 weeks of initiating or increasing doses of antihypertensive

Table 5–8

Parenteral Antihypertensive Agents for Hypertensive Emergency and Special Conditions[28]

Drug	Dose Range[a]	Onset	Duration	Adverse Effects[b]	Special Indications
Adrenergic inhibitors					
Esmolol hydrochloride	500–1000 mcg/kg/min IV over 1 minute, then 50 mcg/kg/min by infusion; may repeat bolus after 5 minutes at 50 mcg/kg/min increment; maximum 200 mcg/kg/min	1–2 minutes	10–20 minutes	Nausea, asthma, first-degree heart block, HF	Preferred agent for acute aortic dissection, ACS and perioperative hypertension. Avoid use in combination with β-blocker therapy, bradycardia or decompensated HF.
Labetalol hydrochloride	0.3–1 mg/kg (maximum 20 mg) slow IV injection or 0.4–1 mg/kg/h IV infusion up to 3 mg/kg/h; may repeat every 4–6 hours; maximum total cumulative dose 300 mg	5–10 minutes	3–6 hours	Vomiting, scalp tingling, dizziness, asthma, COPD, nausea, heart block, orthostatic hypotension, HF	Most hypertensive emergencies, including eclampsia and preeclampsia. Avoid use in reactive airway disease, second- or third-degree heart block or bradycardia.
Phentolamine	5 mg IV bolus, may repeat every 10 minutes	1–2 minutes	10–30 minutes	Tachycardia, flushing, headache, nausea, vomiting	Catecholamine excess such as adrenergic crisis secondary to pheochromocytoma or cocaine or amphetamine overdose or clonidine withdrawal.
Angiotensin converting enzyme inhibitors					
Enalaprilat	1.25 mg IV over 5 minutes, may increase to 5 mg and repeat every 6 hours	15–30 minutes	6–12 hours	Precipitous fall in pressure in high-renin states; variable response	High plasma renin activity; avoid in acute MI, bilateral renal stenosis, pregnancy.
Dihydropyridine calcium channel blockers					
Clevidipine	Initial 1–2 mg/hour IV, doubling every 90 seconds until BP at target, then increasing by less than doubling every 5–10 minutes; maximum 32 mg/hour	2–4 minutes	5–15 minutes; maximum 72 hours	Atrial fibrillation, fever, insomnia, nausea, headache, vomiting, postprocedural hemorrhage, acute renal failure, respiratory failure	Most hypertensive emergencies. Avoid use if hypersensitivity to soy or egg products, pathological hyperlipidemia, lipoid nephrosis, or acute pancreatitis. Use low-end dose range for elderly.
Nicardipine hydrochloride	Initial 5 mg/hour IV, increasing by 2.5 mg/hour every 5 min; maximum 15 mg/hour	5–10 minutes	15–30 minutes, may exceed 4 hours	Tachycardia, headache, flushing, local phlebitis	Preferred agent for most hypertensive emergencies, pregnancy, except acute pulmonary edema. Avoid use in acute aortic dissection. No dose adjustment needed for elderly.
Dopamine$_1$-receptor agonist					
Fenoldopam mesylate	0.1–0.3 mcg/kg/min as IV infusion[c]	< 5 minutes	30 minutes	Tachycardia, headache, nausea, flushing	Preferred agent in acute renal failure. Avoid use in glaucoma, elevated intracranial pressure, and sulfite allergy.
Vasodilators					
Hydralazine hydrochloride	Initial 10 mg as slow IV infusion; maximum initial dose 20 mg; repeat every 4–6 hours as needed	10–20 minutes 20–30 minutes	1–4 hours IV	Tachycardia, flushing, headache, vomiting, aggravation of angina	Preferred agent in pregnancy. Not a first-line in most patients due to unpredictability of response and prolonged duration of action.

(*Continued*)

Table 5–8

Parenteral Antihypertensive Agents for Hypertensive Emergency and Special Conditions[28] (*Continued*)

Drug	Dose Range[a]	Onset	Duration	Adverse Effects[b]	Special Indications
Nitroglycerin	Initial 5 mcg/min as IV infusion; increase in increments of 5 mcg/min to achieve BP target; maximum dose 20 mcg/min	2–5 minutes	5–10 minutes	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Preferred agent in ACS, acute pulmonary edema, and perioperative hypertension
Sodium nitroprusside	Initial 0.3–0.5 mcg/kg/min as IV infusion[d]; increase in increments of 0.5 mcg/kg/min to achieve BP target; maximum dose 10 mcg/kg/min	Immediate	1–2 minutes	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Preferred agent in acute pulmonary edema. Use low dose range for elderly.

[a]These doses may vary from those in the *Physicians' Desk Reference.*

[b]Hypotension may occur with all agents.

[c]Requires special delivery system.

[d]Requires special delivery system. For infusion rates over or equal to 4–10 mcg/kg/min or duration more than 30 minutes, coadminister thiosulfate to prevent cyanide toxicity.

ACS, acute coronary syndrome; BP, blood pressure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; IV, intravenous; MI, myocardial infarction.

Data from Whelton PK CR, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2017; and Saseen JJ, Maclaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill, 2017:74.

Table 5–9

Treatment of Chronic Hypertension in Pregnancy[3,49]

Agent	Category[a]	Comments
Methyldopa	B/C	Preferred first-line therapy on the basis of long-term follow-up studies supporting safety after exposure in utero. Surveillance data do not support an association between drug and congenital defects when the mother took the drug early in the first trimester
Labetalol	C	Increasingly preferred to methyldopa because of reduced side effects. The agent does not seem to pose a risk to the fetus, except possibly in the first trimester
β-Blockers	B/C/D	Generally acceptable on the basis of limited data. Reports of intrauterine growth restriction with atenolol in the first and second trimesters B: acebutolol, pindolol, sotalol C: esmolol, metoprolol, nadolol, nebivolol, penbutolol, propranolol, timolol D: atenolol
Clonidine	C	Limited data; no association between drug and congenital defects when the mother took the drug early in the first trimester, but number of exposures is small
Calcium channel antagonists	C	Limited data; nifedipine in the first trimester was not associated with increased rates of major birth defects, but animal data were associated with fetal hypoxemia and acidosis. This agent should probably be limited to mothers with severe hypertension
Thiazide-type diuretics	B	Not first-line agents; probably safe; available data suggest that throughout gestation, a diuretic is not associated with an increased risk of major fetal anomalies or adverse fetal-neonatal events
Angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and direct renin inhibitors	D	Should be discontinued as soon as possible. Can cause injury and death to the developing fetus

[a]Based on the US Food and Drug Administration (FDA) pregnancy risk categories. See additional information at the FDA website for the updated Pregnancy and Lactation Labeling.

therapy that may affect these parameters (eg, diuretics, aldosterone antagonists, ACE-Is, and ARBs). Earlier monitoring should be considered in those with CKD, baseline electrolyte abnormalities, or HF.

- Increase the dose of initial drug (replace with an alternative if adverse event or no significant reduction in BP) or add an additional drug to current regimen if BP goal is not reached.
- Once BP target is achieved, monitor patient every 3 to 6 months to assess BP control, electrolytes and renal function as appropriate, clinical status and target organ damage.
- Implement lifestyle changes that address risk factors for CVD such as obesity, physical inactivity, insulin resistance, dyslipidemia, smoking cessation, need for low dose aspirin, or statin therapy.
- Monitor for efficacy, adverse events, drug interactions, and adherence to therapy as keys to achieving the long-term goals of reducing risk of morbidity and mortality associated with CVD.

Patient Care Process

Collect Information:

- Perform a medication history including prescription and nonprescription medications, herbal products, and dietary supplements as well as history of allergies to medications or other substances.
- Obtain health data including personal and family medical history, past surgeries/procedures, immunization status, fall risk, health and wellness information, laboratory and physical assessment findings.
- Speak with patient and review records to obtain lifestyle habits (eg, sodium intake, cooking practices, physical activity, use of alcohol/tobacco/recreational drugs), preferences and beliefs, health literacy, cultural factors, health and functional goals, and socioeconomic factors that affect access to medications and other aspects of care.

Assess the Information:

- Document current BP and heart rate (office, HBP or 24 hour-ABPM or AOBP results if available).
- Identify any substances or lifestyle habits that could adversely affect BP control or negatively interact with current medications.
- Based on medical history, physical examination, laboratory results, and review of systems determine whether patient has any target organ damage or comorbidities related to or associated with high BP or if experiencing any signs or symptoms of high BP.
- Calculate patient's 10-year risk of a cardiovascular event to establish BP threshold for initiation of pharmacologic therapy if stage 1 hypertension and no clinical ASCVD, DM, or CKD, and candidacy for other cardioprotective therapies (eg, statin therapy, antiplatelet therapy).
- Establish an appropriate BP goal.
- Determine patient's awareness and knowledge (eg, health literacy) of health effects of high BP and benefits and risks of treatment.
- Identify compelling indications for specific antihypertensives (Table 5–3) or specific considerations (eg, pregnancy [Table 5–9]).
- Evaluate appropriateness, effectiveness, safety (adverse events, drug interactions), and patient adherence to current pharmacotherapy.
- Review immunization status and need for preventive care and other health care services, where appropriate.

Develop a Care Plan:

- Collaborate with patient to identify feasible lifestyle modifications (Table 5–6).
- If patient is not at BP goal, determine whether antihypertensive pharmacotherapy is indicated, and select appropriate therapy based on compelling indications (Tables 5–2 and 5–3), specific patient characteristics (eg, pregnancy [Table 5–9]), and patient preferences.
- Utilize medications with complementary mechanisms of action and at doses that are optimal for patient (Table 5–7).
- Determine affordability of medications (eg, insurance coverage) and availability on health care formulary, if applicable.
- Engage and empower the patient through education and self-management.

Implement the Care Plan:

- Educate and provide resources about implementing lifestyle modifications and changes in drug therapy including medication administration, storage, adherence, and potential adverse effects and their management.
- Help patient select a self-monitoring device and seek commitment on a mutually agreed upon frequency of measurements.
- Advise patient on how to monitor, document, and report BP measurements as well as when to seek medical advice or care.
- Address any patient concerns about management of hypertension.
- Arrange for preventive care (eg, immunizations) and other health care services that were previously identified as warranted.

Follow-up: Monitor and Evaluate:

- Follow at monthly intervals or more frequently in patients with marked elevations or significant comorbidities (eg, HF, CKD), until BP goal is achieved.
- Review medication and lifestyle adherence, BP measurements, adequacy of BP control, and laboratory and other diagnostic tests to assess changes in clinical status and target organ damage.
- Determine whether patient is experiencing any adverse reactions or drug interactions.
- Once BP is controlled, monitor patient every 3 to 6 months to assess BP control, electrolytes and renal function as appropriate, clinical status, and target organ damage.

Abbreviations Introduced in This Chapter

ABPM	Ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE-I	Angiotensin-converting enzyme inhibitor
ACC	American College of Cardiology
ACR	Albumin-to-creatinine ratio
ACS	Acute coronary syndromes
AHA	American Heart Association
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALTITUDE	Aliskiren Trial In Type 2 Diabetes Using Cardio-renal End points
AOBP	Ambulatory office-based blood pressure
ARB	Angiotensin receptor blocker
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm
ASCVD	Atherosclerotic cardiovascular disease
AT1	Angiotensin-1
AT2	Angiotensin-2
BID	Twice daily
BP	Blood pressure
CAD	Coronary artery disease
CCB	Calcium channel blocker
CKD	Chronic kidney disease
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CVD	Cardiovascular disease
CYP	Cytochrome P450
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiogram
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HAART	Highly active antiretroviral therapy
HBP	Home blood pressure
HDL	High-density lipoprotein
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HYVET	Hypertension in the Very Elderly Trial
ISA	Intrinsic sympathomimetic activity
IV	Intravenous
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MAO	Monoamine oxidase
MI	Myocardial infarction
NAT-1	N-acetyltransferase-1
NSAID	Nonsteroidal anti-inflammatory drug
ONTARGET	Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
PRA	Plasma renin activity
PVR	Peripheral vascular resistance
QDay	Once daily
RAAS	Renin-angiotensin-aldosterone system
SBP	Systolic blood pressure
SHEP	Systolic Hypertension in the Elderly Program
SIHD	Stable ischemic heart disease
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
SNS	Sympathetic nervous system
TID	Three times daily
VALUE	Valsartan Antihypertensive Long-term Use Evaluation

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: a report from the American Heart Association. Circulation. 2017;135(10):e146–e603.
2. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. J Am Coll Cardiol. 2017: epub ahead of print.
3. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42(6):1206–1252.
4. Ferrario CM, Flack JM, Strobeck JE, Smits G, Peters C. Individualizing hypertension treatment with impedance cardiography: a meta-analysis of published trials. Ther Adv Cardiovasc Dis. 2010;4(1):5–16.
5. Laragh JH, Sealey JE. The plasma renin test reveals the contribution of body sodium-volume content (V) and renin-angiotensin (R) vasoconstriction to long-term blood pressure. Am J Hypertens. 2011;24(11):1164–1180.
6. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community. J Clin Hypertens. 2014;16(1):14–26.
7. O'Brien E, Parati G, Stergiou G, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31(9):1731–1768.
8. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: World Health Organization; 2014.
9. Kaplan NM, Victor RG. Kaplan's Clinical Hypertension. Philadelphia: Lippincott Williams & Wilkins; 2015.
10. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. Circulation. 2008;117(25):e510–e526.
11. Grossman A, Messerli FH, Grossman E. Drug induced hypertension—an unappreciated cause of secondary hypertension. Eur J Pharmacol. 2015;763:15–22.
12. Parra D, Hough A. Current therapeutic approaches to cardio-protection in hypertension. Curr Hypertens Rep. 2014;16(8):1–12.
13. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. N Eng J Med. 2014;371(7):624–634.
14. Franco V, Oparil S. Salt sensitivity, a determinant of blood pressure, cardiovascular disease and survival. J Am Coll Nutr. 2006;25(suppl 3):247S–255S.
15. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press. 2013;22(4):193–278.
16. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals. Circulation. 2005;111(5):697–716.
17. Wright JT, Jr., Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood pressure control. N Eng J Med. 2015;373(22):2103–2116.
18. Cushman WC EG, Byington RP, Goff DC, Jr., et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Eng J Med. 2010;362:1575–1585.
19. Benavente OR, Coffey CS, Conwit R, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet. 2013;382(9891):507–515.
20. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk

hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. JAMA. 2002;288(23):2981–2997.
21. Hermida RC, Ayala DE, Mojón A, Fernández JR. Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int. 2010;27(8):1629–1651.
22. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2960–2984.
23. Mitka M. IOM report: evidence fails to support guidelines for dietary salt reduction. JAMA. 2013;309(24):2535–2536.
24. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Eng J Med. 2001;344(1):3–10.
25. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895–906.
26. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363(9426):2022–2031.
27. Izzo JL, Sica DA, Black HR, Council for High Blood Pressure Research. Hypertension primer. The Essentials of High Blood Pressure: Basic Science, Population Science, and Clinical Management, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
28. Saseen JJ, MacLaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, et al. (eds.). Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill Education; 2017:45–77.
29. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertens. 2006; 47(3):352–358.
30. National Institute for Health and Clinical Excellence. Hypertension: the clinical management of primary hypertension in adults. Clinical guideline 127. August 2011. https://www.ncbi.nlm.nih.gov/pubmed/22855971. Accessed January 4, 2018.
31. Carter BL, Einhorn PT, Brands M, et al. Thiazide-induced dysglycemia. Hypertens. 2008;52(1):30–36.
32. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–520.
33. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. J Am Coll Cardiol. 2011;57(20):2037–2114.
34. De Souza F, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. Hypertens. 2010;55(1):147–152.
35. Lindholm LH, Carlberg B, Samuelsson O. Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis. Lancet. 2005;366(9496):1545–1553.
36. Rosendorff C, Lackland DT, Allison M, et al. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. J Am Soc Hypertens. 2015;9(6):453–498.
37. Weber MA. The role of the new β-blockers in treating cardiovascular disease. Am J Hypertens. 2005;18(12):169–176.
38. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting–enzyme inhibitors and diuretics for hypertension in the elderly. N Eng J Med. 2003;348(7):583–592.
39. ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Eng J Med. 2008;358:1547–1559.
40. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet. 2008;372(9638):547–553.
41. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. Circulation. 2013;62(16):e147–e239.
42. Parving H-H, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Eng J Med. 2012;367(23):2204–2213.
43. Cameron HA, Ramsay LE. The lupus syndrome induced by hydralazine: a common complication with low dose treatment. Brit Med J. 1984;289(6442):410–412.
44. Reisin E, Harris RC, Rahman M. Commentary on the 2014 BP guidelines from the panel appointed to the Eighth Joint National Committee (JNC 8). J Am Soc Nephrol. 2014;25(11):2419–2424.
45. Hoffman RS, Howland MA, Lewin NA, Nelson L, Goldfrank LR, Flomenbaum N. Goldfrank's Toxicologic Emergencies, 10th ed. Hoffman RS, Howland MA, Lewin NA, et al. (eds.). New York: McGraw-Hill; 2015.
46. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail. 2017;23(8):628–651.
47. Marik PE, Varon J. Hypertensive crises: challenges and management. Chest. 2007;131(6):1949–1962.
48. Beckett NS Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Eng J Med. 2008;358:1887–1898.
49. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol. 2013;122(5):1122–1133.
50. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3): epub ahead of print.

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6 Heart Failure

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LEARNING OBJECTIVES

LO

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

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

INTRODUCTION

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

HF results from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood, and can be classified based on the phase of the cardiac cycle leading to impaired ventricular function.[1] A normal cardiac cycle depends on two components: systole and diastole. Expulsion of blood occurs during systole, or contraction of the ventricles; diastole relates to filling of the ventricles. Ejection fraction (EF) is the fraction of the volume present at the end of diastole that is pushed into the aorta during systole. Abnormal ventricular filling (diastolic dysfunction) and/or ventricular contraction (systolic dysfunction) can result in similar decrease in CO and cause HF symptoms. HF is commonly associated with evidence of left ventricular (LV) systolic dysfunction (evidenced by a reduced EF, or left ventricular ejection fraction [LVEF] ≤ 40% [0.40]), and when accompanied by symptoms is also known as HF with reduced ejection fraction, or HFrEF. HF can occur with or without a component of diastolic dysfunction which coexists in up to two-thirds of patients. Isolated diastolic dysfunction, occurring in approximately one-third to one-half of HF patients, is diagnosed when a patient exhibits impaired ventricular filling without accompanying HF symptoms but normal systolic function, defined as LVEF 50% (0.50) or greater. When isolated diastolic dysfunction occurs with symptoms of HF, this is referred to as HF with preserved ejection fraction (HFpEF). Long-standing hypertension is the leading cause of HFpEF. Patients with symptoms of HF and an LVEF between 41% and 49% (0.41 and 0.49) are termed to have HF with mid-range ejection fraction (HFmrEF). Ventricular dysfunction can also involve either the left or right chamber of the heart or both. This has implications for symptomatology because predominant right-sided failure manifests as systemic congestion, whereas predominant left-sided failure results in pulmonary symptoms.

Thus, HF is a clinical syndrome characterized by a history of specific signs and symptoms related to congestion and hypoperfusion. Because HF can occur in the presence or absence of fluid overload, the term *heart failure* is preferred over the former term *congestive heart failure*. The term *acute heart failure* (AHF) is used to signify either an acute decompensation of a patient with a history of chronic HF or to refer to a patient presenting with new-onset HF symptoms. Many disorders, such as those of the pericardium, epicardium, endocardium, or great vessels, may lead to HF, but most patients develop symptoms due to impairment in LV myocardial function. Terms commonly associated with HF, such as ***cardiomyopathy*** and *LV dysfunction,* are not equivalent to HF but describe possible structural or functional reasons for the development of HF.

EPIDEMIOLOGY

HF is a major public health concern affecting approximately 6.5 million people in the United States. An additional 960,000 new cases are diagnosed each year. HF manifests most commonly in adults older than 60 years.[2] The growing prevalence of HF corresponds to (a) better treatment of patients with acute myocardial infarctions (MIs) who will survive to develop HF later in life, and (b) the increasing proportion of older adults due to the aging baby boomer population. The relative incidence of HF is lower in women compared with men, but there is a greater prevalence in women overall due to their longer life expectancy.

Acute HF accounts for 12 to 15 million office visits per year and 6.5 million hospitalizations annually, and HF is the most common hospital discharge diagnosis for Medicare patients and the most costly diagnosis in this population.[2] According to national registries, patients presenting with AHF are older (mean age: 75 years) and have numerous comorbidities such as coronary artery disease (CAD), renal insufficiency, and diabetes. Total estimated direct and indirect costs for managing both chronic and acute HF in the United States for 2012 was approximately $30.7 billion. Medications account for approximately 10% of that cost.[2]

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

ETIOLOGY

LO 1

HF is the eventual outcome of numerous cardiac diseases or disorders (Table 6–1).[5] HF can be classified by the primary underlying etiology as ischemic or nonischemic, with 70% related to ischemia. KEY CONCEPT The most common causes of HF are CAD, hypertension, and dilated cardiomyopathy. CAD resulting in acute MI and reduced ventricular function is a common presenting history.

Table 6–1

Causes of Heart Failure

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

Diastolic Dysfunction (Restriction in Ventricular Filling)
- Increased ventricular stiffness
- Ventricular hypertrophy (eg, hypertrophic cardiomyopathy, pressure and/or volume overload)
- Infiltrative myocardial diseases (eg, amyloidosis, sarcoidosis, endomyocardial fibrosis)
- Myocardial ischemia and infarction
- Mitral or tricuspid valve stenosis
- Pericardial disease (eg, pericarditis, pericardial tamponade)

Nonischemic Etiologies
- Hypertension
- Viral illness
- Thyroid disease
- Excessive alcohol use
- Illicit drug use
- Pregnancy-related heart disease
- Familial congenital disease
- Valvular disorders such as mitral or tricuspid valve regurgitation or stenosis

From Parker RB, Nappi JM, Cavallari LH. Chronic heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:80, with permission.

PATHOPHYSIOLOGY

A basic grasp of normal cardiac function sets the stage for understanding the pathophysiological processes leading to HF and selecting appropriate therapy for HF. CO is defined as the volume of blood ejected per unit of time (L/min) and is a major determinant of tissue perfusion. CO is the product of heart rate (HR) and stroke volume (SV): CO = HR × SV. The following sections describe how each parameter relates to CO.

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

Compensatory Mechanisms

In the setting of a sustained loss of myocardium (such as after an acute MI), a number of mechanisms aid the heart when faced with an increased hemodynamic burden and reduced CO. They include the Frank-Starling mechanism, tachycardia and increased afterload, and cardiac hypertrophy and remodeling (Table 6–2).[5,7]

▶ *Preload and the Frank-Starling Mechanism*

LO 2

In the setting of a sudden decrease in CO, the natural response of the body is to decrease blood flow to the periphery to maintain perfusion to vital organs such as the heart and brain. Therefore, renal perfusion is compromised due to both decreased CO as well as shunting of blood away from peripheral tissues. This results in activation of the renin-angiotensin-aldosterone system (RAAS). The decrease in renal perfusion is sensed by the juxtaglomerular cells of the kidneys leading to the release of renin and initiation of the cascade for production of angiotensin II. Angiotensin II stimulates the synthesis and release of aldosterone. Aldosterone in turn stimulates sodium and water retention in an attempt to increase intravascular volume and hence preload. In a healthy heart, a large increase in CO is usually accomplished with just a small change in preload. However, in a failing heart, alterations in the contractile filaments reduce the ability of cardiomyocytes to adapt to increases in preload. Thus, an increase in preload actually impairs contractile function in the failing heart and results in a further decrease in CO. See Figure 6–1.

Table 6–2

Beneficial and Detrimental Effects of the Compensatory Responses in Heart Failure[5,7]

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

BP, blood pressure; MVO_2, myocardial oxygen consumption; SNS, sympathetic nervous system.

► *Tachycardia and Increased Afterload*

LO 2

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

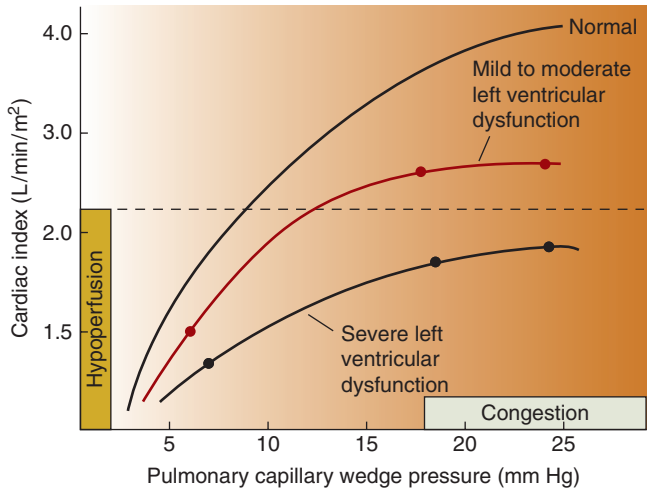

FIGURE 6–1. Relationship between cardiac output (shown as cardiac index) and preload (shown as pulmonary capillary wedge pressure). Cardiac index is expressed in conventional units of L/min/m², and can be converted to SI units of L/s/m² by multiplying by 0.0167. (Reproduced, with permission, from Parker RB, Nappi JM, Cavallari LH. Chronic heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:83.)

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

► *Cardiac Remodeling and Ventricular Hypertrophy*

Cardiac remodeling occurs as a compensatory adaptation to a change in wall stress and is largely regulated by neurohormonal activation, with angiotensin II and aldosterone being key stimuli.[7] The process entails changes in myocardial and extracellular matrix composition and function that results in both structural and functional alterations to the heart. In HF, the changes in cardiac size, shape, and composition are pathological and detrimental to heart function. In addition to myocyte size and extracellular matrix changes, heart geometry shifts from an elliptical to a less efficient spherical shape. Even after remodeling occurs, the heart can maintain CO for many years. However, heart function continues to deteriorate until progression to clinical HF. The timeline for remodeling varies depending on the cardiac insult. For example, in the setting of an acute MI, remodeling starts within a few days.[6] Chronic remodeling, however, is what progressively worsens HF, and therefore is a major target of drug therapy.

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

Neurohormonal Model of Heart Failure

KEY CONCEPT Development and progression of HF involves activation of neurohormonal pathways including the SNS and the RAAS. This model begins with an initial precipitating event or myocardial injury resulting in a decline in CO, followed by the compensatory mechanisms previously discussed. Activation of neurohormonal pathways with pathological consequences include the RAAS, SNS, endothelin, and vasopressin, as well as those with counterregulatory properties such as the natriuretic peptides and nitric oxide. This model currently guides our therapy for chronic HF in terms of preventing disease progression and mortality.

▶ *Angiotensin II*

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

▶ *Aldosterone*

Aldosterone's contribution to HF pathophysiology is multifaceted. Renally, aldosterone causes sodium and water retention in an attempt to enhance intravascular volume and CO. This adaptive mechanism has deleterious consequences because excessive sodium and water retention worsen the already elevated ventricular filling pressures. Aldosterone also contributes to electrolyte abnormalities seen in HF patients. Hypokalemia and hypomagnesemia contribute to the increased risk of arrhythmias. In addition, evidence supports the role of aldosterone as an etiological factor for myocardial fibrosis and cardiac remodeling by causing increased extracellular matrix collagen deposition and cardiac fibrosis.[6] Aldosterone potentially contributes to disease progression via sympathetic potentiation and ventricular remodeling. In addition, the combination of these multiple effects is likely responsible for the increased risk of sudden cardiac death attributed to aldosterone. As elevated aldosterone concentrations have been associated with a poorer prognosis in HF, its blockade has become an important therapeutic target for improvement of long-term prognosis.

▶ *Norepinephrine*

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

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

▶ *Endothelin*

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

▶ *Arginine Vasopressin*

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

▶ *Counterreulatory Hormones (Natriuretic Peptides, Bradykinin, and Nitric Oxide)*

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

Bradykinin is part of the kallikrein-kinin system, which shares a link to the RAAS through ACE. Bradykinin is a vasodilatory peptide that is released in response to a variety of stimuli, including neurohormonal and inflammatory mediators known to be activated in HF.[9] As a consequence, bradykinin levels are elevated in HF patients and thought to partially antagonize the vasoconstrictive peptides.

Nitric oxide, a vasodilatory hormone released by the endothelium, is found in higher concentrations in HF patients and provides two main benefits in HF: vasodilation and neurohormonal antagonism of endothelin.[9] Nitric oxide's production is affected by the enzyme inducible nitric oxide synthetase (iNOS), which is upregulated in the setting of HF,

Table 6–3

Exacerbating or Precipitating Factors in Heart Failure (HF)[5]

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

COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

likely due to increased levels of angiotensin II, norepinephrine, and multiple cytokines. In HF, the physiological response to nitric oxide appears to be blunted, which contributes to the imbalance between vasoconstriction and vasodilation.

▶ *Proinflammatory Cytokines*

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

Precipitating and Exacerbating Factors in Heart Failure

HF patients exist in one of two clinical states. When a patient's volume status and symptoms are stable, their HF condition is said to be "compensated." In situations of volume overload or other worsening symptoms, the patient is considered "decompensated." Acute decompensation can be precipitated by numerous etiologies (Table 6–3).[5]

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

CLINICAL PRESENTATION AND DIAGNOSIS OF HEART FAILURE

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

LO 3

LO 3

General Signs and Symptoms

LO 3 Refer to the Clinical Presentation and Diagnosis of Chronic Heart Failure textbox for additional descriptions of signs and symptoms.

Patients can experience a variety of symptoms related to buildup of fluid. The most recognized finding of systemic venous congestion related to RVF is peripheral edema. It usually occurs in dependent areas of the body, such as the ankles (pedal edema) for ambulatory patients or the sacral region for bedridden patients. Patients may complain of swelling of their feet and ankles, which can extend up to their calves or thighs. Abdominal congestion may cause a bloated feeling, abdominal pain, early satiety, nausea, anorexia, and constipation. Abdominal edema can lead to delayed absorption of oral medications, including diuretics used to treat congestion. Often patients may have difficulty fitting into their shoes or pants due to edema. Weight gain often precedes signs of overt peripheral edema. Therefore, it is crucial for patients to weigh themselves daily even in the absence of symptoms to assess fluid status.

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

It is important to note that in chronic severe HF, unintentional weight loss can occur that leads to a syndrome of cardiac

Clinical Presentation and Diagnosis of Chronic Heart Failure

General

Patient presentation may range from asymptomatic to cardiogenic shock.

Symptoms

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

Signs

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

Laboratory Tests

- BNP greater than 100 pg/mL (ng/L; 28.9 pmol/L) or N-terminal proBNP (NT-proBNP) greater than 300 pg/mL (ng/L; 35.4 pmol/L).
- Electrocardiogram (ECG): May be normal or could show numerous abnormalities including acute ST-T–wave changes from myocardial ischemia, atrial fibrillation, bradycardia, and LV hypertrophy.
- Serum creatinine: May be increased owing to hypoperfusion; preexisting renal dysfunction can contribute to volume overload.
- Complete blood count: Useful to determine if HF is due to reduced oxygen-carrying capacity.
- Chest x-ray: Useful for detection of cardiac enlargement, pulmonary edema, and pleural effusions.
- Echocardiogram: Used to assess LV size, valve function, pericardial effusion, wall motion abnormalities, and ejection fraction.

cachexia, defined as a nonedematous weight loss more than 6% of the previous normal weight over a period of at least 6 months. HF prognosis worsens considerably once cardiac cachexia has been diagnosed, regardless of HF severity. This results from several factors including loss of appetite, malabsorption due to GI edema, elevated metabolic rate, and elevated levels of norepinephrine and proinflammatory cytokines. Absorption of fats is especially affected, leading to deficiencies of fat-soluble vitamins.

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

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

Pulmonary congestion may also cause a nonproductive cough that occurs at night or with exertion. Not all patients with LVF will exhibit signs of pulmonary congestion if lymphatic clearance is intact. In cases of pulmonary edema, the most severe form of pulmonary congestion, patients may produce pink frothy sputum and experience extreme breathlessness and anxiety due to feelings of suffocation and drowning. If not treated aggressively, patients can become cyanotic and acidotic. Severe pulmonary edema can progress to respiratory failure, necessitating mechanical ventilation.

▶ *Patient History*

A thorough history is crucial to identify cardiac and noncardiac disorders or behaviors that may lead to or accelerate the development of HF. Past medical history, family history, and

Table 6–4

Drugs That May Precipitate or Exacerbate Heart Failure

Negative Inotropic Effect
- Antiarrhythmics (eg, disopyramide, flecainide, propafenone)
- β-Blockers (eg, propranolol, metoprolol, carvedilol)
- Calcium channel blockers (eg, verapamil, diltiazem)
- Itraconazole

Cardiotoxic
- Doxorubicin
- Epirubicin
- Daunomycin
- Cyclophosphamide
- Trastuzumab
- Bevacizumab
- Mitoxantrone
- Ifosfamide
- Mitomycin
- Lapatinib
- Sunitinib
- Imatinib
- Ethanol
- Amphetamines (eg, cocaine, methamphetamine)

Sodium and Water Retention
- NSAIDs
- COX-2 inhibitors
- Rosiglitazone and pioglitazone
- Glucocorticoids
- Androgens and estrogens
- Salicylates (high dose)
- Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)

Uncertain Mechanism
- Adalimumab
- Etanercept
- Infliximab

COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

From Parker RB, Nappi JM, Cavallari LH. Chronic heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:86, with permission.

social history are important for identifying comorbid illnesses that are risk factors for the development of HF or underlying etiological factors. A complete medication history (including prescription and nonprescription drugs, herbal therapy, and vitamin supplements) should be obtained each time a patient is seen to evaluate adherence, to assess appropriateness of therapy, to eliminate drugs that may be harmful in HF (Table 6–4), and to determine additional monitoring requirements.[5] For newly diagnosed HF, previous use of radiation or chemotherapeutic agents as well as current or past use of alcohol and illicit drugs should be assessed. In addition, for patients with a known history of HF, questions related to symptomatology and exercise tolerance are essential for assessing any changes in clinical status that may warrant further evaluation or adjustment of the medication regimen.

Heart Failure Classification

LO 3

There are two common systems for categorizing patients with HF. The New York Heart Association (NYHA) Functional Classification (FC) system is based on the patient's activity level and exercise tolerance. It divides patients into one of four classes, with functional class I patients exhibiting no symptoms or limitations of daily activities, and functional class IV patients who are symptomatic at rest (Table 6–5). The NYHA FC system reflects a subjective assessment by a health care provider and can change frequently over short periods of time. In general, anticipated survival declines in conjunction with a decline in functional ability.

Table 6–5

New York Heart Association (NYHA) Functional Classification and American College of Cardiology/ American Heart Association (ACC/AHA) Staging

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

Patient Encounter Part 1

A 71-year-old man with a long-standing history of known hypertension and dyslipidemia presents for follow-up. His most bothersome complaint is coughing at night and an inability to lie down flat without feeling breathless. He has to sleep on a few pillows to get adequate rest and sometimes even that does not help as he wakes up in the middle of the night feeling short of breath. Although he used to be able to walk a few blocks and two to three flights of stairs comfortably before getting breathless, he has had increasing symptoms after one flight of stairs. He also notes his ankles are always swollen and his wedding ring feels tight on his finger. Additionally his appetite is decreased and he has difficulty finishing his meals, becoming full after only a few bites.

What information is suggestive of a diagnosis of HF?

What additional information do you need to create a treatment plan?

The American College of Cardiology/American Heart Association (ACC/AHA) have proposed another system based on the development and progression of the disease. Instead of classifications, patients are placed into stages A through D (Table 6–5).[1] Because the staging system is related to development and progression of cardiac function and the HF syndrome, it also proposes management strategies for each stage including risk factor modification. The staging system is meant to complement the NYHA FC system; however, patients can move between NYHA functional classes as symptoms improve with treatment, whereas HF staging does not allow for patients to move to a lower stage (eg, stage C patients will never revert to stage B, even after treatment). Currently, patients are categorized based on both systems. Functional classification and staging are useful from a clinician's perspective, allowing for longitudinal assessment of a patient's risk and progress, requirements for nonpharmacologic interventions, response to medications, and overall prognosis.

TREATMENT OF CHRONIC HEART FAILURE

Desired Therapeutic Outcomes

LO 4 There is no cure for HF. KEY CONCEPT The general therapeutic management goals for chronic HF include preventing the onset of clinical symptoms or reducing symptoms, preventing or reducing hospitalizations, slowing progression of the disease, improving quality of life, and prolonging survival. The ACC/AHA staging system provides a guide for application of these goals based on the clinical progression of HF for a given patient. The goals are additive as one moves from stage A to stage D.[1] For stage A, risk factor management is the primary goal because it reduces onset of clinical symptoms. Stage B includes the addition of pharmacologic therapies known to slow the disease progression in an attempt to prevent the onset of clinical symptoms. Stage C involves the use of additional therapies aimed at controlling symptoms and decreasing morbidity. Finally, in stage D, the focus shifts toward palliative care and other quality-of-life related issues. Only with aggressive management throughout all the stages can the odds of survival be improved. Attainment of these goals is based on designing a therapeutic approach that encompasses strategies aimed at control and treatment of contributing disorders, nonpharmacologic interventions, and optimal use of pharmacologic therapies.[11]

Control and Treatment of Contributing Disorders

All causes of HF must be investigated to determine the etiology of cardiac dysfunction. The most common etiology of HF in the United States is ischemic heart disease. An ischemic workup that includes stress testing, echocardiography, and coronary angiography is warranted with a history suggestive of underlying CAD, and may be considered in patients who newly exhibit reduced LVEF. Revascularization of those with significant CAD may help restore some cardiac function in patients with reversible ischemic defects. Aggressive control of hypertension (with BP-lowering medication required in most patients with HF and a BP of 130/80 mm Hg or higher), diabetes, and obesity is also essential because each of these conditions, uncontrolled, can cause further cardiac damage. Surgical repair of valvular disease or congenital malformations may be warranted if detected. Clinical HF partly depends on metabolic processes, so correction of imbalances such as thyroid disease, anemia, and nutritional deficiencies is important. Identifying and discontinuing medications that can exacerbate HF is also an important intervention.

Nonpharmacologic Interventions

LO 5 It is imperative that patients recognize the role of self-management in HF. KEY CONCEPT Nonpharmacologic treatment involves dietary modifications such as sodium and fluid restriction, risk factor reduction including smoking cessation, timely immunizations, and supervised regular physical activity. Patient education regarding monitoring symptoms, dietary and medication adherence, exercise and physical fitness, risk factor reduction, and immunizations are important for the prevention of AHF exacerbations.

Patients should be encouraged to become involved in their own care which includes self-monitoring. Home monitoring for fluid status should include daily assessment of weight and exercise tolerance. Daily weights should be done first thing in the morning upon arising and before any food intake to maintain consistency. Patients should record their weight daily in a journal and bring this log to each clinic or office visit. Changes in weight can indicate fluid retention and congestion prior to onset of peripheral or pulmonary symptoms. Individuals who have an increase of 3 pounds (1.4 kg) in a single day or 5 pounds (2.3 kg) over a week should alert their HF care provider. Some patients may be educated about self-adjusting diuretic doses based on daily weights. In addition to weight changes, a marked decline in exercise tolerance should also be reported to the HF care provider.

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

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

LO 5 Exercise, although discouraged when the patient is acutely decompensated to limit cardiac workload, is recommended when patients are stable. The heart is a muscle that requires activity to prevent atrophy. In addition, exercise improves peripheral muscle conditioning and efficiency, which may contribute to better exercise tolerance despite the low CO state. Regular low intensity, aerobic exercise that includes light house/yard work,

Patient Encounter Part 2

Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension (unmanaged for at least a few years), dyslipidemia × 20 years, history of alcohol abuse × 30 years, history of migraines × 40 years

Allergies: No known drug allergies

Meds: Diltiazem CD 240 mg once daily, hydrochlorothiazide 25 mg once daily, atorvastatin 40 mg once daily for dyslipidemia, ibuprofen 600 mg twice daily as needed for headaches, vitamin B_{12} once daily, multivitamin daily, aspirin 81 mg once daily

FH: Significant for early heart disease in mother (MI at age 60)

SH: He is married, has one child, and runs his own business; he smokes 1½ packs per day and drinks at least 10 beers nightly.

PE:

BP 156/94 mm Hg, pulse 88 beats/min and regular, respiratory rate 16/min, Ht 5′8″ (173 cm), Wt 251 lb (114 kg), body mass index (BMI): 38.1 kg/m^2

Lungs: Rales bilaterally upon inspiration

CV: Regular rate and rhythm with normal S_1 and S_2; there is an S_3 and a soft S_4 present; there is a 2/6 systolic ejection murmur heard best at the left lower sternal border; point of maximal impulse is within normal limits at the midclavicular line

Abd: Soft, nontender, and bowel sounds are present, (+) HJR

Ext: 2+ pitting edema extending to below the knees is observed. JVP 13 cm

Chest x-ray: Cardiomegaly

Echocardiogram: EF = 30% (0.30)

Laboratory Values:

Hct: 41.1% (0.411)

WBC: 7.3 × 10^3/μL (7.3 × 10^9/L)

Sodium: 141 mEq/L (mmol/L)

Potassium: 4.2 mEq/L (mmol/L)

Bicarb: 30 mEq/L (mmol/L)

Chloride: 90 mEq/L (mmol/L)

Magnesium: 1.5 mEq/L (0.75 mmol/L)

Fasting blood glucose: 120 mg/dL (6.7 mmol/L)

Uric acid: 6 mg/dL (357 μmol/L)

BUN: 40 mg/dL (14.3 mmol/L)

SCr: 1.6 mg/dL (141 μmol/L)

Alk Phos: 120 IU/L (2.0 μkat/L)

Aspartate aminotransferase: 100 IU/L (1.67 μkat/L)

What other laboratory or diagnostic tests are required for assessment of the patient's condition?

How would you classify his NYHA FC and ACC/AHA HF stage?

Identify exacerbating or precipitating factors that may worsen his HF.

What are your treatment goals for the patient?

walking, swimming, or riding a bike is encouraged; heavy weight training is discouraged. The prescribed exercise regimen needs to be tailored to the individual's functional ability, and thus it is suggested that patients participate in cardiac rehabilitation programs, at least initially. It is important that patients not overexert themselves to fatigue or exertional dyspnea.

LO 5

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

In general, it is suggested that patients remain up-to-date on standard immunizations. Patients should be counseled to receive yearly influenza vaccinations. Additionally, pneumococcal vaccines are recommended.

Pharmacologic Treatment

LO 6

The ACC/AHA staging system delineates specific pharmacotherapy options based on disease progression.[1] For patients in stage A, every effort is made to minimize the impact of diseases that can injure the heart. Antihypertensive (specifically thiazide diuretics) and lipid-lowering therapies should be utilized when appropriate to decrease the risk for stroke, MI, and HF. ACE inhibitors should be considered in high-risk vascular disease patients. For stage B patients, the goal is to prevent or slow disease progression by interfering with neurohormonal pathways that lead to cardiac damage and mediate pathological remodeling. The goal is to prevent the onset of HF symptoms. The backbone of therapy in these patients includes ACE inhibitors or ARBs and β-blockers. In stage C patients with symptomatic LV systolic dysfunction (EF ≤ 40% [0.40]), the goals focus on alleviating fluid retention, minimizing disability, slowing disease progression, and reducing long-term risk for hospitalizations and death. Treatment entails a strategy that combines diuretics to control intravascular fluid balance with neurohormonal antagonists (including ACE inhibitors or ARBs or angiotensin receptor neprilysin inhibitor [ARNI], β-adrenergic blockers, and aldosterone receptor antagonists) to minimize the effects of the RAAS and SNS. In African American patients or patients with an allergy to ACE inhibitor/ARB, hydralazine and isosorbide dinitrate combination has been shown to be beneficial. Digoxin may be added to improve symptoms. Drug dosing and monitoring in the pharmacologic treatment of HF are described in Tables 6–6 and 6–7. Patients with advanced stage D disease are offered more modest goals, such as improvement in quality of life. Enhancing quality of life is often achieved at the expense of expected survival. Treatment options include mechanical support, transplantation, and continuous use of intravenous (IV) vasoactive therapies, in addition to maintaining an optimal regimen of chronic oral medications as possible.

Table 6–6

Drug Dosing in the Pharmacologic Treatment of Heart Failure

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Loop Diuretics					
Furosemide	Lasix®	20–40 mg once or twice daily	20–160 mg once or twice daily	CrCl 20–50 mL/min (0.33–0.83 mL/s): 160 mg once or twice daily CrCl < 20 mL/min (0.33 mL/s): 400 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Bumetanide	Bumex®	0.5–1.0 mg once or twice daily	1–2 mg once or twice daily	CrCl 20–50 mL/min (0.33–0.83 mL/s): 2 mg once or twice daily CrCl < 20 mL/min (0.33 mL/s): 8–10 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
Torsemide	Demadex®	10–20 mg once daily	10–80 mg once daily	CrCl 20–50 mL/min (0.33–0.83 mL/s): 40 mg once daily CrCl < 20 mL/min (0.33 mL/s): 200 mg daily	Single doses exceeding those listed are unlikely to elicit additional response
ACE Inhibitors					
Captopril	Capoten®	6.25 mg three times daily	50 mg three times daily[a]		
Enalapril	Vasotec®	2.5 mg twice daily	10–20 mg twice daily[a]		
Lisinopril	Zestril®, Prinivil®	2.5–5.0 mg once daily	20–40 mg once daily[a]		
Quinapril	Accupril®	5 mg twice daily	20–40 mg twice daily		
Ramipril	Altace®	1.25–2.5 mg	5 mg twice daily[a]		
Fosinopril	Monopril®	5–10 mg once daily	40 mg once daily		Undergoes both hepatic and renal elimination
Trandolapril	Mavik®	0.5–1.0 mg once daily	4 mg once daily[a]		Undergoes both hepatic and renal elimination
Perindopril	Aceon®	2 mg once daily	8–16 mg once daily		Undergoes both hepatic and renal elimination
Angiotensin Receptor Blockers					
Candesartan	Atacand®	4 mg once daily	32 mg once daily[a]		
Valsartan	Diovan®	20–40 mg twice daily	160 mg twice daily[a]		
Losartan	Cozaar®	25–50 mg once daily	150 mg once daily[a]		
Angiotensin Receptor Neprilysin Inhibitor (ARNI)					
Sacubitril/valsartan	Entresto®	49/51 mg sacubitril/valsartan twice daily	97/103 mg sacubitril/valsartan twice daily[a]	For patients taking a low dose of or not taking an ACE inhibitor or ARB or if eGFR is < 30 mL/min/1.73 m^2, the starting dose is 24/26 mg sacubitril/valsartan twice daily	Discontinue ACE inhibitors at least 36 hours before initiating sacubitril/valsartan treatment; allow 36 hours between discontinuing ARNI and starting ACE inhibitor
β-Blockers					
Bisoprolol	Zebeta®	1.25 mg once daily	10 mg once daily[a]		
Carvedilol	Coreg®	3.125 mg twice daily	25 mg twice daily[a]	Target dose for patients weighing > 85 kg (187 lb) is 50 mg twice daily	Take with food
Carvedilol phosphate	Coreg CR®	10 mg once daily	80 mg once daily[a]		Take with food
Metoprolol succinate CR/XL	Toprol-XL®	12.5–25 mg once daily	200 mg once daily[a]		
Aldosterone Receptor Antagonists					
Spironolactone	Aldactone®	eGFR ≥ 50 mL/min/1.73 m^2: 12.5–25 mg once daily	25–50 mg once daily[a]	eGFR 30–49 mL/min/1.73 m^2: 12.5 mg once daily or every other day	The risk of hyperkalemia increases if serum creatinine is > 1.6 mg/dL (141 µmol/L). Avoid if baseline potassium is ≥ 5 mEq/L (mmol/L)

(*Continued*)

Table 6–6

Drug Dosing in the Pharmacologic Treatment of Heart Failure (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Comments
Eplerenone	Inspra®	eGFR ≥ 50 mL/min/1.73 m^2: 25 mg once daily	50 mg once daily[a]	eGFR 30–49 mL/min/1.73 m^2: 25 mg every other day	The risk of hyperkalemia increases if serum creatinine is > 1.6 mg/dL (141 µmol/L). Avoid if baseline potassium is ≥ 5 mEq/L (mmol/L)
Other					
Hydralazine-Isosorbide Dinitrate	Bidil®	Hydralazine 37.5 mg three times daily; Isosorbide dinitrate 20 mg three times daily	Hydralazine 75 mg three times daily[a]; Isosorbide dinitrate 40 mg three times daily[a]		Indicated in conjunction with standard heart failure therapy to improve survival and reduce hospitalizations in self-identified African-American patients
Digoxin	Lanoxin®	0.125–0.25 mg once daily	0.125–0.25 mg once daily	Reduce dose in elderly patients with low lean body mass, and patients with impaired renal function	Target plasma concentration range is 0.5–0.9 ng/mL (mcg/L; 0.6–1.2 nmol/L). Does not improve survival in patients with HFrEF
Ivabradine	Corlanor®	5 mg twice daily	5–7.5 mg twice daily	Avoid if resting heart rate < 60 BPM before treatment	Indicated to reduce the risk of hospitalization in patients with HFrEF who are in normal sinus rhythm, with a resting heart rate ≥ 70 BPM receiving maximally tolerated β-blocker doses. Take with meals

[a]Regimens proven in large clinical trials to reduce mortality.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BPM, beats per minute; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction.

From Parker RB, Nappi JM, Cavallari LH. Chronic heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:95-96, with permission.

▶ *Diuretics*

LO 6 Diuretics have been the mainstay for HF symptom management for many years. KEY CONCEPT Diuretics are used for relief of acute symptoms of congestion and maintenance of euvolemia. These agents interfere with sodium retention by increasing urinary sodium and free water excretion. The primary rationale for the use of diuretic therapy is to maintain euvolemia in symptomatic or stages C and D HF. Diuretic therapy is recommended for all patients with clinical evidence of fluid overload. In mild HF, diuretics may be used on an as-needed basis. However, once the development of edema is persistent, regularly scheduled doses will be required.

Two types of diuretics are used for volume management in HF: thiazides and loop diuretics. Thiazide diuretics such as hydrochlorothiazide, chlorthalidone, and metolazone block sodium and chloride reabsorption in the distal convoluted tubule. Thiazides are weaker than loop diuretics in terms of affecting an increase in urine output and therefore are not utilized frequently as monotherapy. They are optimally suited for patients with hypertension who have mild congestion. Additionally, the action of thiazides is limited in patients with renal insufficiency (creatinine clearance [CrCL] < 30 mL/min [0.50 mL/s]) due to reduced secretion into their site of action. An exception is metolazone, which retains its potent action in patients with renal dysfunction. Metolazone is often used in combination with loop diuretics when patients exhibit diuretic resistance, defined as edema unresponsive to loop diuretics alone.

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

In patients with evidence of mild to moderate volume overload, diuretics should be initiated at a low dose and titrated to achieve a weight loss of up to 2 pounds (0.9 kg) per day. Patients with severe volume overload should be managed in an inpatient

Table 6–7

Drug Monitoring

Drug Class	Adverse Effect	Monitoring Parameters	Comments
ACE inhibitors	Angioedema, cough, hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis, history of angioedema, or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1–2 weeks after initiation or increase in dose. Goal is target dose from clinical trials or highest tolerated.
Angiotensin receptor blockers (ARB)	Hyperkalemia, hypotension, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with bilateral renal artery stenosis or pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1–2 weeks after initiation or increase in dose. Use with caution in patients with a history of ACE inhibitor-associated angioedema. Goal is target dose from clinical trials or highest tolerated.
Sacubitril/ valsartan	Angioedema, hyperkalemia, hypotension, dizziness, renal dysfunction	BP, electrolytes, BUN, and creatinine	Contraindicated in patients with a history of angioedema associated with ACE inhibitor or ARB therapy or in pregnancy. Assess BP, BUN, creatinine, and electrolytes at baseline and 1–2 weeks after initiation or increase in dose. Start with a low dose and double the dose every 2–4 weeks as tolerated based on BP, serum potassium, and renal function. Goal is target dose from clinical trials or highest tolerated.
Aldosterone receptor antagonists	Gynecomastia/breast tenderness/ menstrual irregularities (spironolactone), hyperkalemia, worsening renal function	BP, electrolytes, BUN, and creatinine	Assess BP, BUN, creatinine, and electrolytes at baseline. Check potassium 3 days and 1 week after initiation and then monthly for the first 3 months, then every 3 months. Change to eplerenone if gynecomastia develops with spironolactone.
β-Blockers	Bradycardia, heart block, bronchospasm, hypotension, worsening HF	BP, HR, ECG, signs and symptoms of worsening HF, blood glucose	Start with low dose and titrate upward no more often than every 2 weeks as tolerated based on BP, HR, and symptoms. Goal is target dose from clinical trials or highest tolerated. Patients may feel worse before they feel better.
Digoxin	GI and CNS adverse effects, brady- and tachyarrhythmias	Electrolytes, BUN, creatinine, ECG, serum digoxin concentration	Target serum digoxin concentration 0.5–0.9 ng/mL (mcg/L; 0.6–1.2 nmol/L).
Ivabradine	Bradycardia, hypertension, atrial fibrillation, luminous phenomena (phosphenes, transiently enhanced brightness in a portion of the visual field)	BP, HR, ECG	Start with 5 mg twice daily and after 2 weeks adjust dose to achieve a resting HR 50–60 BPM. Only use in patients in sinus rhythm.
Diuretics	Hypovolemia, hypotension, hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, renal dysfunction, thirst	BP, electrolytes, BUN, creatinine, glucose, uric acid, changes in weight, JVD	Dose should be adjusted based on volume status, renal function, electrolytes, and BP. Reassess these parameters 1–2 weeks after dose changes. Goal is lowest dose that maintains euvolemia.
Hydralazine	Hypotension, headache, rash, arthralgia, lupus, tachycardia	BP, HR	
Nitrates	Hypotension, headache, lightheadedness	BP, HR	

ACE, angiotensin-converting enzyme; BP, blood pressure; BPM, beats per minute; BUN, blood urea nitrogen; CNS, central nervous system; ECG, electrocardiogram; GI, gastrointestinal; HF, heart failure; HR, heart failure; JVD, jugular venous distention.

From Parker RB, Nappi JM, Cavallari LH. Chronic heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:96, with permission.

setting. Once diuretic therapy is initiated, dosage adjustments are based on symptomatic improvement and daily body weight. Because body weight changes are a sensitive marker of fluid retention or loss, patients should continue to weigh themselves daily. Once a patient reaches a euvolemic state, diuretics may be cautiously tapered and then withdrawn in appropriate patients. In stable, educated, and adherent patients, another option is self-adjusted diuretic dosing. Based on daily body weight, patients may temporarily increase their diuretic regimen to reduce the incidence of overt edema, or reduce diuretic doses in the setting of acute illness or exposure to hot temperatures such as during summer. Self-adjustment also avoids overuse of diuretics and possible complications of overdiuresis such as hypotension, fatigue, electrolyte imbalances, and renal impairment.

The maximal response to diuretics is reduced in HF, creating a "ceiling dose" above which there is limited added benefit. This diuretic resistance is due to a compensatory increase in sodium reabsorption in the distal tubules, which decreases the effect of blocking sodium reabsorption in the loop of Henle. In addition, there is a simultaneous increase in the reabsorption of sodium from the proximal tubule, allowing less to reach the site of action for loop diuretics. Apart from increasing diuretic doses, strategies to improve diuretic efficacy include increasing the frequency of dosing to two or three times daily, utilizing a continuous

infusion of a loop diuretic, and/or combining a loop diuretic with a thiazide diuretic. The latter strategy theoretically prevents sodium and water reabsorption at both the loop of Henle and the compensating distal convoluted tubule. Metolazone is used most often for this purpose because it retains its activity in settings of low CrCL. Metolazone can be dosed daily or as little as once weekly. This combination is usually maintained until the patient reaches his or her baseline weight. The clinician must use metolazone cautiously because its potent activity predisposes a patient to metabolic abnormalities as outlined next.

Diuretics cause numerous adverse effects and metabolic abnormalities, with severity linked to diuretic potency (Table 6–7). A particularly worrisome adverse effect is hypokalemia which can predispose patients to arrhythmias and sudden death. Hypomagnesemia often occurs concomitantly with diuretic-induced hypokalemia, and therefore both should be assessed and replaced in patients needing correction of hypokalemia. Magnesium is an essential cofactor for movement of potassium intracellularly to restore body stores. Patients taking diuretics are also at risk for renal insufficiency due to overdiuresis and reflex activation of the renin-angiotensin system. The potential reduction in renal blood flow and glomerular pressure is amplified by concomitant use of ACE inhibitors or ARBs.

► *Neurohormonal Blocking Agents*

KEY CONCEPT Agents with proven benefits in improving symptoms, slowing disease progression, and improving survival in chronic HF target neurohormonal blockade. These include ACE inhibitors, ARBs, ARNIs, β-adrenergic blockers, and aldosterone receptor antagonists (Tables 6–6 and 6–7).

LO 6

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

There is extensive clinical experience with ACE inhibitors in systolic HF. Numerous clinical studies show ACE inhibitor therapy is associated with improvements in clinical symptoms, exercise tolerance, NYHA FC, LV size and function, and quality of life as compared with placebo.[12-14] ACE inhibitors significantly reduce hospitalization rates and mortality regardless of underlying disease severity or etiology. ACE inhibitors are also effective in preventing HF development in high-risk patients. Studies in acute MI patients show a reduction in new-onset HF and death with ACE inhibitors whether they are initiated early (within 36 hours) or started later. In addition, ACE inhibition decreases the risk of HF hospitalization and death in patients with asymptomatic LV dysfunction. The exact mechanisms for decreased HF progression and mortality are postulated to involve both the hemodynamic improvement and the inhibition of AT_2's growth promoting and remodeling effects. All patients with documented LV systolic dysfunction, regardless of existing HF symptoms, should receive ACE inhibitors unless a contraindication or intolerance is present.

LO 6

There is no evidence to suggest that one ACE inhibitor is preferred over another. ACE inhibitors should be initiated using low doses and titrated up to target doses over several weeks depending on tolerability (adverse effects and BP). The ACC/AHA 2013 guidelines advocate using doses that were proven to decrease mortality in clinical trials as the target doses (Table 6–6).[1] If the target dose cannot be attained, the highest tolerated dose should be used chronically. Although there is incremental benefit with higher doses of ACE inhibitors, it is accepted that lower doses provide substantial if not most of the effect.[15] Because ACE inhibitors are only one component of a mortality-reducing treatment plan in HF, targeting a high ACE inhibitor dose should be used cautiously to avoid a hypotensive effect that precludes starting a β-blocker or aldosterone receptor antagonist.

Despite their clear benefits, ACE inhibitors are still underutilized in HF. One reason is undue concern or confusion regarding absolute versus relative contraindications for their use. Absolute contraindications include a history of angioedema, bilateral renal artery stenosis, and pregnancy (Table 6–7). Relative contraindications include unilateral renal artery stenosis, renal insufficiency, hypotension, hyperkalemia, and cough. Relative contraindications provide a warning that close monitoring is required, but they do not necessarily preclude their use.

Clinicians are especially concerned about the use of ACE inhibitors in patients with renal insufficiency. It is important to recognize that ACE inhibitors can potentially contribute to the preservation or decline of renal function depending on the clinical scenario. Through preferential efferent arteriole vasodilation, ACE inhibitors can reduce intraglomerular pressure. Reduced glomerular pressures are renoprotective chronically; however, in situations of reduced or fixed renal blood flow, this leads to a reduction in filtration. In general, ACE inhibitors can be used in patients with serum creatinine less than 2.5 to 3.0 mg/dL (221–265 μmol/L). In HF, their addition can result in improved renal function through an increase in CO and renal perfusion. Although a small increase in serum creatinine (< 0.5 mg/dL [44 μmol/L]) is possible with the addition of an ACE inhibitor, it is usually transient or becomes the patient's new serum creatinine baseline level. However, ACE inhibition can also worsen renal function because glomerular filtration is maintained in the setting of reduced CO through AT_2's constriction of the efferent arteriole. Patients most dependent on AT_2 for maintenance of glomerular filtration pressure, and hence most susceptible to ACE inhibitor worsening of renal function, include those with hyponatremia, severely depressed LV function, or dehydration. The most common reason for creatinine elevation in a patient without a history of renal dysfunction is overdiuresis. Therefore, clinicians should consider decreasing or holding diuretic doses if an elevation in serum creatinine occurs concomitantly with a rise in blood urea nitrogen (BUN).

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

Hyperkalemia results from reduced angiotensin II–stimulated aldosterone release. The risk of hyperkalemia with ACE inhibitors is also increased in HF due to a propensity for impaired renal function and additive effects with aldosterone receptor

antagonists. ACE inhibitor dose may need to be decreased or held if serum potassium increases above 5 mEq/L (mmol/L). Persistent hyperkalemia in the setting of renal insufficiency may preclude the use of an ACE inhibitor. Assessment of potential causes of hyperkalemia should include dietary intake as well as potassium-containing salt-substitutes.

Cough is commonly seen with ACE inhibitors (5%–15%) and may be related to accumulation of tissue bradykinins.[5] It can be challenging to distinguish an ACE inhibitor–induced cough from cough caused by pulmonary congestion. A productive or wet cough usually signifies congestion, whereas a dry, hacking cough is more indicative of a drug-related etiology. If a cough is determined to be ACE inhibitor–induced, its severity should be evaluated before deciding on a course of action. If the cough is truly bothersome, a trial with a different ACE inhibitor or switching to an ARB is warranted.

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

Prospective randomized trials suggest that the clinical efficacy of ARBs is similar to that of ACE inhibitors for reduction of hospitalizations for HF, sudden cardiac death, and all-cause mortality.[16-18] Despite poorer suppression of AT_2, comparable efficacy of ACE inhibitors may be due to the additional effects on the kallikrein-kinin system. Although ARBs produce hemodynamic and neurohormonal effects similar to those of ACE inhibitors, they are considered second-line therapy due to the overwhelming clinical trial experience with ACE inhibitors. LO 6

Because the mechanism for long-term benefit appears different for ACE inhibitors and ARBs, the combination has been studied for additive benefits. In one study, candesartan reduced the combined incidence of cardiovascular death and hospitalization for HF; however, the greatest benefit was noted in those not on an ACE inhibitor. Candesartan also significantly decreased mortality compared with placebo. Based on this study, the addition of an ARB to ACE inhibitor therapy can be considered in patients with evidence of disease progression despite optimal ACE inhibitor therapy and when aldosterone receptor antagonists are not tolerated, although this strategy is not widely applied.[1] LO 6

ARBs show similar tolerability to ACE inhibitors with regard to hypotension and hyperkalemia, but they are less likely to induce cough because ARBs do not cause an accumulation of bradykinin. ARBs can be considered in patients with ACE inhibitor–induced angioedema, but should be initiated cautiously because cross-reactivity has been reported. Many of the other considerations for use of ARBs are similar to those of ACE inhibitors, including the need for monitoring renal function, BP, and potassium. Contraindications are similar to those of ACE inhibitors (Table 6–7). In patients truly intolerant or contraindicated to ACE inhibitors or ARBs, the combination of hydralazine and isosorbide dinitrate should be considered. LO 6

Sacubitril/Valsartan Sacubitril/valsartan (formerly known as the compound LCZ696) is a first in class ARNI.[19] Neprilysin is a neutral endopeptidase responsible for the breakdown of natriuretic peptides, in addition to substance P, adrenomedullin, bradykinin, and AT_2. Blockade of neprilysin increases circulating natriuretic peptide levels. Because neprilysin inhibition alone would also result in elevated levels of AT_2, combination of a neprilysin inhibitor with a RAAS blocker prevents this potentially deleterious effect. Sacubitril/valsartan is a crystalline complex composed of equal parts of the neprilysin inhibitor sacubitril and the ARB valsartan. Shortly after ingestion, sacubitril/valsartan breaks apart into sacubitril, a prodrug which is cleaved to the active form sacubitrilat, and valsartan. The target dose is 97/103 mg twice daily, which was found to reduce the composite end point of cardiovascular death or hospitalization for HF by 20% compared to enalapril 10 mg twice daily in patients with symptomatic HF and reduced LVEF.[20] As such, the 2017 ACC/AHA/Heart Failure Society of America Focused Update of the 2013 American College of Cardiology Foundation/AHA Guideline for the Management of Heart Failure recommend that in patients with symptomatic HFrEF who are tolerating an ACE inhibitor or an ARB, replacement with sacubitril/valsartan is warranted to further reduce morbidity and mortality.[21] Compared to enalapril, patients taking sacubitril/valsartan experienced more symptomatic hypotension, necessitating caution with initiating or switching to this medication in patients with lower BP. Sacubitril/valsartan is contraindicated for use with an ACE inhibitor due to an increased risk for angioedema (Table 6–7), and a 36-hour washout period is necessary when switching to sacubitril/valsartan from an ACE inhibitor, or when switching from sacubitril/valsartan to an ACE inhibitor. The starting dose of sacubitril/valsartan is 49/51 mg twice daily, unless the patient has not previously been on an ACE inhibitor or ARB, or is taking a low dose of an ACE inhibitor, in which case the recommended initial dose is 24/26 mg twice daily (Table 6–6). Titration to a goal dose of 97/103 mg twice daily is recommended. LO 6

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

The combination of hydralazine and isosorbide dinitrate was the first therapy shown to improve long-term survival in patients with systolic HF, but it has largely been supplanted by ACE inhibitors and ARBs.[22,23] Therefore, until recently, this combination therapy was reserved for patients intolerant to ACE inhibitors or ARBs secondary to renal impairment, angioedema, or hyperkalemia. New insight into the pathophysiological role of nitric oxide has reinvigorated research into this combination therapy. LO 6

The nitrate–hydralazine combination was first shown to improve survival compared with placebo,[22] but was inferior with respect to mortality reduction when compared to the ACE inhibitor enalapril.[23] Therefore, the combination is considered a third-line vasodilatory option for patients truly intolerant of ACE inhibitors and ARBs.

More recently, the value of adding the combination of isosorbide dinitrate 40 mg and hydralazine 75 mg three times daily to therapy including ACE inhibitors, β-blockers, digoxin, and diuretics was shown in a prospective randomized trial in African American patients.[24] KEY CONCEPT Combination therapy with hydralazine and isosorbide dinitrate is an appropriate substitute for AT_2 antagonism in those unable to tolerate an ACE inhibitor or ARB or as add-on therapy in African Americans. The ACC/AHA HF guidelines recommend considering the addition of isosorbide dinitrate and hydralazine in African Americans already on ACE inhibitors or ARBs.[1] Combination therapy with isosorbide dinitrate and hydralazine should be initiated and titrated as are other neurohormonal agents such as ACE inhibitors and β-blockers. Low doses are used to initiate therapy with subsequent titration of the dose toward target doses based on tolerability. Adverse effects such as hypotension and headache cause frequent discontinuations in patients taking this combination, and full doses often cannot be tolerated. Patients should be monitored for headache, hypotension, and tachycardia (Table 6–7). Hydralazine is also associated with a dose-dependent risk for lupus.

The frequent dosing of isosorbide dinitrate (eg, three to four times daily) is not conducive to patient adherence; therefore, a once-daily isosorbide mononitrate is commonly substituted for isosorbide dinitrate to simplify the dosing regimen.

β-Adrenergic Antagonists β-Adrenergic antagonists, or β-blockers, competitively block the influence of the SNS at β-adrenergic receptors. As recently as 15 to 20 years ago, β-adrenergic blockers were thought to be detrimental in HF due to their negative inotropic actions, which could potentially worsen symptoms and cause acute decompensations. Since then, the benefits of inhibiting the SNS have been recognized as far outweighing the acute negative inotropic effects. Chronic β-blockade reduces ventricular mass, improves ventricular shape, and reduces LV end-systolic and diastolic volumes.[6,8] β-blockers also exhibit antiarrhythmic effects, slow or reverse catecholamine-induced ventricular remodeling, decrease myocyte death from catecholamine-induced necrosis or apoptosis, and prevent myocardial fetal gene expression. Consequently, β-blockers improve EF, reduce all-cause and HF-related hospitalizations, and decrease all-cause mortality in patients with systolic HF.[25-27]

The ACC/AHA recommend that β-blockers be initiated in all HF patients with NYHA FC I to IV or ACC/AHA stages B through D if clinically stable.[1] To date, only three β-blockers have been shown to reduce mortality in systolic HF including the selective β_1-antagonists bisoprolol and metoprolol succinate, and the nonselective β_1-, β_2-, and α_1-antagonist carvedilol.[25-27] The positive findings of β-blockers are not a class effect because bucindolol did not exhibit a beneficial effect on mortality when studied for HF, and there is limited information with propranolol and atenolol.

Bisoprolol is not as commonly used since it is not Food and Drug Administration (FDA) approved for HF. Although metoprolol succinate and carvedilol are the most commonly used β-antagonists in HF, it is unknown whether one agent should be considered first line. Carvedilol was shown to lower all-cause mortality significantly more than metoprolol tartrate, but carvedilol has not been directly compared to metoprolol succinate.[28]

The key to utilizing β-blockers in systolic HF is initiation with low doses and slow titration to target doses over weeks to months. It is important that the β-blocker be initiated when a patient is clinically stable and euvolemic. Volume overload at the time of β-blocker initiation increases the risk for worsening symptoms. β-Blockade should begin with the lowest possible dose (Table 6–6), after which the dose may be doubled every 2 to 4 weeks depending on patient tolerability. β-Blockers may cause an acute decrease in LVEF and short-term worsening of HF symptoms upon initiation and at each dosage titration. After each dose titration, if the patient experiences symptomatic hypotension, bradycardia, orthostasis, or worsening symptoms, further increases in dose should be withheld until the patient stabilizes. After stabilization, attempts to increase the dose should be reinstituted. If mild congestion ensues as a result of the β-blocker, an increase in diuretic dose may be warranted. If moderate or severe symptoms of congestion occur, a reduction in β-blocker dose should be considered along with an increase in diuretic dose. Dose titration should continue until target clinical trial doses are achieved (Table 6–6) or until limited by repeated hemodynamic or symptomatic intolerance. Patient education regarding the possibility of acutely worsening symptoms but improved long-term function and survival is essential to ensure adherence.

Apart from possible clinical differences between the β-blockers approved for HF, selection of a β-blocker may also be affected by pharmacologic differences. Carvedilol exhibits a more pronounced BP-lowering effect, and thus causes more frequent dizziness and hypotension as a consequence of its β_1- and α_1-receptor blocking activities. Therefore, in patients predisposed to symptomatic hypotension, such as those with advanced LV dysfunction (LVEF < 20% [0.20]) who normally exhibit low systolic BP, metoprolol succinate may be the more desirable first-line β-blocker. In patients with uncontrolled hypertension, carvedilol may provide additional antihypertensive efficacy.

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

Both metoprolol and carvedilol are metabolized by the liver through cytochrome P-450 (CYP) 2D6 and undergo extensive first-pass metabolism. β-Blockers should not be used in patients with severe hepatic failure.

There is some debate regarding which class of agents should be initiated first in a patient with HF, namely, ACE inhibitors or β-blockers. A recent study evaluated whether the order of initiation affects all-cause mortality or hospitalization and found no difference but that more events occurred during the 6-month single-treatment phase of the study.[29] These findings reinforce the importance of using both ACE inhibitors and β-blockers in the HF patient. As such, doses of the agent initiated first should not prohibit initiation of the second class of agents.

Mineralocorticoid Receptor Antagonists (MRAs) The MRAs currently available are spironolactone and eplerenone. Both agents are inhibitors of aldosterone that produce weak diuretic effects while sparing potassium concentrations. Eplerenone is selective for the mineralocorticoid receptor and hence does not exhibit the endocrine adverse effect profile commonly seen with spironolactone. The initial rationale for specifically targeting aldosterone for treatment of HF was based on the knowledge that ACE inhibitors do not suppress the chronic production and release of aldosterone. Aldosterone is a key pathological neurohormone that exerts multiple detrimental effects in HF. Similar to norepinephrine and AT_2, aldosterone levels are increased in HF and correlate with disease severity and patient outcomes.

MRAs improved clinical outcomes, including mortality, across the spectrum of HF in three separate clinical trials. These comprised patients who were post-MI with LVEF less than 40% (0.40), patients with NYHA FC II HF, and patients with NYHA FC III-IV HF.[30-32] It is postulated that MRAs reduce mortality at least in part through prevention of sudden cardiac death. Based on these studies, the ACC/AHA guidelines recommended MRAs in NYHA FC II through IV patients with LVEF less than or equal to 35% (0.35), unless contraindicated, in addition to patients post-MI with evidence of LV dysfunction. For individuals with mild symptoms (NYHA FC II), it is recommended they also exhibit a history of hospitalization or elevated BNP levels.[1]

LO 6

The major risk related to MRAs is hyperkalemia (Table 6–7). Therefore, the decision for use of these agents should balance the benefit of decreasing death and hospitalization from HF and the potential risks of life-threatening hyperkalemia. Before and within 1 week of initiating therapy, two parameters must be assessed: serum potassium and CrCL (or serum creatinine). MRAs should not be initiated in patients with potassium concentrations greater than 5.0 mEq/L (mmol/L). Likewise, these agents should not be given when CrCL is less than 30 mL/min (0.50 mL/s) or serum creatinine is greater than 2.5 mg/dL (221 μmol/L).

In patients without contraindications, spironolactone is initiated at a dose of 12.5 to 25 mg daily (Table 6–6), or occasionally on alternate days for patients with baseline renal insufficiency. Eplerenone is used at a dose of 25 mg daily, with the option to titrate up to 50 mg daily. Doses should be halved or switched to alternate-day dosing if CrCL falls below 50 mL/min (0.83 mL/s). Potassium supplementation is often decreased or stopped after MRAs are initiated, and patients should be counseled to avoid high-potassium foods. At any time after initiation of therapy, if potassium concentrations exceed 5.5 mEq/L (mmol/L), the dose of the MRA should be reduced or discontinued. In addition, worsening renal function dictates consideration for stopping the MRA. Other adverse effects observed mainly with spironolactone include gynecomastia for men and breast tenderness and menstrual irregularities for women. Gynecomastia leads to discontinuation in up to 10% of patients on spironolactone. Eplerenone is a CYP3A4 substrate and should not be used concomitantly with strong inhibitors of 3A4.

► *Digoxin*

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

The exact role of digoxin in therapy remains controversial largely due to disagreement on the risk versus benefit of routinely using this drug in patients with systolic HF. Digoxin was shown to decrease HF-related hospitalizations but did not decrease HF progression or improve survival.[33] Moreover, digoxin was associated with an increased risk for concentration-related toxicity and numerous adverse effects. Post hoc study analyses demonstrated a clear relationship between digoxin plasma concentration and outcomes. Concentrations below 1.2 ng/mL (mcg/L; 1.5 nmol/L) were associated with no apparent adverse effect on survival, whereas higher concentrations increased the relative risk of mortality.[34]

LO 6

Current recommendations are for the addition of digoxin for patients who remain symptomatic despite an optimal HF regimen consisting of an ACE inhibitor or ARB, β-blocker, and diuretic. In patients with concomitant atrial fibrillation, digoxin may occasionally be added to slow ventricular rate; however, β-blockers are more effective at controlling ventricular rate, especially in the setting of exercise. Clinicians may also consider adding digoxin in patients with severe HF who have not responded symptomatically to neurohormonal blockade.

Digoxin is initiated at a dose of 0.125 to 0.25 mg daily depending on age, renal function, weight, and risk for toxicity (Table 6–6). The lower dose should be used if the patient satisfies any of the following criteria: older than 65 years, CrCL less than 60 mL/min (1.0 mL/s), or ideal body weight less than 70 kg (154 lb). The 0.125-mg daily dose is adequate in most patients. Doses are halved or switched to alternate-day dosing in patients with moderate to severe renal failure. The desired concentration range for digoxin is 0.5 to 0.9 ng/mL (mcg/L; 0.6–1.2 nmol/L), preferably with concentrations at or less than 0.8 ng/mL (mcg/L; 1.0 nmol/L). Routine monitoring of serum drug concentrations is not required but recommended in those with changes in renal function, suspected toxicity, or after addition or subtraction of an interacting drug.

Digoxin toxicity may manifest as nonspecific findings such as fatigue or weakness and other central nervous system (CNS) effects such as confusion, delirium, and psychosis (Table 6–7). GI manifestations include nausea, vomiting, or anorexia, and visual disturbances may occur such as halos, photophobia, and color perception problems (red-green or yellow-green vision). Cardiac findings include numerous types of arrhythmias related to enhanced automaticity, slowed or accelerated conduction, or delayed after-depolarizations. These include ventricular tachycardia and fibrillation, atrioventricular nodal block, and sinus bradycardia. Risk of digoxin toxicity, in particular, the cardiac manifestations, are increased with electrolyte disturbances such as hypokalemia, hypercalcemia, and hypomagnesemia. To reduce the proarrhythmic risk of digoxin, serum potassium and magnesium should be monitored closely and supplemented when appropriate to ensure adequate concentrations (potassium > 4.0 mEq/L [mmol/L] and magnesium > 2.0 mEq/L [1.0 mmol/L]). In patients with life-threatening digoxin toxicity due to cardiac or other findings, administration of digoxin-specific Fab antibody fragments usually reverses adverse effects within an hour in most cases.

► *Calcium Channel Blockers*

Treatment with nondihydropyridine calcium channel blockers (diltiazem and verapamil) may worsen HF and increase the risk of death in patients with advanced LV systolic dysfunction due to their negative inotropic effects. Conversely, dihydropyridine calcium channel blockers, although negative inotropes in vitro, do not appear to decrease contractility in vivo. Amlodipine and felodipine are the two most extensively studied dihydropyridine calcium channel blockers for systolic HF.[35,36] These two agents have not been shown to affect patient survival, either positively or negatively. As such, they are not routinely recommended as part of a standard HF regimen; however, amlodipine and felodipine can safely be used in HF patients to treat uncontrolled hypertension or angina once all other appropriate drugs are maximized.

LO 6

► *Antiplatelets and Anticoagulation*

Patients with HF are at an increased risk of thromboembolic events secondary to a combination of hypercoagulability, relative

stasis of blood, and endothelial dysfunction. However, the role of antiplatelets and anticoagulants remains debatable due to a lack of positive prospective clinical trials.

LO 6

Aspirin is generally used in HF patients with an underlying ischemic etiology, a history of ischemic heart disease, or other compelling indications such as history of embolic stroke. Routine use in nonischemic cardiomyopathy patients is currently discouraged because of a lack of data supporting any long-term benefit, as well as the potential negative drug–drug interaction with ACE inhibitors and ARBs. If aspirin is indicated, the preference is to use a low dose (81 mg daily).

LO 6

Current guidelines support chronic anticoagulation in patients with reduced LV systolic dysfunction and a compelling indication such as atrial fibrillation or prosthetic heart valves. For atrial fibrillation, a stronger level of evidence is given for use of anticoagulation in patients with an additional risk factor for cardioembolic stroke, such as history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or age 75 years or older.[1] The choice of anticoagulant (warfarin vs novel anticoagulants) should be based on risk factors, tolerability, cost, and potential for drug–drug interactions. Patients with HF often have difficulty maintaining a therapeutic international normalized ratio (INR) due to fluctuating volume status and varying drug absorption.

▶ *Ivabradine*

Ivabradine is a novel medication that specifically targets lowering HR through blockade through the I_f channel (otherwise referred to as the "funny" current channel) in the sinoatrial node, without affecting BP or contractility. In one study, ivabradine was shown to reduce the composite of cardiovascular death or hospitalization for HF, although results were mainly driven by a reduction in hospitalizations.[37] Ivabradine is indicated in patients with HFrEF with an LVEF less than or equal to 35% (0.35), NYHA FC II-III, in normal sinus rhythm (without atrial fibrillation), taking maximally tolerated or target doses of β-blockers, and who have an HR 70 beats/min or greater. It is important that the β-blocker is optimized prior to initiating therapy with ivabradine, as β-blockers have proven benefits on lowering mortality; thus reaching target doses of a β-blocker takes priority. The starting dose of ivabradine is 5 mg twice daily (or 2.5 mg twice daily in those with conduction defects or those in whom a low HR could result in hemodynamic compromise), which may be titrated to 7.5 mg twice daily after 2 weeks (Table 6–6). Ivabradine is contraindicated for use in patients concomitantly taking strong CYP3A4 inhibitors. Frequently observed adverse effects in clinical trials included bradycardia, atrial fibrillation, hypertension, and visual phenomena (Table 6–7). Termed "phosphenes," these visual disturbances consist of temporarily enhanced brightness, usually in response to sudden variations in light (ie, headlights from other cars while driving). These occur in limited areas of the visual field and may also include halos, image decomposition (stroboscopic or kaleidoscopic effects), or colored bright lights. These visual effects may reduce in severity after a few months of therapy.

Heart Failure with Preserved Left Ventricular Ejection Fraction

It is now recognized that a significant number of patients exhibiting HF symptoms have normal systolic function or preserved LVEF (40%–60% [0.40–0.60]). It is believed that the primary defect in these patients is impaired ventricular relaxation and filling, commonly referred to as HF with preserved EF (HFpEF). HFpEF is more prevalent in older women and closely associated with hypertension or diabetes and, to a lesser extent, CAD and atrial fibrillation. Morbidity in HFpEF is comparable to those with reduced EF because both are characterized by frequent, repeated hospitalizations. However, HFpEF appears to be associated with slightly lower mortality. The diagnosis is based on findings of typical signs and symptoms of HF, in conjunction with echocardiographic evidence of abnormal diastolic function, absence of significant LV chamber dilation, and no valvular disease.

Unlike HFrEF, few prospective trials have evaluated the safety and efficacy of various cardiac medications in patients with HFpEF. The PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) study did not find differences in mortality and hospitalizations between perindopril and placebo, but premature withdrawal of many patients after 1 year could have contributed to the neutral findings.[38] The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) study demonstrated that angiotensin receptor blockade with candesartan resulted in beneficial effects on HF morbidity in patients with preserved LVEF similar to those seen in depressed LV function.[18] However, the largest clinical trial in HFpEF, the I-PRESERVE (Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction) study did not find a reduction in the primary composite outcome of death or hospitalizations between irbesartan and placebo.[39] In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, spironolactone did not reduce the composite end point of cardiovascular death, aborted cardiac arrest, or HF hospitalizations, but resulted in a reduction of the secondary end point, hospitalizations due to HF.[40] In the absence of more landmark clinical studies, the current treatment approach for HFpEF is: (a) correction or control of underlying etiologies (including optimal treatment of hypertension and CAD and maintenance of normal sinus rhythm); (b) reduction of cardiac filling pressures at rest and during exertion; (c) increased diastolic filling time, and (d) reduction of hospitalizations with spironolactone in select patients (LVEF 45% [0.45] or greater, elevated BNP levels or hospitalization for HF in the past year). Diuretics are frequently used to control congestion. β-Blockers and calcium channel blockers can theoretically improve ventricular relaxation through negative inotropic and chronotropic effects. Unlike in systolic HF, nondihydropyridine calcium channel blockers (diltiazem and verapamil) may be especially useful in improving diastolic function by limiting the availability of calcium that mediates contractility. A recent study did not find favorable effects with digoxin in patients with mild to moderate diastolic HF. Therefore, the role of digoxin for symptom management and HR control in these patients is not well established.

Patient Encounter Part 3

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

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

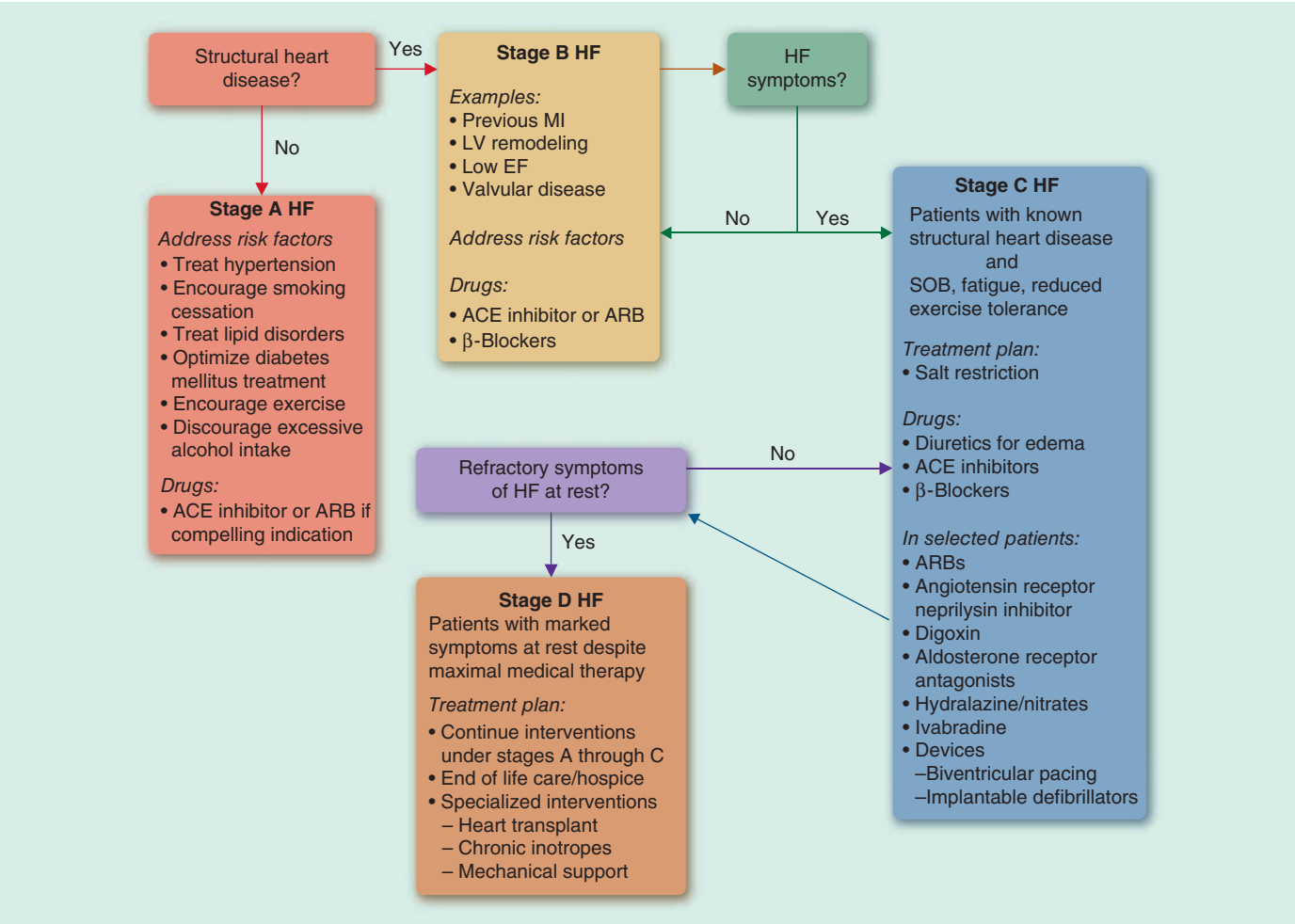

FIGURE 6–2. Treatment algorithm for heart failure with reduced ejection fraction. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; EF, ejection fraction; HF, heart failure; LV, left ventricular; MI, myocardial infarction; SOB, shortness of breath.) Table 6–5 describes the staging of heart failure.

Outcome Evaluation of Chronic Heart Failure

LO 7

- The evaluation of therapy is influenced by the ability of treatment to successfully reduce symptoms, improve quality of life, decrease frequency of hospitalizations for acute HF, reduce disease progression, and prolong survival (Figure 6–2).
- The major outcome parameters focus on (a) volume status, (b) exercise tolerance, (c) overall symptoms/quality of life, (d) adverse drug reactions, and (e) disease progression and cardiac function.
- Assess quality of life by evaluating patients' ability to continue their activities of daily living.
- Assess symptoms of HF such as dyspnea on exertion, orthopnea, weight gain, and edema, and abdominal manifestations such as nausea, bloating, and loss of appetite.
- If diuretic therapy is warranted, monitor for therapeutic response by assessing weight loss and improvement of fluid retention, as well as exercise tolerance and presence of fatigue.
- Once therapy for preventing disease progression is initiated, continue to monitor for symptomatic improvement.
- Keep in mind that patients' symptoms can worsen with β-blockers, and it may take weeks or months before patients notice improvement.
- Monitor BP to evaluate for hypotension caused by drug therapy.
- Occasional exercise testing is conducted to ascertain disease prognosis or suitability for heart transplant. Even though these tests can demonstrate improvement in heart function and therefore slowed disease progression, patient symptoms may not improve.

ACUTE AND ADVANCED HEART FAILURE

Clinical Presentation and Diagnosis of Acute Heart Failure

LO 3

Patients with AHF present with symptoms of worsening fluid retention or decreasing exercise tolerance and fatigue (typically worsening of symptoms presented in the chronic HF clinical presentation textbox). These symptoms reflect congestion behind the failing ventricle and/or hypoperfusion. Patients can be categorized into hemodynamic subsets based on assessment of physical signs and symptoms of congestion and/or hypoperfusion.[41] Patients can be described as "wet" or "dry" depending on volume status, as well as "warm" or "cool" based on adequacy of tissue perfusion. "Wet" refers to patients with volume/fluid overload (eg, edema and jugular venous distension [JVD]), whereas "dry" refers to euvolemic patients. "Warm" refers to patients with adequate CO to perfuse peripheral tissues (and

hence the skin will be warm to touch), whereas "cool" refers to patients with evidence of hypoperfusion (skin cool to touch with diminished pulses). Additionally, invasive hemodynamic monitoring can be used in some cases to provide objective data for assessing volume status (pulmonary capillary wedge pressure [PCWP]) and perfusion (CO). A CI below 2.2 L/min/m^2 (0.037 L/s/m^2) is consistent with hypoperfusion and reduced contractility, and a PCWP above 15 mm Hg (2.0 kPa) correlates with congestion and an elevated preload. The four possible hemodynamic subsets a patient may fall into are "warm and dry," "warm and wet," "cool and dry," or "cool and wet."

▶ *Precipitating Factors*

KEY CONCEPT It is important for the clinician to identify the cause(s) of AHF to maximize treatment efficacy and reduce future disease exacerbations. Cardiovascular, metabolic, and lifestyle factors can all precipitate AHF. The most common precipitating factors for acute decompensation and how they contribute pathophysiologically are listed in Table 6–3.

▶ *Laboratory Assessment*

Routine laboratory testing of patients with AHF includes electrolytes and blood glucose, as well as serum creatinine and BUN to assess renal function. Complete blood cell count is measured to determine if anemia or infection is present. Creatine kinase and/or troponin concentrations are used to diagnose ischemia, and hepatic transaminases are measured to assess hepatic congestion. Thyroid function tests are measured to assess hyperthyroidism or hypothyroidism as causes of AHF. A urinalysis is attained in patients with an unknown history of renal disease to rule out nephrotic syndrome. Lastly, a toxicology screen is obtained in patients in whom the use of illicit drugs is suspected.

Assays measuring BNP and its degradation product N-terminal proBNP (NT-proBNP) are being used with greater frequency in clinical practice. BNP is synthesized, stored, and released from the ventricles in response to increased ventricular filling pressures. Hence plasma levels of BNP can be used as a marker for volume overload. The most widely accepted indication for BNP measurement is as an adjunctive aid for diagnosing a cardiac etiology for dyspnea.[10] The current values for ruling out a cardiac etiology for dyspnea are a BNP less than 100 pg/mL (ng/L; 28.9 pmol/L) or an NT-proBNP less than 300 pg/mL (ng/L; 35.4 pmol/L). BNP measurements require cautious interpretation because numerous conditions can also elevate BNP concentrations. These include older age, renal dysfunction, pulmonary embolism, and chronic pulmonary disease. Nesiritide, a recombinant BNP drug, has an identical structure to native BNP and will interfere with the commercial BNP assay, resulting in a falsely elevated level. Therefore, blood for BNP determination should be obtained 2 hours after the end of a nesiritide infusion, or alternatively the NT-proBNP assay should be utilized. In addition, treatment with sacubitril/valsartan would also be expected to raise BNP levels based on the drug's inhibition of neprilysin. As such, monitoring of NT-proBNP should be utilized instead of BNP in patients taking sacubitril/valsartan, as NT-proBNP is not a substrate for neprilysin. Other diagnostic tests should also be obtained to rule out precipitating factors (chest radiograph) and to evaluate cardiac function (ECG).

Invasive hemodynamic monitoring in patients with HF entails placement of a right heart catheter or pulmonary artery catheter (PAC). The catheter is inserted percutaneously through a central vein and advanced through the right side of the heart to the pulmonary artery. Inflation of a balloon proximal to the end port allows the catheter to "wedge," yielding the PCWP, which estimates pressures in the left ventricle during diastole. Additionally, CO can be estimated and SVR calculated (Table 6–8).

There are no universally accepted guidelines dictating when invasive monitoring in HF is required, and invasive monitoring has not been shown to improve mortality or reduce hospitalizations in high-risk patients. Nonetheless, the use of a PAC remains a helpful component of management and monitoring of patients with signs significantly reduced cardiac output; however, use of inotropic agents does not mandate invasive monitoring. Invasive hemodynamic monitoring is most commonly used to aid in assessment of hemodynamics when there is disagreement between signs and symptoms and clinical response. In addition, invasive monitoring is helpful in guiding ongoing therapy for

Clinical Presentation of Acute Heart Failure

Subset I (Warm and Dry)

- CI *greater than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *less than* 18 mm Hg (2.4 kPa)
- Patients considered well compensated and perfused, without evidence of congestion
- No immediate interventions necessary except optimizing oral medications and monitoring

Subset II (Warm and Wet)

- CI *greater than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *greater than* or equal to 18 mm Hg (2.4 kPa)
- Patients adequately perfused and display signs and symptoms of congestion
- Main goal is to reduce preload (PCWP) carefully with loop diuretics and vasodilators

Subset III (Cool and Dry)

- CI *less than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *less than* 18 mm Hg (2.4 kPa)
- Patients are inadequately perfused and not congested
- Hypoperfusion leads to increased mortality, elevating death rates fourfold compared with those who are adequately perfused
- Treatment focuses on increasing CO with positive inotropic agents and/or replacing intravascular fluids
- Fluid replacement must be performed cautiously because patients can rapidly become congested

Subset IV (Cool and Wet)

- CI *less than* 2.2 L/min/m^2 (0.037 L/s/m^2), PCWP *greater than* 18 mm Hg (2.4 kPa)
- Patients are inadequately perfused and congested
- Classified as the most complicated clinical presentation of AHF with the worst prognosis
- Most challenging to treat; therapy targets alleviating signs and symptoms of congestion by increasing CI as well as reducing PCWP while maintaining adequate mean arterial pressure
- Treatment involves a delicate balance between diuretics, vasodilators, and inotropic agents
- Use of vasopressors is sometimes necessary to maintain BP

Table 6–8

Hemodynamic Monitoring: Normal Values

Hemodynamic Variable	Normal Value
Central venous (right atrial) pressure, mean	< 5 mm Hg[a] (0.7 kPa)
Right ventricular pressure	25/0 mm Hg[a]
Pulmonary artery pressure	25/10 mm Hg[a]
Pulmonary artery pressure, mean	< 18 mm Hg[a] (2.4 kPa)
Pulmonary artery occlusion pressure, mean[b]	< 12 mm Hg[a] (1.6 kPa)
Systemic arterial pressure	120/80 mm Hg[a]
Mean arterial pressure	70–110 mm Hg[a] (9.3–14.6 kPa)
Cardiac output	4–6 L/min (0.07–0.10 L/s)
Cardiac index	2.8–4.2 L/min/m^2 (0.047–0.070 L/s/m^2)
Stroke volume index	30–65 mL/beat/m^{2a} (0.030–0.065 L·$beat^{-1}$·m^{-2})
Systemic vascular resistance	900–1400 dyn·s·cm^{-5c} (90–140 MPa·s·m^{-3})
Pulmonary vascular resistance	150–250 dyn·s·cm^{-5c} (15–25 MPa·s·m^{-3})
Arterial oxygen content	20 mL/dL[c] (200 mL/L)
Mixed venous oxygen content	15 mL/dL[c] (150 mL/L)
Arteriovenous oxygen content difference	3–5 mL/dL[c] (30–50 mL/L)

[a]1 mm Hg = 0.133 kPa; 1 mL/beat per square meter = 0.001 L·$beat^{-1}$·m^{-2}.

[b]Also referred to as pulmonary artery wedge pressure (PCWP).

[c]1 dyn·s·cm^{-5} = 0.1 MPa·s·m^{-3}; 1 mL/dL = 10 mL/L.

From Rodgers JE, Reed BN. Acute decompensated heart failure. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:121, with permission.

AHF and offers the advantage of immediate hemodynamic assessment of an intervention, allowing for prompt adjustments. Risks with PACs include infection, bleeding, thrombosis, catheter malfunction, and ventricular ectopy.

Desired Therapeutic Outcomes

LO 4

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

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

Pharmacologic Treatment

LO 6

KEY CONCEPT Treatment of AHF targets relief of congestion and optimization of CO utilizing oral or IV diuretics, IV vasodilators, and, when appropriate, inotropes based on presenting hemodynamics. Current treatment strategies in AHF target improving hemodynamics while preserving organ function. A specific treatment approach is formulated depending on the patient's symptoms (congestion vs hypoperfusion) and hemodynamic indices (CI and PCWP).[42] If the patient primarily exhibits signs and symptoms of congestion, treatment entails use of diuretics as first-line agents to decrease PCWP. Additionally, IV vasodilators are added to provide rapid relief of congestion and additional reductions in PCWP. By reducing congestion in the heart, cardiac contractile function may improve, which results in an increase in SV and CO, and hence perfusion to vital organs. The patient's presenting BP can also help guide the clinician on choice of diuretic, vasodilator, or both. For the patient with a systolic BP of 120 to 160 mm Hg in the setting of progressive worsening of chronic HF with pulmonary and systemic congestion, aggressive diuresis can be beneficial. In the patient with systolic BP greater than 160 mm Hg and abrupt onset of pulmonary congestion, IV vasodilators may be indicated in addition to diuretics. For patients primarily displaying symptoms of hypoperfusion, treatment relies on use of agents that increase cardiac contractility, known as positive inotropes. Some patients display both symptoms of congestion as well as hypoperfusion and thus require use of combination therapies. One of the current challenges to the treatment of AHF is achieving hemodynamic improvement without adversely affecting organ function. In the case of inotropes, the increased contractility occurs at the expense of an increase in cardiac workload and potential for proarrhythmia. In addition, high-dose diuretic therapy is associated with worsened renal function and possibly neurohormonal activation.

▶ *Diuretics*

Loop diuretics, including furosemide, bumetanide, and torsemide, are the diuretics of choice in the management of AHF. Furosemide is the most commonly used agent. Diuretics decrease preload by functional venodilation within 5 to 15 minutes of administration and subsequently by an increase in sodium and water excretion. This provides rapid improvement in symptoms of pulmonary congestion. Diuretics reduce PCWP but do not increase CI like positive inotropes and arterial vasodilators. Patients who have significant volume overload often have impaired absorption of oral loop diuretics because of intestinal edema or altered transit time. Therefore, doses are usually administered via IV boluses or continuous IV infusions (Table 6–9). Higher doses may be required for patients with renal insufficiency due to decreased drug delivery to the site of action in the loop of Henle. A good rule of thumb is to initiate the IV diuretic at twice the dose of the outpatient oral dose.

There is limited clinical trial evidence comparing the benefit of diuretics with other therapies for symptom relief or long-term outcomes. Careful monitoring of diuresis is needed as excessive preload reduction can lead to a decrease in CO resulting in reflex increase in sympathetic activation, renin release, and the expected consequences of vasoconstriction, tachycardia, and

Table 6–9

Intravenous Diuretics Used to Treat Heart Failure–Related Fluid Retention

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

LO 7

increased myocardial oxygen demand. Monitoring of serum electrolytes such as potassium, sodium, and magnesium is done frequently to identify and correct imbalances. Monitor serum creatinine and BUN daily at a minimum to assess volume depletion and renal function.

Occasionally, patients with HF do not respond to a diuretic, defined as failure to achieve a weight reduction of at least 0.5 kg (or negative net fluid balance of at least 500 mL) after several increasing bolus doses. Several strategies are used to overcome diuretic resistance. These include using larger oral doses, converting to IV dosing, increasing the frequency of administration, or adding metolazone. A small study using low-dose continuous infusions of furosemide and torsemide has shown an increase in urine output compared with intermittent bolus dosing, but newer evidence suggests that there may be little difference between intermittent bolus dosing and continuous infusion strategies on symptom relief at 72 hours.[43] (See Table 6–9.) Another useful strategy is to combine two diuretics with different sites of action within the nephron. The most common combination is the use of a loop diuretic with a thiazide diuretic such as metolazone. Combining diuretics should be used with caution due to an increased risk for cardiovascular collapse due to rapid intravascular volume depletion. Strict monitoring of electrolytes, vital signs, and fluid balance is warranted. Also, poor CO may contribute to diuretic resistance. In these patients, it may become necessary to add vasodilators or inotropes to enhance perfusion to the kidneys. Care must be taken because vasodilators can decrease renal blood flow despite increasing CO through dilation of central and peripheral vascular beds.

▶ *Vasodilators*

IV vasodilators cause a rapid decrease in arterial tone, resulting in a decrease in SVR and a subsequent increase in SV and CO. Additionally, vasodilators reduce ventricular filling pressures (PCWP) within 24 to 48 hours, reduce myocardial oxygen consumption (MVO_2), and decrease ventricular workload.

LO 6

Vasodilators are commonly used in patients presenting with AHF accompanied by moderate to severe congestion. This class includes nitroglycerin, nitroprusside, and nesiritide. Hemodynamic effects and dosages for these agents are included in Tables 6–10 and 6–11, respectively. Although vasodilators are generally safe and effective, identification of the proper patient for use is important to minimize the risk of significant hypotension. In addition, vasodilators are contraindicated in patients whose cardiac filling (and hence CO) depends on venous return or intravascular volume, as well as patients who present with cardiogenic shock.

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

LO 6

Continuous infusions of nitroglycerin should be initiated at a dose of 5 to 10 mcg/min and increased every 5 to 10 minutes until symptomatic or hemodynamic improvement. Effective doses range from 35 to 200 mcg/min. The most common adverse events reported are headache, dose-related hypotension, and tachycardia. Tachyphylaxis, or tolerance of effects, limits nitroglycerin's use within 12 hours of initiation. Nitroglycerin's effectiveness requires titration to higher doses.

Nitroprusside Nitroprusside, like nitroglycerin, causes the formation of nitric oxide and vascular smooth muscle relaxation. In contrast to nitroglycerin, nitroprusside is both a venous and arterial vasodilator regardless of dosage. Nitroprusside causes a pronounced decrease in PCWP, SVR, and BP, with a modest increase in CO. Nitroprusside has been studied to a limited extent in AHF, and no studies have evaluated its effects on mortality. Nitroprusside is initiated at 0.1 to 0.25 mcg/kg/min, followed by dose adjustments in 0.1 to 0.2 mcg/kg/min increments if necessary to achieve desired effect. Because of its rapid onset of action and metabolism, nitroprusside is administered as a continuous infusion that is easy to titrate and provides predictable hemodynamic effects. Nitroprusside requires strict monitoring

LO 6

of BP and HR. Nitroprusside's use is limited in AHF due to recommended hemodynamic monitoring with an arterial line and mandatory intensive care unit admission at many institutions. Abrupt withdrawal of therapy should be avoided because rebound neurohormonal activation may occur. Therefore, the dose should

Table 6–10

Usual Hemodynamic Effects of Commonly Used Intravenous Agents for Treatment of Acute or Severe Heart Failure

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

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

Table 6–11

Usual Doses and Monitoring of Commonly Used Hemodynamic Medications

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

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

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

be tapered slowly. Nitroprusside has the potential to cause cyanide and thiocyanate toxicity, especially in patients with hepatic and renal insufficiency, respectively. Toxicity is most common with use longer than 3 days and with higher doses. Nitroprusside should be avoided in patients with active ischemia because its powerful afterload-reducing effects within the myocardium can "steal" coronary blood flow from myocardial segments that are supplied by epicardial vessels with high-grade lesions.

Nesiritide Recombinant BNP, or nesiritide, binds to guanylate cyclase receptors in vascular smooth muscle and endothelial cells, causing an increase in cGMP concentrations leading to vasodilation (venous and arterial) and natriuresis. Nesiritide also antagonizes the effects of the RAAS and endothelin. Nesiritide reduces PCWP, right atrial pressure, and SVR. Consequently, it also increases SV and CO without affecting HR. Continuous infusions result in sustained effects for 24 hours without tachyphylaxis, although experience with its use beyond 72 hours is limited.

Nesiritide has been shown to improve symptoms of dyspnea and fatigue. In a randomized clinical trial, nesiritide was found to significantly decrease PCWP more than nitroglycerin and placebo over 3 hours.[44] Nesiritide improved patients' self-reported dyspnea scores compared with placebo at 3 hours, but there was no difference compared with nitroglycerin. In another study, nesiritide did not decrease death or rehospitalization for HF within 30 days, worsen renal function, or increase the risk for mortality, despite previous concerns regarding its association with elevations in serum creatinine.[45]

LO 6 Currently, nesiritide is indicated for patients with AHF exhibiting dyspnea at rest or with minimal activity. The recommended dose regimen is a bolus of 2 mcg/kg, followed by a continuous infusion for up to 24 hours of 0.01 mcg/kg/min. Because nesiritide's effects are predictable and sustained at the recommended dosage, titration of the infusion rate (maximum of 0.03 mcg/kg/min) is not commonly required nor is invasive hemodynamic monitoring. Nesiritide should be avoided in patients with systolic BP less than 90 mm Hg. Although nesiritide's place in AHF therapy is not firmly defined, it can be used in combination with diuretics for patients presenting in moderate to severe decompensation, and it offers a unique mechanism of action. One potential disadvantage compared with other vasodilators is its longer half-life. Combination therapy may result in hypotension, which can be prolonged (2 hours).

► *Inotropic Agents*

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

Dobutamine Dobutamine has historically been the inotrope of choice for AHF. As a synthetic catecholamine, it acts as an agonist mainly on β_1- and β_2-receptors and minimally on α_1-receptors. The resulting hemodynamic effects are due to both receptor- and reflex-mediated activities. These effects include increased contractility and HR through β_1- (and β_2-) receptors and vasodilation through a relatively greater effect on β_2- than α_1-receptors. Dobutamine can increase, decrease, or cause little change in mean arterial pressure depending on whether the resulting increase in CO is enough to offset the modest vasodilation. Although dobutamine has a half-life of approximately 2 minutes, its positive hemodynamic effects can be observed for several days to months after administration. LO 6 The use of dobutamine is supported by several small studies documenting improved hemodynamics, but large-scale clinical trials in AHF are lacking.

Dobutamine is initiated at a dose of 2.5 to 5 mcg/kg/min, which can be gradually titrated to 20 mcg/kg/min based on clinical response. There are several practical considerations to dobutamine therapy. LO 6 First, owing to its vasodilatory potential, monotherapy with dobutamine is reserved for patients with systolic BP greater than 90 mm Hg. However, it is commonly used in combination with vasopressors in patients with lower systolic BP. Second, due to downregulation of β_1-receptors or uncoupling of β_2-receptors from adenylate cyclase with prolonged exposure to dobutamine, attenuation of hemodynamic effects has been reported to occur as early as 48 hours after initiation of a continuous infusion, although tachyphylaxis is more evident with use spanning longer than 72 hours. Full sensitivity to dobutamine's effects can be restored 7 to 10 days after the drug is withdrawn. Third, many patients with AHF will be taking β-blockers chronically. Because of β-blockers' high affinity for β-receptors, the effectiveness of β-agonists such as dobutamine will be reduced. LO 6 In patients on β-blocker therapy, it is recommended that consideration be given to the use of phosphodiesterase inhibitors such as milrinone, which do not depend on β-receptors for effect.[46,47] Although commonly practiced, use of high doses of dobutamine to overcome the β-blockade should be discouraged because this negates any of the protective benefits of the β-blocker and may increase risk for arrhythmias.

LO 6 **Dopamine** Dopamine is most commonly reserved for patients with low systolic BP and those approaching cardiogenic shock. Dopamine exerts its effects through direct stimulation of adrenergic receptors, as well as release of norepinephrine from adrenergic nerve terminals. Dopamine produces hemodynamic effects that differ based on dosing. At lower doses, dopamine stimulates dopamine type 1 (D1) receptors and thus increases renal perfusion. Positive inotropic effects are more pronounced at doses of 3 to 10 mcg/kg/min. CI is increased due to increased SV and HR. At doses higher than 10 mcg/kg/min, chronotropic and α_1-mediated vasoconstriction effects are evident. This causes an increase in mean arterial pressure due to higher CI and SVR. The ultimate effect on cardiac hemodynamics will depend largely on the dosage prescribed and must be individually tailored to the patient's clinical status. Dopamine is generally associated with an increase in CO and BP, with a concomitant increase in PCWP. Dopamine increases myocardial oxygen demand and may decrease coronary blood flow through vasoconstriction and increased wall tension. As with other inotropes, dopamine is associated with a risk for arrhythmias.

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

Milrinone has both positive inotropic and vasodilating properties and as such is referred to as an "inodilator." Its vasodilating activities are especially prominent on venous capacitance vessels and pulmonary vascular beds, although a reduction in arterial tone is also noted. IV administration results in an increase in SV and CO, and usually only minor changes in HR. Milrinone also lowers PCWP through venodilation. Routine use of milrinone during acute decompensations in NYHA FC II to IV HF is not recommended, and milrinone use remains limited to patients who require inotropic support.[48]

Dosing recommendations for milrinone may include a loading dose of 50 mcg/kg, followed by an infusion beginning at 0.5 mcg/kg/min (range: 0.23 mcg/kg/min for patients with renal failure up to 0.75 mcg/kg/min). A loading dose is not necessary if immediate hemodynamic effects are not required or if patients have low systolic BP (< 90 mm Hg). Decreases in BP during an infusion may necessitate dose reductions as well. Lower doses are also used in patients with renal insufficiency.

LO 6 Milrinone is a good option for patients requiring an inotrope who are also chronically receiving β-blockers because the inotropic effects are achieved independent of β-adrenergic receptors. However, milrinone exhibits a long distribution and elimination half-life compared with β-agonists. Potential adverse effects include hypotension, arrhythmias, and, less commonly, thrombocytopenia. Additionally, milrinone has been associated with increased risk for death in some studies. Milrinone should not be used in patients in whom vasodilation is contraindicated.

Mechanical, Surgical, and Device Therapies

▶ *Intraaortic Balloon Counterpulsation*

Intraaortic balloon counterpulsation (IABC) or intraaortic balloon pumps (IABPs) are widely used mechanical circulatory assistance devices for patients with cardiac failure who do not respond to standard therapies. An IABP is placed percutaneously into the femoral artery and advanced to the high descending thoracic aorta. Once in position, the balloon is programmed to inflate during diastole and deflate during systole. Two main beneficial mechanisms are: (a) inflation during diastole increases aortic pressure and perfusion of the coronary arteries; and (b) deflation just prior to the aortic valve opening reduces afterload. As such, IABP increases myocardial oxygen supply and decreases oxygen demand. This device has many indications, including cardiogenic shock, high-risk unstable angina in conjunction with percutaneous interventions, preoperative stabilization of high-risk patients prior to surgery, and in patients who cannot be weaned from cardiopulmonary bypass. Possible complications include infection, bleeding, thrombosis, limb ischemia, and device malfunction. The device is typically useful for short-term therapy due to its invasiveness, need for limb immobilization, and requirement for anticoagulation.

▶ *Ventricular Assist Device*

The ventricular assist device (VAD) is a surgically implanted pump that reduces or replaces the work of the right, left, or both ventricles. VADs are indicated for short-term support in patients refractory to pharmacologic therapies, as long-term bridge therapy (a temporary transition treatment) in patients awaiting cardiac transplant, or in some instances as destination therapy (for patients who are not appropriate candidates for transplantation).[1] The most common complications are infection and thromboembolism. Other adverse effects include bleeding, air embolism, device failure, and multiorgan failure.

▶ *Heart Transplant*

Heart transplantation represents the final option for refractory end-stage HF patients who have exhausted medical and device therapies. Heart transplantation should be considered a trade between a life-threatening syndrome and the risks associated with the operation and long-term immunosuppression. Assessment of appropriate candidates includes comorbid illnesses, psychosocial behavior, available financial and social support, and patient willingness to adhere to lifelong therapy and close medical follow-up.[1] Overall, the transplant recipient's quality of life may be improved, but not all patients receive this benefit. Posttransplant survival continues to improve due to advances in immunosuppression, treatment and prevention of infection, and optimal management of patient comorbidities.

Outcome Evaluation of Acute Heart Failure

LO 7
- Focus on (a) acute improvement of symptoms and hemodynamics due to IV therapies, and (b) optimization of oral therapy.
- Initially, monitor patients for rapid relief of symptoms related to the chief complaint on admission. This includes improvement of dyspnea, oxygenation, fatigue, JVD, and other markers of congestion or distress.
- Monitor for adequate perfusion of vital organs through assessment of mental status, creatinine clearance, liver function tests, and a stable HR between 50 and 100 beats/min. Additionally, adequate skin and muscle blood perfusion and normal pH are desirable.
- Monitor changes in hemodynamic variables if available. CI should increase, with a goal to maintain it above 2.2 L/min/m^2 (0.037 L/s/m^2). PCWP should decrease in volume-overloaded patients to a goal of less than 18 mm Hg (2.4 kPa).
- Closely monitor BP and renal function while decreasing preload with diuretics and vasodilators.

Patient Encounter Part 4

After 6 months, the patient returns to the clinic complaining of extreme SOB with any activity, as well as at rest. He sleeps sitting up due to severe orthopnea, feels too nauseous and bloated to eat, and states he has gained 25 lb (11.4 kg) from his baseline weight. He states that he does not feel his furosemide therapy is working. He is admitted to the cardiology unit.

SH: Admits to resuming previous alcohol intake; additionally, he has been eating out in restaurants more often in the past few weeks. He has also resumed smoking

Meds: Atorvastatin 40 mg once daily, lisinopril 10 mg once daily, carvedilol 6.25 mg twice daily, furosemide 80 mg twice daily, multivitamin daily, aspirin 81 mg daily

VS: BP 106/54 mm Hg, pulse 102 beats/min and regular, respiratory rate 22/min, temperature 37°C (98.6°F), Wt 276 lb (125.5 kg), BMI 41.9 kg/m^2

Lungs: Decreased breath sounds and rales present bilaterally

CV: Regular rate and rhythm with normal S_1 and S_2; there is an S_3 and an S_4; a 4/6 systolic ejection murmur is present and heard best at the left lower sternal border; point of maximal impulse is displaced laterally; jugular veins are distended, JVP is 14 cm above sternal angle

Abd: Hard, tender, and bowel sounds are present; 3+ pitting edema of extremities is observed

CXR: Bilateral pleural effusions and cardiomegaly

Echo: EF = 20% (0.20)

Pertinent labs: NT-proBNP 2210 pg/mL (ng/L; 261 pmol/L), K: 3.4 mEq/L (mmol/L), BUN 64 mg/dL (22.8 mmol/L), SCr 2.4 mg/dL (212 µmol/L), Mg 1.8 mEq/L (0.9 mmol/L); A pulmonary catheter is placed, revealing the following: PCWP 32 mm Hg (4.3 kPa); CI 2.3 L/min/m^2 (0.038 L/s/m^2)

What NYHA functional class, ACC/AHA stage, and hemodynamic subset is the patient currently in?

What are your initial treatment goals?

What pharmacologic agents are appropriate to use at this time?

Identify a monitoring plan to assess for efficacy and toxicity of the recommended drug therapy.

Once symptoms are improved, how would you optimize oral medication therapy for this patient's HF?

Patient Care Process

Collect Information:

- Obtain a thorough history of prescription, nonprescription, and herbal medication use.
- Review the patient's lifestyle habits including salt and alcohol intake, tobacco product use, exercise routine.
- Gather recent history of symptoms of congestion and hypoperfusion, including weight gain, swelling in extremities, etc.

Assess the Information:

- Assess the severity and duration of the patient's symptoms of HF and hypoperfusion, including limitations in activity. Rule out potential exacerbating factors. See Clinical Presentation and Diagnosis of Chronic Heart Failure textbox and Tables 6–1, 6–3, and 6–4.
- Review available diagnostic information from the chest radiograph, ECG, and echocardiogram. Investigate the patient's underlying etiology of HF.

Develop a Care Plan:

- Determine whether additional adjustment or new therapy is needed to address patient's acute and chronic conditions.
- Develop a treatment plan to alleviate symptoms and maintain euvolemia with diuretics (Tables 6–6 and 6–7). Daily weights to assess fluid retention are recommended.
- Develop a medication regimen to slow the progression of HF with the use of neurohormonal blockers such as vasodilators (ACE inhibitors, ARBs, sacubitril/valsartan, or hydralazine/isosorbide dinitrate), β-blockers, and aldosterone receptor antagonists (Tables 6–6 and 6–7). Utilize digoxin if the patient remains symptomatic despite optimization of the therapies just described, and ivabradine in patients with HRs of 70 beats/min or higher despite optimization of β-blocker.

Implement the Care Plan:

- Ensure the patient is at goal or maximally tolerated doses of vasodilator and β-blocker therapy (Table 6–6), or titrate to the next dosing level if possible.
- Educate the patient on lifestyle modifications such as salt restriction (maximum 2 g/day), fluid restriction if appropriate, limitation of alcohol, tobacco cessation, participation in a cardiac rehabilitation and exercise program, and proper immunizations such as the pneumococcal vaccine and yearly influenza vaccine.
- Stress the importance of adherence to the therapeutic regimen and lifestyle changes for maintenance of a compensated state and slowing of disease progression.

Follow-up: Monitor and Evaluate:

- Monitor patient, including appropriate hemodynamic monitoring for AHF (Table 6–8), for desired outcomes.
- Evaluate the patient for presence of adverse drug reactions, drug allergies, and drug interactions.
- Provide patient education with regard to disease state and drug therapy, and reinforce medication adherence and self-monitoring for symptoms of HF (eg, daily weights). Emphasize follow-up with health care practitioners.
- Assess changes in echocardiographic parameters from a follow-up echocardiography, ideally performed 2 months after medication optimization. Has the LVEF risen to above 40% (0.40)?

- Ensure patients are euvolemic or nearly euvolemic prior to discharge.
- Because oral therapies can both improve symptoms and prolong survival, optimizing outpatient HF management is a priority when preparing a patient for hospital discharge. Ensure the patient's regimen includes an ACE inhibitor, ARB, or ARNI, β-blocker, a diuretic at an adequate dose to maintain euvolemia, and aldosterone antagonist or digoxin if indicated.

Abbreviations Introduced in This Chapter

ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
AHF	Acute heart failure
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
AT_1	Angiotensin I
AT_2	Angiotensin II
ATP	Adenosine triphosphate
BMI	Body mass index
BNP	B-type natriuretic peptide
BPM	Beats per minute
BP	Blood pressure
BUN	Blood urea nitrogen
CAD	Coronary artery disease
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CHARM	Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity
CI	Cardiac index
CNS	Central nervous system
CO	Cardiac output
COX-2	Cyclooxygenase-2
CrCL	Creatinine clearance
CYP	Cytochrome P-450 isoenzyme
D1	Dopamine receptor type 1
ECG	Electrocardiogram
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ET-1	Endothelin-1
ET-A	Endothelin-A
ET-B	Endothelin-B
FDA	Food and Drug Administration
GI	Gastrointestinal
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HJR	Hepatojugular reflux
HR	Heart rate
IABC	Intraaortic balloon counterpulsation
IABP	Intraaortic balloon pump
iNOS	Inducible nitric oxide synthetase
INR	International normalized ratio
I-PRESERVE	Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction
IV	Intravenous
JVD	Jugular venous distention
JVP	Jugular venous pressure
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVF	Left ventricular failure
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
MVO_2	Myocardial oxygen consumption
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal proBNP
NYHA FC	New York Heart Association Functional Class
PAC	Pulmonary artery catheter
PCWP	Pulmonary capillary wedge pressure
PEP-CHF	Perindopril in Elderly People with Chronic Heart Failure
PND	Paroxysmal nocturnal dyspnea
RAAS	Renin-angiotensin-aldosterone system
RVF	Right ventricular failure
SCr	Serum creatinine
SNS	Sympathetic nervous system
SOB	Shortness of breath
SV	Stroke volume
SVR	Systemic vascular resistance
TNF-α	Tumor necrosis factor-α
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
V_{1a}	Vasopressin type 1a
V_2	Vasopressin type 2
VAD	Ventricular assist device

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240–e327.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135:e146–e160.
3. Nieminen MS, Harjola VP. Definition and epidemiology of acute heart failure syndromes. Am J Cardiol. 2005;96(6A):5G–10G.
4. Bonow RO, Bennett S, Casey DE, Jr, et al. ACC/AHA Clinical Performance Measures for Adults with Chronic Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures): endorsed by the Heart Failure Society of America. Circulation. 2005;112(12):1853–1887.
5. Parker RB, Cavallari LH. Systolic heart failure. In DiPiro JY, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill; 2011:137–172.
6. Jessup M, Brozena S. Heart failure. New Eng J Med. 2003;348(20):2007–2018.
7. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med. 1999;341(8):577–585.
8. Mann DL. Mechanisms and models in heart failure: a combinatorial approach. Circulation. 1999;100(9):999–1008.
9. Mann DL. Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circulation Research. 2002;91(11):988–998.
10. Silver MA, Maisel A, Yancy CW, et al. BNP Consensus Panel 2004: a clinical approach for the diagnostic, prognostic, screening, treatment monitoring, and therapeutic roles of natriuretic peptides in cardiovascular diseases. Congest Heart Fail. 2004;10(5 suppl 3):1–30.
11. Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010;16(6):e1–e194.
12. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril

Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Eng J Med. 1987;316(23):1429–1435.
13. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Eng J Med. 1991;325(5):293–302.
14. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Eng J Med. 1992;327(10):685–691.
15. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999;100(23):2312–2318.
16. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000;355(9215):1582–1587.
17. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Eng J Med. 2001;345(23):1667–1675.
18. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet. 2003;362(9386):759–766.
19. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. JACC Heart Fail. 2014;2(6):663–670.
20. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Eng J Med. 2014;371(11):993–1004.
21. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70(6):776–803.
22. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Eng J Med. 1986;314(24):1547–1552.
23. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Eng J Med. 1991;325(5):303–310.
24. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Eng J Med. 2004;351(20):2049–2057.
25. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Eng J Med. 1996;334(21):1349–1355.
26. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9–13.
27. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001–2007.
28. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362(9377):7–13.
29. Funck-Brentano C, van Veldhuisen DJ, van de Ven LL, Follath F, Goulder M, Willenheimer R. Influence of order and type of drug (bisoprolol vs. enalapril) on outcome and adverse events in patients with chronic heart failure: a post hoc analysis of the CIBIS-III trial. Eur J Heart Fail. 2011;13(7):765–772.
30. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Eng J Med. 1999;341(10):709–717.
31. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Eng J Med. 2003;348(14):1309–1321.
32. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Eng J Med. 2011;364(1):11–21.
33. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digoxin Investigation Group. N Eng J Med. 1997;336(8):525–533.
34. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA. 2003;289(7):871–878.
35. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Eng J Med. 1996;335(15):1107–1114.
36. Packer M, Carson P, Elkayam U, et al. Effect of amlodipine on the survival of patients with severe chronic heart failure due to a nonischemic cardiomyopathy: results of the PRAISE-2 study (prospective randomized amlodipine survival evaluation 2). JACC Heart Fail. 2013;1(4):308–314.
37. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376(9744):875–885.
38. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27(19):2338–2345.
39. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Eng J Med. 2008;359(23):2456–2467.
40. Pfeffer MA, Pitt B, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. N Eng J Med. 2014;371(2):181–182.
41. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. Eur J Heart Fail. 1999;1(3):251–257.
42. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. JAMA. 2002;287(5):628–640.
43. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Eng J Med. 2011;364(9):797–805.
44. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. Publication Committee for the VMAC Investigators. JAMA. 2002;287(12):1531–1540.
45. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Eng J Med. 2011;365(1):32–43.
46. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part I: Inotropic infusions during hospitalization. Circulation. 2003;108(3):367–372.
47. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part II: Chronic inotropic therapy. Circulation. 2003;108(4):492–497.
48. Cuffe MS, Califf RM, Adams KF, Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA. 2002;287(12):1541–1547.

7 Stable Ischemic Heart Disease

Dejan Landup and Robert J. DiDomenico

LEARNING OBJECTIVES

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

1. Identify risk factors for the development of ischemic heart disease (IHD).
2. Differentiate between the pathophysiology of chronic stable angina and acute coronary syndromes (ACS).
3. Recognize symptoms and diagnostic criteria of IHD in a specific patient.
4. Compare and contrast the diagnostic criteria of IHD and ACS.
5. Identify treatment goals of stable IHD (SIHD).
6. Identify appropriate lifestyle modifications and pharmacologic therapy to address each treatment goal.
7. Design an appropriate treatment regimen for the management of SIHD based on patient-specific information.
8. Formulate a monitoring plan to assess effectiveness and adverse effects of a SIHD drug regimen.

INTRODUCTION

Ischemic heart disease (IHD) is also called coronary heart disease (CHD) or coronary artery disease (CAD). The term *ischemic* refers to a decreased supply of oxygenated blood to the heart muscle. IHD is caused by stenosis, or narrowing, in one or more of the major coronary arteries that supply blood to the heart, most commonly by atherosclerotic plaques. Atherosclerotic plaques may impede coronary blood flow to the extent that cardiac tissue distal to the coronary artery narrowing is deprived of sufficient oxygen to meet oxygen demand. KEY CONCEPT IHD results from an imbalance between myocardial oxygen supply and oxygen demand (Figure 7–1). Common clinical manifestations of IHD include chronic stable angina and the ACS of unstable angina (UA), non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).

Angina pectoris, or simply angina, is the most common symptom of IHD. Angina is discomfort in the chest that occurs when the blood supply to the myocardium is compromised. Chronic stable angina is a chronic occurrence of chest discomfort due to transient myocardial ischemia with physical exertion or other conditions that increase oxygen demand. The primary focus of this chapter is the management of stable IHD (SIHD), the most common manifestation of which is chronic stable angina. However, some information is also provided related to acute coronary syndrome (ACS), given the overlap between the two disease states. The American College of Cardiology (ACC), the American Heart Association (AHA), and several other organizations have jointly published practice guidelines for the management of SIHD. Refer to these and related guidelines for further information.[1-3]

EPIDEMIOLOGY AND ETIOLOGY

IHD affects over 16 million Americans and is the leading cause of death for both men and women in the United States.[4] The incidence of IHD is higher in middle-aged men compared with women. However, the rate of IHD increases twofold to threefold in women after menopause. Chronic stable angina is the initial manifestation of IHD in about 50% of patients, whereas ACS is the first sign of IHD in other patients. Patients with SIHD experience considerable morbidity and frequently require hospitalization for chest pain and evaluation for potential ACS. In addition, SIHD negatively impacts health-related quality of life. Thus, in patients with SIHD, it is important to optimize pharmacotherapy to reduce symptoms, improve quality of life, slow disease progression, and prevent ACS.

Conditions Associated with Angina

Figure 7–2 shows the anatomy of the coronary arteries. The major epicardial coronary arteries are the left main, left anterior descending, left circumflex, and right coronary arteries. Atherosclerosis leading to obstructive lesions in one or more of the major coronary arteries or their principal branches is the major cause of angina. Vasospasm at the site of an atherosclerotic plaque may further constrict blood flow and contribute to angina. Less commonly, vasospasm in coronary arteries with no or minimal atherosclerotic disease can produce angina and even precipitate ACS. This uncommon form of angina is referred to as variant or Prinzmetal angina. Other nonatherosclerotic conditions that can cause angina-like symptoms are listed in Table 7–1.[1] It is important to differentiate the etiology of chest discomfort because treatment varies depending on the underlying disease process.

Risk Factors

LO 1 Factors that predispose an individual to IHD are listed in Table 7–2. Optimization of modifiable risk factors can significantly reduce the risk of myocardial infarction (MI).[1]

LO 1 Hypertension, diabetes, dyslipidemia, and cigarette smoking are associated with endothelial damage and dysfunction and contribute to the development of atherosclerosis. Physical inactivity and obesity independently increase the risk for

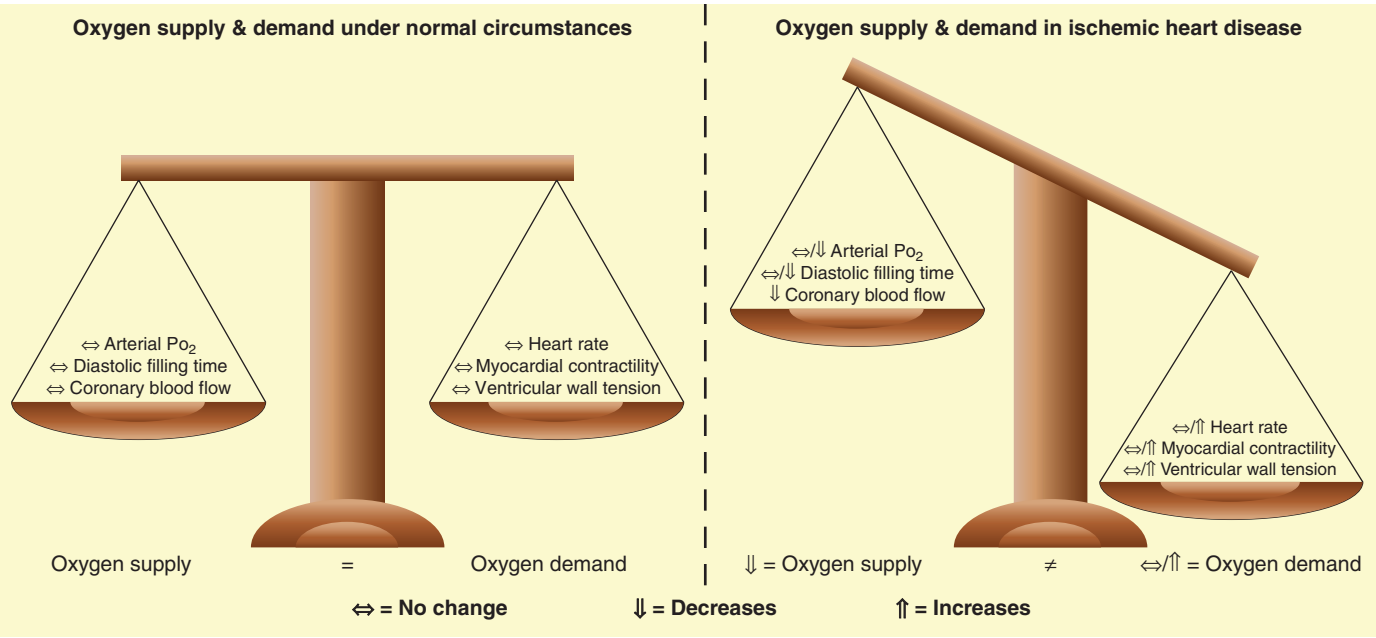

FIGURE 7–1. This illustration depicts the balance between myocardial oxygen supply and demand and various factors that affect each. It should be noted that diastolic filling time is not an independent predictor of myocardial oxygen supply per se, but rather a determinant of coronary blood flow. On the left is myocardial oxygen supply and demand under normal circumstances. On the right is the mismatch between oxygen supply and demand in patients with IHD. In patients without IHD, coronary blood flow increases in response to increases in myocardial oxygen demand. However, in patients with IHD, coronary blood flow cannot sufficiently increase (and may decrease) in response to increased oxygen demand, resulting in angina. (IHD, ischemic heart disease; Po_2, partial pressure of oxygen.)

IHD, in addition to predisposing individuals to hypertension, dyslipidemia, and diabetes.

Patients with multiple risk factors, particularly those with diabetes, are at the greatest risk for IHD, experiencing fivefold to sevenfold higher risk compared to individuals without risk factors.[4] Although alternative definitions exist, metabolic syndrome is generally considered a constellation of common cardiovascular risk factors including hypertension, abdominal obesity, dyslipidemia, and insulin resistance. Metabolic syndrome increases the risk of developing IHD and related complications by twofold.[5] According to a joint statement from the International Diabetes Federation, National Heart, Lung, and Blood Institute, AHA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity, patients must meet at least three of the following criteria for the diagnosis of metabolic syndrome[5]:

- Increased waist circumference (40 in [102 cm] or greater in men and 35 in [89 cm] or greater in women).
- Triglycerides of 150 mg/dL (1.70 mmol/L) or greater or active treatment to lower triglycerides.
- Low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL [1.03 mmol/L] in men and < 50 mg/dL [1.29 mmol/L] in women) or active treatment to raise HDL cholesterol.
- Systolic blood pressure (BP) of 130 mm Hg or greater, diastolic BP of 85 mm Hg or greater, or active treatment with antihypertensive therapy.
- Fasting blood glucose of 100 mg/dL (5.6 mmol/L) or greater or active treatment for diabetes.

KEY CONCEPT Early detection and aggressive modification of risk factors are among the primary strategies for delaying IHD progression and preventing IHD-related events including death.

PATHOPHYSIOLOGY

The determinants of myocardial oxygen supply and demand are shown in Figure 7–1. Increases in heart rate, cardiac contractility, and left ventricular wall tension increase the rate of myocardial oxygen consumption (MVO_2). Ventricular wall tension is a function of BP, systemic vascular resistance, left ventricular end-diastolic volume, and ventricular wall thickness. Physical exertion increases MVO_2 and commonly precipitates symptoms of angina in patients with significant coronary atherosclerosis.

Reductions in coronary blood flow (secondary to atherosclerotic plaques, vasospasm, or thrombus formation) and arterial oxygen content (secondary to hypoxia) decrease myocardial oxygen supply. Because the coronary arteries fill during diastole, decreases in diastolic filling time (eg, tachycardia) can also reduce coronary perfusion and myocardial oxygen supply. Anemia, carbon monoxide poisoning, and cyanotic congenital heart disease are examples of conditions that can lead to diminished myocardial oxygen delivery and precipitate angina in the face of adequate coronary perfusion.

Coronary Atherosclerosis

The normal arterial wall is illustrated in panel A of Figure 7–3. The intima consists of a layer of endothelial cells that line the lumen of the artery and form a selective barrier between the vessel wall and blood contents. Vascular smooth muscle cells are found in the media. The vascular adventitia comprises the artery's outer layer. Atherosclerotic lesions form in the subendothelial space in the intimal layer.

LO 2 Endothelial damage and dysfunction, commonly caused by hypertension, diabetes, and smoking, allow low-density lipoprotein (LDL) cholesterol and inflammatory cells (eg,

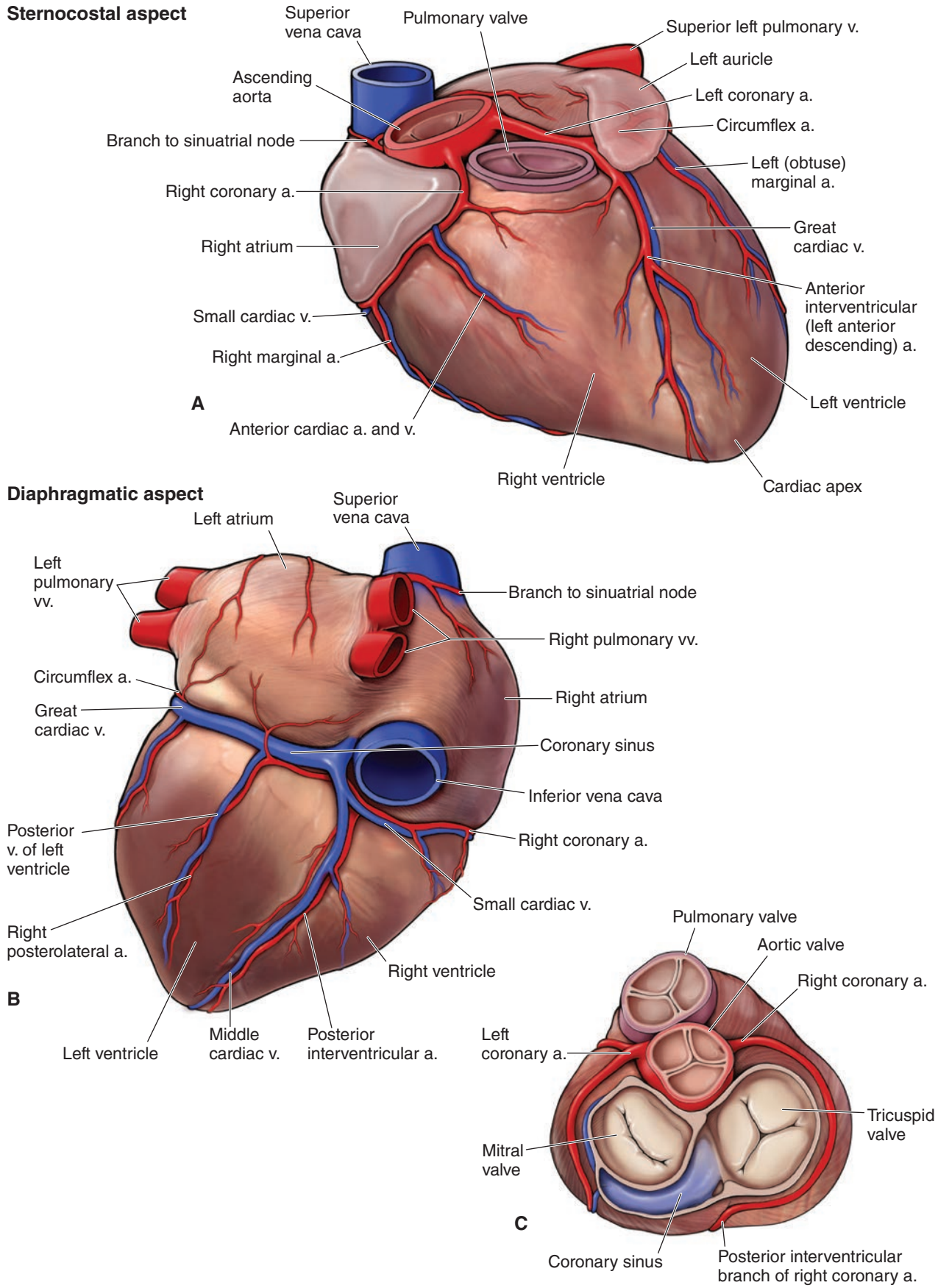

FIGURE 7–2. Coronary artery anatomy with sternocostal and diaphragmatic views. (a., artery; v., vein.) (Reproduced from Chapter 4. Heart. In: Morton DA, Foreman K, Albertine KH, eds. The Big Picture: Gross Anatomy. New York, NY: McGraw-Hill; 2011. http://accesspharmacy.mhmedical.com/content.aspx?bookid=381&sectionid=40140010, with permission.)

Table 7–1

Nonatherosclerotic Conditions That Can Cause Angina-Like Symptoms[1]

Organ System	Condition
Cardiac	Aortic dissection, aortic stenosis, coronary artery vasospasm, pericarditis, valvular heart disease, severe uncontrolled hypertension
Noncardiac	Anemia, anxiety disorders, carbon monoxide poisoning, chest wall trauma, cocaine use, esophageal reflux or spasm, peptic ulcer disease, pleuritis, pneumonia, pneumothorax, pulmonary embolus, pulmonary hypertension, thyrotoxicosis

monocytes and T lymphocytes) to migrate from the plasma to the subendothelial space, as illustrated in Figure 12–5 in Chapter 12, "Dyslipidemias." The process begins by monocyte-derived macrophages ingesting lipoproteins to form foam cells. Macrophages also secrete growth factors that promote smooth muscle cell migration from the media to the intima. The result is the development of early atherosclerosis in the form of a fatty streak consisting of lipid-laden macrophages and smooth muscle cells.

The fatty streak enlarges as foam cells, smooth muscle cells, and necrotic debris accumulate in the subendothelial space. A collagen matrix forms a fibrous cap that covers the lipid core of the lesion to establish an atherosclerotic plaque. The atherosclerotic plaque may progress until it protrudes into the artery lumen and impedes blood flow. When the plaque occludes 70% or more of a major coronary artery or 50% or more of the left main coronary artery, the patient may experience angina during activities that increase myocardial oxygen demand.

Compared with men, women with angina are more likely to present with microvascular disease. Microvascular angina, also called cardiac syndrome X, refers to disease of the smaller coronary vessels causing typical angina in the absence of obstructive CAD of the epicardial arteries. Endothelial dysfunction and reduced smooth muscle relaxation, resulting in reduced vasodilation and enhanced vasoconstriction, are proposed to contribute to microvascular disease.[6]

Table 7–2

Major Risk Factors for Ischemic Heart Disease

Modifiable	Nonmodifiable
Cigarette smoking	Age ≥ 45 years for men, age ≥ 55 years for women
Dyslipidemia • Elevated LDL or total cholesterol • Reduced HDL cholesterol	Gender (men and postmenopausal women)
Diabetes mellitus	Family history of premature cardiovascular disease, defined as cardiovascular disease in a male first-degree relative (ie, father or brother) < 55 years or a female first-degree relative (ie, mother or sister) < 65 years
Hypertension	
Physical inactivity	
Obesity (body mass index ≥ 30 kg/m^2)	
Low daily fruit and vegetable consumption	
Alcohol overconsumption	

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Stable versus Unstable Atherosclerotic Plaques

LO 2

The hallmark feature in the pathophysiology of SIHD is an established atherosclerotic plaque in one or more of the major coronary arteries that impedes coronary blood flow such that myocardial oxygen supply can no longer meet myocardial oxygen demand. In contrast, the hallmark feature in the pathophysiology of ACS is atherosclerotic plaque rupture with subsequent thrombus formation. Plaque rupture refers to fissuring of the fibrous cap and exposure of the plaque contents to elements in the blood. Plaque composition, rather than the degree of coronary stenosis, determines the stability of the plaque and the likelihood of rupture and ACS. As depicted in Figure 7–3B, a stable lesion characteristic of SIHD consists of a small lipid core surrounded by a thick fibrous cap that protects the lesion from the shear stress of blood flow. In contrast, an unstable plaque consists of a thin, weak cap covering a large lipid-rich core that renders the plaque vulnerable to rupture (Figure 7–3C). The transformation of a stable plaque into an unstable plaque involves the degradation of the fibrous cap by substances released from macrophages and other inflammatory cells. Following plaque rupture, platelets adhere to the site of rupture (Figure 7–3D), aggregate (Figure 7–3E), and generate thrombin leading to the development of a fibrin clot (Figure 7–3F). Coronary thrombi extend into the vessel lumen, where they partially or completely occlude blood flow, potentially resulting in UA or MI.

Unstable plaque often produces minimal occlusion of the coronary vessel, and the patient remains asymptomatic until the plaque ruptures. In fact, many ACS arise from vulnerable plaques that occlude less than 50% of the coronary lumen.[7]

Coronary Artery Vasospasm

Prinzmetal or variant angina results from spasm (or vasoconstriction) of a coronary artery in the absence of significant atherosclerosis. Variant angina usually occurs at rest, especially in the early morning hours. Although vasospasm is generally transient, it may persist long enough to cause myocardial ischemia and subsequent infarction. Patients with variant angina are typically younger than those with chronic stable angina and often do not possess the classic risk factors for IHD. The cause of variant angina is unclear but appears to involve vagal withdrawal, endothelial dysfunction, and paradoxical response to agents that normally cause vasodilation. Precipitants of variant angina include cigarette smoking, cocaine or amphetamine use, hyperventilation, and exposure to cold temperatures. The management of variant angina differs from that of classic angina, and thus it is important to distinguish between the two.

CLINICAL PRESENTATION AND DIAGNOSIS

History

LO 3

The evaluation of a patient with suspected IHD begins with a detailed history of symptoms. KEY CONCEPT The classic presentation of angina is described in the Clinical Presentation and Diagnosis text box. Chronic stable angina should be distinguished from UA because the latter is associated with a greater risk for MI and

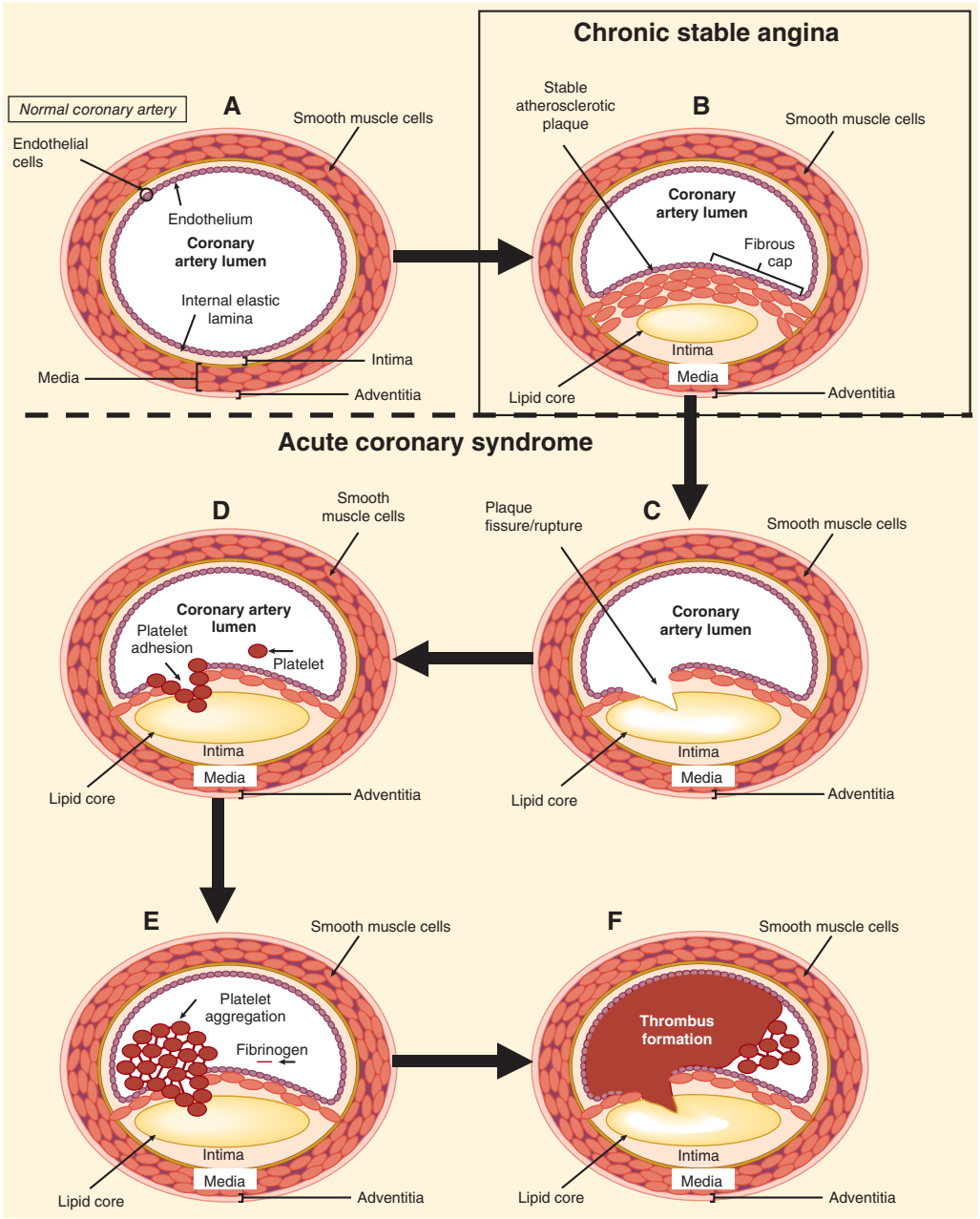

FIGURE 7–3. Pathophysiology of chronic stable angina versus acute coronary syndromes. **Panel A** depicts the cross-section of a normal coronary artery. **Panel B** depicts the cross-section of a coronary artery with a stable atherosclerotic plaque. Note that the lipid core is relatively small in size and the fibrous cap is made up of several layers of smooth muscle cells. **Panel C** depicts an unstable atherosclerotic plaque with a larger lipid core, and a thin fibrous cap composed of a single layer of smooth muscle cells with a fissure or rupture. **Panel D** depicts platelet adhesion in response to the fissured plaque. Platelet activation may ensue, leading to platelet aggregation as fibrinogen binds platelets to one another to form a mesh-like occlusion in the coronary lumen (**Panel E**). At this stage, patients may experience symptoms of acute coronary syndrome. If endogenous anticoagulant proteins fail to halt this process, platelet aggregation continues and fibrinogen is converted to fibrin, resulting in an occlusive thrombus (**Panel F**).

LO 3

death and requires hospitalization for more aggressive treatment. Because the pathophysiology of SIHD is due primarily to increases in oxygen demand rather than acute changes in oxygen supply, symptoms are typically reproducible when provoked by exertion, exercise, or stress. The exception may be a patient with coronary artery vasospasm, in whom symptoms may be more variable and unpredictable. In contrast to SIHD, ACS generally occurs in response to an acute decrease in coronary blood flow leading to inadequate oxygen supply.

LO 4

Consequently, ACS is marked by prolonged symptoms, often occurring at rest, or an escalation in the frequency or severity of angina over a short period of time. The presentation of UA is described in Table 7–3.[8]

Canadian Cardiovascular Society Classification System

LO 3

The Canadian Cardiovascular Society Classification System (Table 7–4) is commonly used to assess the degree of disability

Clinical Presentation and Diagnosis of Ischemic Heart Disease

General

- Patients with SIHD will generally be in no acute distress. In patients presenting in acute distress, the clinician should be suspicious of ACS.

Symptoms of Angina Pectoris

- The five components commonly used to characterize chest pain are: quality, location, duration, provoking factors, and mitigating factors.
- Patients typically describe pain as a sensation of pressure, heaviness, tightness, or squeezing in the anterior chest area. Sharp pain and pain reproducible by palpation are not typical symptoms of angina.
- Pain may radiate to the neck, jaw, shoulder, back, or arm.
- Pain may be accompanied by dyspnea, nausea, vomiting, or diaphoresis.
- Pain typically persists for several minutes.
- Symptoms are often provoked by exertion (eg, walking, climbing stairs, doing yard or housework) or emotional stress and relieved within minutes by rest or sublingual nitroglycerin. Other precipitating factors include exposure to cold temperatures and heavy meals. Pain that occurs at rest (without provocation) or that is prolonged and unrelieved by sublingual nitroglycerin is indicative of ACS.
- Some patients, most commonly women, the elderly, and patients with diabetes, may present with atypical symptoms including indigestion, gastric fullness, back pain, and shortness of breath. Patients with diabetes and the elderly may experience associated symptoms, such as dyspnea, diaphoresis, nausea, fatigue, and dizziness, without having any of the classic angina symptoms.
- In some cases, "silent ischemia" occurs in which patients are asymptomatic.

Signs

- Findings on physical examination are often normal with SIHD. However, during episodes of ischemia, patients may present with abnormal heart sounds, such as paradoxical splitting of the second heart sound, a third heart sound, or a loud fourth heart sound.

Laboratory Tests

- Cardiac troponin (troponin I or troponin T) is the most sensitive biomarker to detect myocardial damage and is elevated in MI but typically normal in chronic stable angina and UA.
- Hemoglobin, fasting glucose, and fasting lipid profile should be determined for assessing cardiovascular risk factors and establishing the differential diagnosis.

Other Diagnostic Tests

- A 12-lead electrocardiogram (ECG) recorded during rest is often normal in patients with SIHD in the absence of active ischemia. Significant Q waves may indicate prior MI. ST-segment changes (ST-segment depression or elevation) or T-wave inversion in two or more contiguous leads during symptoms of angina support the diagnosis of IHD. ST-segment depression or T-wave inversion may be observed in chronic stable angina, UA, and NSTEMI, whereas ST-segment elevation occurs with STEMI and Prinzmetal (variant) angina.
- Treadmill or bicycle exercise ECG, commonly referred to as a "stress test," is considered positive for IHD if the ECG shows at least a 1-mm deviation of the ST-segment (depression or elevation).
- Wall motion abnormalities or left ventricular dilation with stress echocardiography or cardiac magnetic resonance (MR) (exercise or pharmacological) are indicative of IHD.
- Perfusion abnormalities can be detected by stress myocardial perfusion imaging using either radionuclides technetium-99m sestamibi or thallium-201 or cardiac MR (with or without late gadolinium enhancement).
- Coronary angiography detects the location and degree of coronary atherosclerosis and is used to evaluate the potential benefit from revascularization procedures. Stenosis of at least 70% of the diameter of at least one of the major epicardial arteries (50% or greater for the left main coronary artery) on coronary angiography is indicative of significant IHD.
- Coronary angiography may be normal with microvascular angina.

Table 7–3

Presentations of Acute Coronary Syndromes[8]

- Angina at rest that is prolonged in duration, usually lasting over 20 minutes.
- Angina of recent onset (within 2 months) that markedly limits usual activity.
- Angina that increases in severity (ie, by Canadian Cardiovascular Society Classification System Class of one level or greater [Table 7–4]), frequency, or duration, or that occurs with less provocation over a short time period (ie, within 2 months).

resulting from IHD.[9] Patients are categorized into one of four classes depending on the extent of activity that produces angina. Grouping patients according to this or a similar method is commonly used to assess changes in IHD severity over time and the effectiveness of pharmacologic therapy.

Physical Findings and Laboratory Analysis

LO 3

A thorough medical history, physical examination, and laboratory analysis are necessary to ascertain cardiovascular risk factors and to exclude nonischemic and noncardiac conditions that could mimic angina-like symptoms. Laboratory analyses

Table 7–4

Canadian Cardiovascular Society Classification System of Angina[9]

Class	Description
I	Able to perform ordinary physical activity (eg, walking, climbing stairs) without symptoms. Strenuous, rapid, or prolonged exertion causes symptoms.
II	Symptoms slightly limit ordinary physical activity. Walking rapidly or for more than two blocks, climbing stairs rapidly, or climbing more than one flight of stairs causes symptoms.
III	Symptoms markedly limit ordinary physical activity. Walking less than two blocks or climbing one flight of stairs causes symptoms.
IV	Angina may occur at rest. Any physical activity causes symptoms.

should assess for glycemic control (ie, fasting glucose, glycated hemoglobin), fasting lipids, hemoglobin, and organ function (ie, blood urea nitrogen, creatinine, liver function tests, thyroid function tests). For patients with ACS, serial measurements of cardiac troponin (usually 2–3 measurements over a period of 3–12 hours) are performed to exclude the diagnosis of an acute MI. Cardiac findings on the physical examination are often normal in patients with SIHD. However, findings such as **carotid bruits**, abdominal and/or renal bruits, or abnormal peripheral pulses would indicate atherosclerosis in other vessel systems and raise the suspicion for IHD.

Diagnostic Tests

A resting 12-lead ECG is indicated in all patients with new or worsening symptoms of ischemia. Patients with characteristic chest discomfort, accompanied by ST-segment elevation in two or more contiguous leads, or a new left bundle branch block are often diagnosed with MI (STEMI) and are at the highest risk of death. Consequently, STEMI is treated as a medical emergency, often requiring expeditious percutaneous coronary intervention (PCI) or fibrinolytic therapy to restore blood flow in the occluded artery and reperfuse the myocardium. For patients with ACS, cardiac troponin is measured serially to distinguish between MI (elevated cardiac troponin) and either UA or noncardiac causes of chest discomfort (normal cardiac troponin).

"Stress" testing with either exercise or pharmacologic agents increases myocardial oxygen demand and is commonly used to evaluate the patient with suspected IHD. Approximately 50% of patients with IHD who have a normal ECG at rest will develop ECG changes with exercise on a treadmill (most commonly) or bicycle ergometer. Dobutamine is a common pharmacologic agent administered as an IV infusion to patients who are unable to exercise. Dobutamine increases oxygen demand by stimulating the β_1-receptor, increasing heart rate and contractility. Echocardiography is commonly performed along with exercise or dobutamine (eg, treadmill or dobutamine stress echocardiography) to identify stress-induced wall motion abnormalities of the left ventricle indicative of IHD.

Exercise or pharmacologic agents are also commonly combined with radionuclide myocardial perfusion imaging (nuclear imaging studies) or cardiac MR to detect IHD. An intravenous (IV) radioactive tracer is administered and accumulates in normal myocytes in proportion to coronary blood flow. Adenosine, dipyridamole, and regadenoson are coronary vasodilators that increase coronary blood flow in healthy arteries but not in atherosclerotic vessels. Radionuclide myocardial perfusion imaging is performed at rest and following exercise or pharmacologic stressor to detect perfusion defects indicative of IHD. Positive emission tomography, which utilizes a radioactive tracer that emits γ rays, is an alternative to conventional myocardial perfusion imaging that may be preferred in obese patients. Similar to other myocardial perfusion imaging, stress cardiac MR can detect wall motion abnormalities as well as perfusion defects, the latter often performed using late gadolinium enhancement, to determine the extent and severity of myocardial scarring that may be present.

Coronary artery calcium scoring via computed tomography (CT), also known as electron beam CT (EBCT) or "ultra-fast CT," may be performed as a noninvasive means to assess for CAD. Calcium deposits within the atherosclerotic coronary arteries are detected on CT, a calcium score is calculated, and the risk for IHD-related events is estimated.

Coronary angiography (also referred to as a cardiac catheterization or "cardiac cath") is indicated when stress testing results are either abnormal or inconclusive, symptoms of angina are poorly controlled, or in patients for whom the clinical suspicion of IHD remains high despite a normal stress test result. Angiography involves catheter insertion into either the femoral or radial artery with advancement of the catheter into the ascending aorta near the coronary ostia. Contrast medium is injected through the catheter into the coronary arteries and fluoroscopy is performed to visualize the coronary anatomy and detect IHD. Contrast medium must be used cautiously in patients with preexisting renal disease (especially in those with diabetes) to avoid contrast-induced nephropathy and often warrants prophylactic hydration periprocedurally. The decision to establish the diagnosis of IHD via stress testing, coronary angiography, or both is often individualized for each patient based on several factors including baseline assessment of IHD risk (eg, pretest probability), sensitivity and specificity of the diagnostic test, results of previous diagnostic tests, and risk for complications (eg, contrast nephropathy).

TREATMENT

Desired Outcomes

Once a patient is diagnosed with IHD, the clinician should provide counseling on lifestyle modifications, institute appropriate pharmacologic therapy, and evaluate the need for revascularization. Optimal medical therapy is essential for managing patients with SIHD. KEY CONCEPT The major goals for the treatment of SIHD are to:

- Prevent ACS and death
- Alleviate acute symptoms of angina
- Prevent recurrent symptoms of angina
- Prevent progression of the disease
- Reduce complications of IHD
- Avoid or minimize adverse treatment effects

The treatment approach to address these goals is illustrated in Figure 7–4.

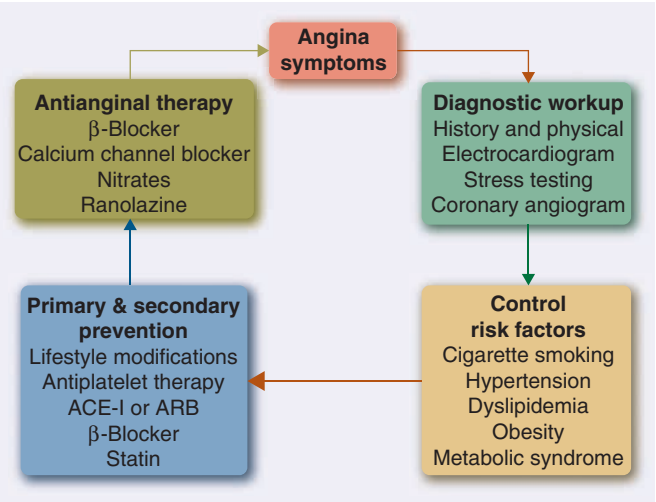

FIGURE 7–4. General treatment strategies for angina follow in clockwise fashion from the top center. (ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.)

General Approach to Treatment

The primary strategies for preventing ACS and death (eg, primary or secondary prevention) are to:

- Aggressively modify cardiovascular risk factors
- Slow the progression of coronary atherosclerosis
- Stabilize existing atherosclerotic plaques

LO 6 The treatment algorithm in Figure 7–5 summarizes the appropriate management of IHD. Risk factor modification is accomplished through lifestyle changes and pharmacologic therapy. KEY CONCEPT Both 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) and angiotensin-converting enzyme (ACE) inhibitors possess vasculoprotective effects (eg, anti-inflammatory effects, antiplatelet effects, improvement in endothelial function, and/or improvement in arterial compliance and tone). Together with aspirin, these drugs reduce the risk of acute coronary events and death in patients with SIHD. In select patients with IHD (following hospitalization for ACS ± PCI and/or following intracoronary stent placement), dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ antagonist has also been shown to reduce ischemic events. Angiotensin receptor blockers (ARBs) may be used in patients who cannot tolerate ACE inhibitors because of side effects (eg, chronic cough). β-Blockers decrease morbidity and improve survival in patients who have suffered an MI, particularly in patients with concomitant heart failure with reduced ejection fraction (HFrEF).

The goal of therapies that alleviate and prevent angina is improving the balance between myocardial oxygen demand and supply. Drug treatment is primarily used to reduce oxygen demand, whereas revascularization by PCI and coronary artery bypass graft (CABG) surgery effectively restore coronary blood flow, improving myocardial oxygen supply.

Adverse treatment effects can be averted by avoiding drug interactions and the use of drugs that may have unfavorable effects on comorbid diseases. Appropriate drug dosing and monitoring reduces the risk for adverse treatment effects. Drugs should be initiated in low doses, with careful up-titration as necessary to control symptoms of angina and cardiovascular risk factors.

Patient Encounter Part 1

A 55-year-old black woman with a history of hypertension, diabetes, and a cerebral vascular accident presents to your clinic complaining of chest discomfort that occurred several times over the past few weeks. She describes her chest discomfort as indigestion, stating her "stomach feels full". She first noticed the discomfort while carrying her grandson to a second floor bedroom. Since then, she experienced the same symptoms while walking in the grocery store and carrying laundry upstairs. The discomfort was located in the substernal area and was associated with nausea and dyspnea. In each instance, the pain resolved after about 5 minutes of rest.

What information is suggestive of angina?

What tests would be beneficial in establishing a diagnosis?

What additional information do you need to create a treatment plan for this patient?

Lifestyle Modifications

LO 6 Lifestyle modifications (smoking cessation, avoidance of secondhand smoke, dietary modifications, increased physical activity, and weight loss) reduce cardiovascular risk factors, slow the progression of SIHD, and decrease the risk for SIHD-related complications. Cigarette smoking is the single most preventable cause of SIHD and SIHD-related death. Smoking may also attenuate the antianginal effects of drug therapy. Clinicians should counsel patients and/or family members who smoke on the importance of smoking cessation at each encounter and offer referral to smoking cessation programs. There are several pharmacologic aids for smoking cessation. Transdermal nicotine replacement therapy and bupropion have been studied in patients with SIHD and appear safe and effective.[10,11] Varenicline, a partial nicotine receptor agonist, is similarly efficacious but has been associated with worsening of preexisting depression and suicidal ideation.[12,13] Thus, it should be used cautiously, particularly in patients treated for depression, and the risk:benefit ratio should be discussed with patients. Weight loss, through caloric restriction and increased physical activity, should be encouraged in patients who have a body mass index greater than 25 kg/m^2. Dietary counseling should be provided to all patients with newly diagnosed angina regardless of weight. The AHA recommends a diet that includes a variety of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats.[14] The addition of plant stanols/sterols (2 g/day) and/or viscous fiber (over 10 g/day) are effective in lowering LDL cholesterol.[15] Specific dietary recommendations for patients with IHD should include the following[1,14]:

LO 6

- Limit cholesterol intake to less than 200 mg/day.
- Limit consumption of saturated fat to less than 7% and *trans* fatty acids to less than 1% of total calories.
- Limit daily sodium intake to 2.4 g (6 g of salt) for BP control.
- Limit alcohol consumption to 1 drink/day for women and 1 to 2 drinks/day for men unless otherwise contraindicated.

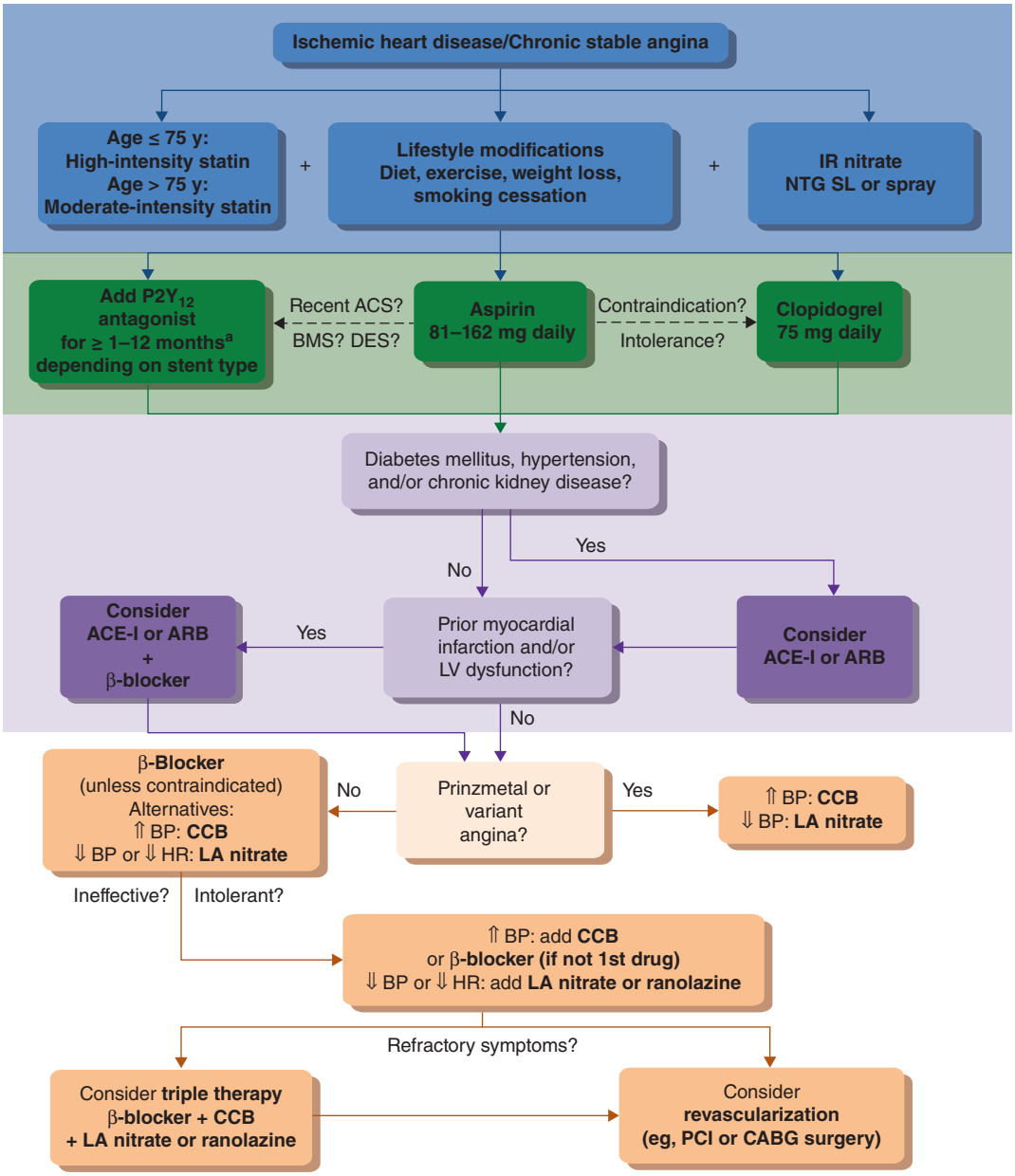

FIGURE 7–5. Treatment algorithm for ischemic heart disease. It begins at the top (blue section), which suggests risk factor modifications as the first treatment modality. Moving down to the green section, appropriate antiplatelet therapy is selected. The purple section identifies patients at high risk for major adverse cardiac events (MACE) and suggests appropriate drug therapy to decrease cardiovascular risk. The orange section at the bottom recommends appropriate antianginal therapy. [a]The minimum duration of $P2Y_{12}$ inhibitors in combination with aspirin (DAPT) following intracoronary stent placement is as follows: at least 1 month for BMSs and at least 6 months for DESs for patients with stable ischemic heart disease, at least 12 months in patients with stents placed for ACS regardless of stent type. (ACE-I, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMS, bare metal stent; BP, blood pressure; CABG, coronary artery bypass graft; CCB, calcium channel blocker; DES, drug-eluting stent; HR, heart rate; IR, immediate release; LA, long acting; LDL, low-density lipoprotein; LV, left ventricular; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SL, sublingual.)

LO 6

Exercise facilitates weight loss, BP reduction, and glycemic control. In addition, regular exercise in patients with SIHD improves functional capacity, reduces symptoms of angina, and reduces mortality.[1,16] Guidelines recommend moderate intensity aerobic activity, such as brisk walking, ideally for 30 to 60 minutes at least 5 and preferably 7 days weekly.[1] Medically supervised cardiac rehabilitation programs are recommended for high-risk patients.

Interventional Approaches to Revascularization

▶ *Percutaneous Coronary Intervention*

LO 7

For patients with SIHD, optimal medical therapy is equivalent to PCI in reducing major adverse cardiac events (MACE), which include death, nonfatal MI, and revascularization.[17] Therefore, medical therapy is preferred as the initial treatment strategy. However, when optimal medical therapy fails, symptoms are

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension, diagnosed 13 years ago; diabetes, diagnosed 8 years ago; cerebral vascular accident, diagnosed 3 years ago

FH: Father with coronary artery disease, died of myocardial infarction at age 50 years; mother alive and well

SH: Active smoker, 40-year pack history; denies alcohol or illicit drug use; no regular exercise program

Meds: Aspirin 81 mg PO daily, hydrochlorothiazide 25 mg PO daily, metformin 500 mg PO twice daily, conjugated estrogen 0.625 mg PO daily, medroxyprogesterone 2.5 mg PO daily

Allergies/intolerances (reaction): No known drug allergies nor intolerances

PE:

VS: Blood pressure 152/98 mm Hg, HR 84 beats/min, RR 22 breaths/min, T 37°C (98.6°F), Ht 5′5″ (165 cm), Wt 212 lb (96.4 kg)

Cardiovascular: Regular rate and rhythm, normal S_1 and S_2, no S_3 or S_4; no murmurs, rubs, gallops

Lungs: Clear to auscultation and percussion

Abd: Nontender, nondistended, + bowel sounds

Ext: No clubbing, cyanosis, or edema

Labs: Fasting lipid profile: total cholesterol 206 mg/dL (5.33 mmol/L), HDL cholesterol 38 mg/dL (0.98 mmol/L), LDL cholesterol 119 mg/dL (3.08 mmol/L), triglycerides 246 mg/dL (2.78 mmol/L); fasting glucose 217 mg/dL (12.0 mmol/L); other labs within normal limits

Dobutamine stress echocardiography: Left ventricular ejection fraction at rest 35% (0.35), regional wall motion abnormalities during peak exercise suggestive of ischemia

Identify the patient's risk factors for stable ischemic heart disease.

How might her current drug regimen adversely affect the patient's stable ischemic heart disease?

Does she appear to have any SIHD-related complications?

What therapeutic alternatives are available to manage her stable ischemic heart disease?

unstable, or extensive coronary atherosclerosis is present (eg, > 70% occlusion of coronary lumen), PCI is often performed to restore coronary blood flow and relieve symptoms. Several catheter-based interventions may be used during PCI, including:

- Percutaneous transluminal coronary angioplasty (PTCA)
- Intracoronary bare metal stent (BMS) placement
- Intracoronary drug-eluting stent (DES) placement
- Rotational atherectomy

During PCI, a catheter is advanced into the diseased coronary artery, as described for cardiac catheterization. If PTCA is performed, a balloon at the end of the catheter is inflated inside the artery at the site of the critical stenosis, compressing the atherosclerotic plaque from the coronary lumen and restoring normal myocardial blood flow. Most PCI procedures involve the placement of a stent, a small metal scaffold-like device similar in size and shape to the spring at the tip of a ballpoint pen, at the site of angioplasty. Coronary stents are contained on special balloon catheters that are inflated at the site of stenosis to deploy the stent in the wall of the coronary artery, forming a sort of bridge to maintain a patent artery and improve coronary blood flow. Either a BMS or a DES may be used. DESs are impregnated with low concentrations of an antiproliferative drug (paclitaxel, everolimus, sirolimus, or zotarolimus), which is released locally over a period of weeks to inhibit **in-stent restenosis** of the coronary artery after PCI. Compared to BMS, DESs have been associated with a significant reduction in all-cause mortality for patients with IHD.[18] Stents are thrombogenic, especially until they become endothelialized (covered in endothelial cells like a normal coronary artery). To reduce the risk for in-stent thrombosis, MI, or death, DAPT (discussed later) is required until the stent becomes endothelialized. Lastly, rotational atherectomy may be performed wherein a special catheter is used to essentially cut away the atherosclerotic plaque, restoring coronary blood flow.

► *Coronary Artery Bypass Graft Surgery*

LO 7

As an alternative to PCI, CABG surgery, or open-heart surgery, may be performed if the patient is found to have extensive coronary atherosclerosis (generally > 70% occlusion of three or more coronary arteries) or is refractory to optimal medical treatment. In the former case, recent evidence suggests that CABG surgery is associated with a reduction in both the need for revascularization and mortality compared with PCI, particularly in patients with diabetes.[19] During CABG surgery, veins from the leg (ie, saphenous veins) and/or arteries from the chest wall (ie, internal mammary arteries) or less commonly from the arm (ie, radial artery) or stomach (gastroepiploic artery) are harvested and used as conduits to restore coronary blood flow. A median sternotomy, in which an incision is made the length of the sternum followed by surgical division of the sternum with an oscillating saw, is commonly required to gain access to the thoracic cavity and expose the heart. As the "new" blood vessels are being engrafted, the patient is typically placed on cardiopulmonary bypass (ie, heart-lung machine) to maintain appropriate myocardial and systemic perfusion. Alternative surgical approaches for advanced IHD may be used in some settings including "off-pump" CABG (cardiopulmonary bypass is not required) and minimally invasive CABG (ie, thoracoscopic surgery), although these techniques are uncommon. Because of its extremely invasive nature, CABG surgery is generally reserved for patients with extensive IHD or as a treatment of last resort in patients with symptoms refractory to medical therapy.

Pharmacologic Therapy

▶ *Pharmacotherapy to Prevent Acute Coronary Syndromes and Death*

LO 6 **Control of Risk Factors** A major component of any SIHD treatment plan is control of modifiable risk factors, including dyslipidemia, hypertension, and diabetes. Treatment strategies for dyslipidemia and hypertension in the patient with IHD are summarized in the following paragraphs. Visit chapters in this textbook on the management of hypertension (see Chapter 5) and dyslipidemias (see Chapter 12) for further information.

Because lipoprotein metabolism and the pathophysiology of atherosclerosis are closely linked, treatment of dyslipidemias is critical for both primary and secondary prevention of IHD-related cardiac events. In 2013, the ACC/AHA revised guidelines for the management of patients with dyslipidemia.[20] Unlike previous guidelines for dyslipidemia, current guidelines no longer recommend specific targets for LDL and non-HDL cholesterol and de-emphasize the use of non-statin therapies for the treatment of dyslipidemia. Rather, current guidelines focus on the use of statins stratified by presence of or 10-year risk for atherosclerotic cardiovascular disease (ASCVD). Recommendations for initiation of statin therapy for dyslipidemia include:[20]

LO 7

- High-intensity statin therapy in the presence of clinical ASCVD and for patients without clinical ASCVD in whom LDL cholesterol is 190 mg/dL (4.91 mmol/L) or greater; moderate-intensity therapy for elderly patients (age > 75 years) or those for whom safety concerns exist.
- Moderate to high-intensity statin therapy for patients at least 40 years of age with diabetes.
- Moderate to high-intensity statin therapy for patients with LDL cholesterol less than 190 mg/dL (4.91 mmol/L) who are at least 40 years of age and have a 10-year ASCVD risk of 7.5% or greater in the absence of diabetes; consideration may be given to moderate-intensity statin therapy in patients with a 10-year ASCVD risk between 5% and 7.5%.

Hypertension is another major, modifiable risk factor for the development of IHD and related complications. Aggressive identification and control of hypertension are warranted in patients with SIHD to minimize the risk of MACE. Most recently, the ACC and AHA released updated guidelines for the management of hypertension in adults, with specific recommendations for patients with SIHD.[21] Patients with SIHD and a BP of 130/80 mm Hg or higher should be started on antihypertensive therapy to reduce BP to a target of less than 130/80 mm Hg. Selection of initial agent is guided by the presence of compelling indications (eg, chronic stable angina, HFrEF, previous MI). β-Blockers (with the exception of atenolol and β-blockers with intrinsic sympathomimetic activity), ACE inhibitors, or ARBs are all recommended as first-line therapy in these patients. For patients who remain hypertensive (BP > 130/80 mm Hg) despite treatment with a β-blocker, ACE inhibitor, or ARB, additional medications should be added to further reduce BP to target. The choice of agent is dependent on the presence of angina symptoms. For patients with uncontrolled hypertension with angina, addition of a dihydropyridine calcium channel blocker (CCB) is recommended. For patients with SIHD whose angina symptoms are controlled, the addition of dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists (MRAs) may all be considered.

LO 7

Antiplatelet Agents Platelets play a major role in the pathophysiology of ACS. Thromboxane A_2 (TXA_2) is a potent platelet activator. Aspirin inhibits cyclooxygenase, an enzyme responsible for the production of TXA_2, thereby inhibiting platelet activation and aggregation. In patients with IHD, aspirin has been consistently shown to reduce the risk of MACE, particularly MI.[22] KEY CONCEPT Antiplatelet therapy with aspirin should be considered for all patients with SIHD, particularly in patients with a history of MI, in the absence of contraindications. Aspirin doses of 75 to 162 mg daily are recommended in patients with or at risk for SIHD.[1,3,23] Daily doses of aspirin above 162 mg offer no additional benefit but increase bleeding risk. If aspirin is contraindicated (eg, aspirin allergy) or is not tolerated by the patient, an alternative antiplatelet agent such as clopidogrel should be considered.[1]

LO 7

Binding of adenosine diphosphate to the $P2Y_{12}$ receptors on platelets activates glycoprotein IIb/IIIa receptors leading to platelet aggregation and thrombus formation. KEY CONCEPT Inhibition of the $P2Y_{12}$ receptor with either a thienopyridine (clopidogrel, prasugrel) or ticagrelor prevents platelet aggregation and is indicated in combination with aspirin in select patients with IHD. Ticlopidine is a $P2Y_{12}$ receptor inhibitor used historically in combination with aspirin, but is rarely used in practice because of hematologic toxicity. DAPT with aspirin and a $P2Y_{12}$ inhibitor is recommended following hospitalization for ACS and/or following PCI with stent placement to prevent ischemic events, although indications for specific drugs differ slightly.[3,24,25] Clopidogrel is a prodrug that is converted via a two-step process to its active thiol metabolite. The cytochrome P450 (CYP) 2C19 enzyme is involved in both steps of the biotransformation. Individuals with reduced CYP2C19 activity, either from inherited deficiencies of CYP2C19 or use of CYP2C19 inhibitors (eg, proton pump inhibitors), may produce less of the active thiol metabolite. These individuals are at increased risk for stent thrombosis and MACE during clopidogrel treatment compared to those with "normal" CYP2C19 activity.[26] The clopidogrel labeling now warns of reduced effectiveness in CYP2C19 poor metabolizers, who carry two dysfunctional *CYP2C19* gene alleles. The *CYP2C19*2* and *CYP2C19*3* alleles are the most common alleles leading to reduced CYP2C19 activity.

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Prasugrel is a thienopyridine that also requires biotransformation to its active metabolite. However, unlike clopidogrel, CYP2C19 deficiency does not alter its effectiveness. Ticagrelor is a direct-acting $P2Y_{12}$ inhibitor that does not require biotransformation to exert its antiplatelet effects and is unaffected by CYP2C19 activity. Thus, prasugrel or ticagrelor may be suitable alternatives to clopidogrel when reduced CYP2C19 activity is suspected.

LO 7

Antiproliferative drugs in DES reduce the risk of in-stent restenosis but delay endothelialization. Until endothelialization occurs, platelets are exposed to the foreign surface of the stent and can stimulate platelet adhesion, activation, aggregation, and eventual thrombus formation within the implanted stent resulting in acute ischemia. Thus, a longer period of DAPT is recommended in patients with SIHD treated with DES compared with BMS to prevent in-stent thrombosis. Following BMS implantation, patients with SIHD should be treated with DAPT for a minimum of 1 month compared to a minimum of 6 months following DES implantation.[3] In contrast to patients with SIHD, a longer duration of DAPT (minimum of 12 months) is recommended for patients who have had stent implantation in the setting of ACS, regardless of the type of stent implanted.[3] Select patients with IHD who have not experienced a bleeding

LO 7

Table 7–5

"DAPT" Score Calculation to Guide Prolonged Dual Antiplatelet Therapy (DAPT) Following Stent Implantation[3,27]

Variable	Points
Age ≥ 75 years	−2
Age 65 to < 75 years	−1
Age < 65 years	0
Current cigarette smoker	1
Diabetes mellitus	1
Myocardial infarction (MI) at presentation	1
Prior percutaneous coronary intervention (PCI) or MI	1
Stent diameter < 3 mm	1
Paclitaxel-eluting stent	1
Heart failure of left ventricular ejection fraction < 30% (0.30)	2
PCI of saphenous vein graft	2

A score of ≥ 2 is associated with a favorable benefit:risk ratio for prolonged DAPT while a score of < 2 is associated with unfavorable benefit:risk ratio.

complication on DAPT and are not at high risk for bleeding (eg, prior bleeding on DAPT, coagulopathy, oral anticoagulant use) may be considered for "prolonged" or "extended" duration of DAPT (> 1 month in SIHD with BMS, > 6 months in SIHD with DES, > 12 months in ACS with either BMS or DES) to further reduce the risk of ischemic complications, including late in-stent thrombosis, but at the expense of an increased risk of bleeding.[3] Given the delicate balance between benefit and harm associated with prolonged DAPT following stent implantation, use of a "DAPT score" (Table 7–5) may be useful to individualize the decision to continue DAPT by predicting patients who will derive benefit.[3,27] Conversely, patients who experience a significant bleeding complication, are at high risk for bleeding, or have a high risk of severe bleeding complications (eg, major intracranial surgery) may be considered for a shorter duration of DAPT (3 months for SIHD with DES, 6 months after ACS with stent implantation).[3] Because the risk for in-stent thrombosis is increased with premature discontinuation of DAPT, it is imperative for clinicians to educate patients on this risk, and the need for continuation of combination antiplatelet therapy for the recommended duration.

LO 7 Clopidogrel, prasugrel, and ticagrelor are all indicated in combination with aspirin for at least 1 year in patients with ACS who undergo PCI.[3,24,25] Both clopidogrel and ticagrelor are also indicated in combination with aspirin in patients with NSTEMI who do not undergo PCI.[24] In patients with ACS, DAPT more effectively reduces the risk of death, MI, and stroke compared with aspirin alone even in patients who are managed medically (eg, in the absence of PCI).[28-30] Compared to clopidogrel, prasugrel and ticagrelor provide greater protection against cardiovascular events in ACS but increase risk for bleeding.[29,30] For more information regarding the use of DAPT in the setting of ACS, see Chapter 8.

Statins Statins are the preferred drugs to lower LDL cholesterol based on their potency and efficacy in preventing cardiac events. Several studies in tens of thousands of patients with or at high-risk for SIHD demonstrate that lowering cholesterol with statins reduces the risk of MACE by 21%.[31]

In addition to their LDL cholesterol-lowering effect, statins likely confer additional benefits in patients with SIHD.[32] Prompted by evidence that patients with "normal" LDL cholesterol derive benefit from statins, studies suggest statins modulate the following characteristics thought to stabilize atherosclerotic plaques and contribute to the cardiovascular risk reduction seen with these drugs:

- Shift LDL cholesterol particle size from predominantly small, dense, highly atherogenic particles to larger, less atherogenic particles.
- Improve endothelial function leading to more effective vasoactive response of the coronary arteries.
- Prevent or inhibit inflammation by lowering C-reactive protein and other inflammatory mediators implicated in atherosclerosis.
- Possibly improve atherosclerotic plaque stability.

LO 6 LO 7 KEY CONCEPT In summary, to control risk factors and prevent MACE, statin therapy should be considered in all patients with SIHD, particularly in those with elevated LDL cholesterol or diabetes. Statins are potent lipid-lowering agents, possess non–lipid-lowering effects that may provide additional benefit to patients with SIHD, and have been shown to reduce morbidity and mortality in patients with and at high risk for SIHD. LO 7 Moreover, because statins improve outcomes in patients with SIHD and "normal" LDL cholesterol, statins should be considered in all patients with SIHD, regardless of baseline LDL cholesterol.

ACE Inhibitors and Angiotensin Receptor Blockers

Angiotensin II, a neurohormone produced primarily in the kidney, is a potent vasoconstrictor and stimulates the production of aldosterone. Together, angiotensin II and aldosterone increase BP and sodium and water retention (increasing ventricular wall tension), cause endothelial dysfunction, promote thrombus formation, and cause myocardial fibrosis.

ACE inhibitors decrease angiotensin II production and have consistently been shown to decrease morbidity and mortality in patients with HFrEF or history of MI.[33,34] In addition, there is evidence that ACE inhibitors reduce the risk of vascular events in patients with chronic stable angina or risk factors for SIHD.[35,36] In patients with vascular disease (including SIHD) or risk factors for vascular disease, both ramipril and perindopril reduced the risk of MACE by 20% or more in separate studies.[35,36]

LO 7 KEY CONCEPT In the absence of contraindications, ACE inhibitors should be considered in all patients with SIHD, particularly those individuals who also have hypertension, diabetes mellitus, chronic kidney disease, left ventricular dysfunction, history of MI, or any combination of these.[1] Additionally, ACE inhibitors should also be considered in patients at high risk for developing SIHD based on findings from the studies summarized above. ARBs may be used in patients with indications for ACE inhibitors but who cannot tolerate them due to side effects (eg, chronic cough). ARBs also antagonize the effects of angiotensin II. In one large trial, valsartan was as effective as captopril at reducing morbidity and mortality in post-MI patients.[33] However, there are far more data supporting LO 7 the use of ACE inhibitors in SIHD. Therefore, ACE inhibitors are preferred over ARBs in patients with a history of MI, diabetes, chronic kidney disease, or left ventricular dysfunction. The ACE inhibitors and ARBs with indications for patients with or at risk for SIHD or IHD-related complications are listed in Table 7–6.

Side effects with ACE inhibitors and ARBs include hyperkalemia, deterioration in renal function, and angioedema. Serum potassium increases are secondary to aldosterone inhibition and are more likely in the presence of preexisting renal

Table 7–6

Doses of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Indicated in Ischemic Heart Disease (IHD)

Drug	Indications	Usual Dosage in IHD[a]
Angiotensin-Converting Enzyme Inhibitors		
Captopril	HTN, HF, post-MI, diabetic nephropathy	6.25–50 mg three times daily
Enalapril	HTN, HF	2.5–40 mg daily in one to two divided doses
Fosinopril	HTN, HF	10–80 mg daily in one to two divided doses
Lisinopril	HTN, HF, post-MI	2.5–40 mg daily
Perindopril	HTN, IHD	4–8 mg daily
Quinapril	HTN, HF, post-MI	5–20 mg twice daily
Ramipril	HTN, high-risk for IHD, HF, post-MI	2.5–10 mg daily in one to two divided doses
Trandolapril	HTN, HF, post-MI	1–4 mg daily
Angiotensin Receptor Blockers		
Candesartan	HTN, HF	4–32 mg daily
Valsartan	HTN, HF, post-MI	80–320 mg daily in one to two divided doses
Telmisartan	HTN, high-risk for IHD	20–80 mg daily

[a]Reduce initial dose and gradually titrate upward as tolerated in renal impairment.

HF, heart failure; HTN, hypertension; MI, myocardial infarction.

impairment, diabetes, or concomitant therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), potassium supplements, or potassium-sparing diuretics. Reductions in glomerular filtration may occur during ACE inhibitor or ARB initiation or up-titration due to inhibition of angiotensin II-mediated vasoconstriction of the efferent arteriole. This type of renal impairment is usually temporary and more common in patients with preexisting renal dysfunction or unilateral renal artery stenosis. Bilateral renal artery stenosis is a contraindication for ACE inhibitors and ARBs because of the risk for overt renal failure. Angioedema is a potentially life-threatening adverse effect that occurs in less than 1% of white patients but up to 8% of African Americans treated with ACE inhibitors. Angioedema may also occur with the administration of ARBs. Patients treated with ACE inhibitors may develop a chronic cough secondary to bradykinin accumulation. For patients who develop a persistent ACE inhibitor-induced cough or mild angioedema, substitution of an ARB for an ACE inhibitor may be appropriate. Both ACE inhibitors and ARBs can cause fetal injury and death and are contraindicated in pregnancy.

LO 7

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► *Nitroglycerin to Relieve Acute Symptoms*

LO 6

Short-acting nitrates are first-line treatment to terminate acute episodes of angina. KEY CONCEPT Patients with SIHD should have sublingual nitroglycerin tablets or spray to relieve acute ischemic symptoms. Nitrates undergo biotransformation to nitric oxide. Nitric oxide activates smooth muscle guanylate cyclase, leading to increased intracellular concentrations of cyclic guanosine monophosphate (cGMP), release of calcium from the muscle cell, and ultimately, to smooth muscle relaxation. Nitrates primarily cause venodilation, leading to reductions in preload. The resultant decrease in ventricular volume and wall tension leads to a reduction in myocardial oxygen demand. In higher doses, nitrates cause arterial dilation and reduce afterload and BP. In addition to reducing oxygen demand, nitrates increase myocardial oxygen supply by dilating the epicardial coronary arteries and collateral vessels, as well as relieving vasospasm.

Short-acting nitrates are available in tablet and spray formulations for sublingual administration. Sublingual nitroglycerin tablets are well absorbed across the oral mucosa, produce an antianginal effect within 1 to 3 minutes, and are less expensive than the spray. However, the spray is preferred for patients who have difficulty opening the tablet container or produce insufficient saliva for rapid dissolution of sublingual tablets. At the onset of an angina attack, a 0.3 to 0.4 mg dose of nitroglycerin (tablet or spray) should be administered sublingually, and repeated every 5 minutes up to three times or until symptoms resolve. Standing enhances venous pooling and may contribute to hypotension, dizziness, or lightheadedness. Sublingual nitroglycerin may be used to prevent effort- or exertion-induced angina. In this case, the patient should use sublingual nitroglycerin 2 to 5 minutes prior to an activity known to cause angina, with the effects persisting for approximately 30 minutes. Isosorbide dinitrate, also available in sublingual form, has a longer half-life with antianginal effects lasting up to 2 hours. The use of short-acting nitrates alone, without concomitant long-acting antianginal therapy, may be acceptable for patients who experience angina symptoms once every few days. However, for patients with more frequent attacks, other antianginal therapies are recommended.

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The use of nitrates within 24 to 48 hours of a phosphodiesterase type 5 inhibitor (eg, sildenafil, vardenafil, and tadalafil), commonly prescribed for erectile dysfunction, is contraindicated. Phosphodiesterase degrades cGMP, which is responsible for the vasodilatory effects of nitrates. Concomitant use of nitrates and phosphodiesterase type 5 inhibitors enhances cGMP-mediated vasodilation and can result in serious hypotension, decreased coronary perfusion, and even death. All patients with SIHD should be prescribed sublingual nitroglycerin and educated regarding its use. Points to emphasize when counseling a patient on sublingual nitroglycerin use include:

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- The seated position is generally preferred when using nitroglycerin because the drug may cause dizziness.
- Call 911 if symptoms are unimproved or worsen 5 minutes after the first dose.
- Keep nitroglycerin tablets in the original glass container and close the cap tightly after use.
- Nitroglycerin should not be stored in the same container as other medications because this may reduce nitroglycerin's effectiveness.
- Repeated use of nitroglycerin is not harmful or addictive and does not result in any long-term side effects. Patients should not hesitate to use nitroglycerin whenever needed.
- Nitroglycerin should not be used within 24 hours of taking sildenafil or vardenafil or within 48 hours of taking tadalafil because of the potential for life-threatening hypotension.

► *Pharmacotherapy to Prevent Recurrent Ischemic Symptoms*

LO 5

LO 6

The overall goal of antianginal therapy is to allow patients with IHD to resume normal activities without symptoms of angina and to experience minimal to no adverse drug effects. The drugs used to prevent ischemic symptoms are β-blockers, CCBs, nitrates, and ranolazine. These drugs exert their antianginal

Table 7–7

Effects of Antianginal Medications on Myocardial Oxygen Demand and Supply

	Oxygen Demand			
Antianginal Agent	**Heart Rate**	**Wall Tension**	**Cardiac Contractility**	**Oxygen Supply**
β-Blockers	↓	↔ or ↓	↓	↔
Calcium channel blockers				
Verapamil, diltiazem	↓	↓	↓	↑
Dihydropyridines	↔ or ↑	↓	↓	↑
Nitrates	↑	↓	↔	↑
Ranolazine[a]	↔	↓	↔	↔

[a]The exact mechanism of the anti-ischemic effects of ranolazine is not known.

↓ decreases; ↔, no change; ↑, increases.

effects by improving the balance between myocardial oxygen supply and demand, with specific effects listed in Table 7–7. β-Blockers, CCBs, nitrates, and ranolazine decrease the frequency of angina and delay the onset of angina during exercise. However, there is no evidence that any of these agents prevent ACS or improve survival in patients with SIHD. Combination therapy with two or three antianginal drugs is often needed.

β-Blockers β-Blockers antagonize β_1- and β_2-adrenergic receptors in the heart, reducing heart rate and cardiac contractility, and decreasing myocardial oxygen demand. β-Blockers may also reduce oxygen demand by lowering BP and ventricular wall tension through inhibition of renin release from juxtaglomerular cells. By slowing heart rate, β-blockers prolong diastole, thus increasing coronary blood flow. However, β-blockers do not improve myocardial oxygen supply.

β-Blockers with intrinsic sympathomimetic activity (eg, acebutolol, pindolol, and penbutolol) have partial β-agonist effects and cause lesser reductions in heart rate at rest. As a result, β-blockers with intrinsic sympathomimetic activity may produce lesser reductions in myocardial oxygen demand and should be avoided in patients with SIHD. Other β-blockers appear equally effective at controlling symptoms of angina. The properties and recommended doses of various β-blockers used to prevent angina are summarized in Table 7–8. The frequency of dosing and drug cost should be taken into consideration when choosing a particular drug. Most β-blockers are available in inexpensive generic versions. β-Blockers should be initiated in doses at the lower end of the usual dosing range, with titration according to symptom and hemodynamic response. The β-blocker dose is commonly titrated to achieve the following:

- Resting heart rate between 55 and 60 beats/min.
- Maximum heart rate with exercise of 100 beats/min or less or 20 beats/min above the resting heart rate.

KEY CONCEPT In the absence of contraindications, β-blockers are the preferred initial therapy to prevent symptoms of angina in patients with SIHD because of their potential cardioprotective effects (eg, after MI and/or in patients with HFrEF). The long-term effects of β-blockers on morbidity and mortality in patients with SIHD are largely unknown. Yet, β-blockers decrease the risk of reinfarction and death by 23% in patients who have suffered an MI.[37] However, controversy exists regarding the role of β-blockers as first-line therapy for all patients with SIHD. In a recent observational study, β-blockers did not lower the risk of MACE in patients with SIHD or IHD risk factors.[38] Additionally, recommendations for using β-blockers for risk reduction in patients with SIHD or other vascular disease, in the absence of MI or heart failure, were recently downgraded.[39]

β-Blockers are contraindicated in patients with severe bradycardia (heart rate < 50 beats/min) or atrioventricular (AV)

Table 7–8

Properties and Dosing of β-Blockers in Ischemic Heart Disease

Drug	Receptor Affinity	Usual Dose Range	Dose Adjust in Hepatic Impairment	Dose Adjust in Renal Impairment
Atenolol	β_1-Selective	25–200 mg once daily	No	Yes
Betaxolol	β_1-Selective	5–20 mg once daily	No	Yes
Bisoprolol	β_1-Selective	2.5–10 mg once daily	Yes	Yes
Carvedilol	α_1, β_1, and β_2	3.125–25 mg twice daily	Avoid in severe impairment	No
Carvedilol phosphate	α_1, β_1, and β_2	10–80 mg once daily	Avoid in severe impairment	No
Labetalol	α_1, β_1, and β_2	100–400 mg twice daily	Yes	No
Metoprolol	β_1-Selective	50–200 mg twice daily (once daily for extended release)	Yes	No
Nadolol	β_1 and β_2	40–120 mg once daily	No	Yes
Nebivolol	β_1-Selective	5–10 mg once daily	Yes, avoid in severe impairment	Yes
Propranolol	β_1 and β_2	20–120 mg twice daily (60–240 mg once daily for long-acting formulation)	Yes	No
Timolol	β_1 and β_2	10–20 mg twice daily	Yes	Yes

conduction defects in the absence of a pacemaker. β-Blockers should be used with particular caution in combination with other agents that depress AV conduction (eg, digoxin, verapamil, and diltiazem) because of the increased risk for bradycardia and heart block. Relative contraindications include asthma, bronchospastic disease, and severe depression. β_1-Selective blockers are preferred in patients with asthma or chronic obstructive pulmonary disease. However, selectivity is dose dependent, and β_1-selective agents may induce bronchospasm in higher doses.

There are several precautions to consider with the use of β-blockers in patients with diabetes or heart failure. All β-blockers may mask the tachycardia and tremor (but not sweating) that commonly accompany episodes of hypoglycemia in diabetes. In addition, nonselective β-blockers may alter glucose metabolism and slow recovery from hypoglycemia in insulin-dependent diabetes. β_1-Selective agents are preferred because they are less likely to prolong recovery from hypoglycemia. Importantly, β-blockers should not be avoided in patients with SIHD and diabetes, particularly in patients with a history of MI who are at high risk for recurrent cardiovascular events. β-Blockers are indicated in patients with chronic HFrEF who are euvolemic due to their mortality benefit in this population. However, β-blockers are negative inotropes (ie, they decrease cardiac contractility). Therefore, β-blockers may worsen symptoms of heart failure in patients with left ventricular dysfunction (ie, ejection fraction < 40% [0.40]) and initiation or titration should be delayed in patients with acute heart failure until symptoms have resolved. In particular, when used for the management of SIHD in a patient with heart failure, β-blockers should be initiated in very low doses with slow up-titration to avoid worsening heart failure symptoms.

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Other potential adverse effects from β-blockers include fatigue, sleep disturbances, malaise, depression, and sexual dysfunction. Abrupt β-blocker withdrawal may increase the frequency and severity of angina, possibly because of increased receptor sensitivity to catecholamines after long-term β-blockade. If the decision is made to stop β-blocker therapy, the dose should be tapered over several days to weeks to avoid exacerbating angina.

LO 7

Calcium Channel Blockers CCBs inhibit calcium entry into vascular smooth muscle and cardiac cells, resulting in the inhibition of the actin-myosin complex and contraction of the cell. Inhibition of calcium entry into the vascular smooth muscle cells leads to systemic vasodilation and reductions in afterload. Inhibition of calcium entry into the cardiac cells leads to reductions in cardiac contractility. Thus, CCBs reduce myocardial oxygen demand by lowering both wall tension (through reductions in afterload) and cardiac contractility. The nondihydropyridine CCBs, verapamil and diltiazem, slow sinoatrial and AV nodal conduction, decrease heart rate, and further decrease myocardial oxygen demand. Because of their negative **chronotropic** effects, verapamil and diltiazem are generally more effective antianginal agents than the dihydropyridine CCBs. In contrast, dihydropyridine CCBs, nifedipine in particular, inhibit calcium in the vasculature and are potent vasodilators that can cause baroreflex-mediated increases in sympathetic tone and heart rate. In addition to decreasing myocardial oxygen demand, all CCBs increase myocardial oxygen supply by dilating coronary arteries, thus increasing coronary blood flow and relieving vasospasm.

CCBs are as effective as β-blockers at preventing ischemic symptoms. KEY CONCEPT CCBs are recommended as alternative treatment in SIHD when β-blockers are contraindicated or not tolerated. In addition, CCBs may be used in combination with β-blockers when initial treatment is unsuccessful. The combination of a β-blocker and a dihydropyridine CCB may improve symptoms better than either drug used alone.[40] However, the combination of a β-blocker with either verapamil or diltiazem should be used with extreme caution because both drugs decrease AV nodal conduction, increasing the risk for severe bradycardia or AV block when used together. If combination therapy is warranted, a long-acting dihydropyridine CCB is preferred. β-Blockers will prevent reflex increases in sympathetic tone and heart rate with the use of CCBs with potent vasodilatory effects. For patients with variable and unpredictable occurrences of angina, indicating possible coronary vasospasm, CCBs may be more effective than β-blockers in preventing angina episodes. The dosing of CCBs in IHD is described in Table 7–9.

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Table 7–9

Dosing of Calcium Channel Blockers in Ischemic Heart Disease

Drug	Usual Dose Range
Nondihydropyridines	
Diltiazem, extended release	120–360 mg once daily; consider dose adjustment in hepatic dysfunction
Verapamil, extended release	180–480 mg once daily; use initial dose of 120 mg in hepatic dysfunction
Dihydropyridines	
Amlodipine	5–10 mg once daily
Felodipine	5–10 mg once daily; use initial dose of 2.5 mg once daily in hepatic dysfunction
Nifedipine, extended release	30–90 mg once daily; dose adjust and monitor closely in hepatic dysfunction
Nicardipine	20–40 mg thrice daily; dose twice daily in hepatic dysfunction and up-titrate slowly in both hepatic and renal dysfunction

Verapamil and diltiazem are contraindicated in patients with bradycardia and preexisting conduction disease in the absence of a pacemaker. As previously noted, verapamil and diltiazem should be used with particular caution in combination with other drugs that depress AV nodal conduction (eg, β-blockers and digoxin). Because of their negative **inotropic** effects, CCBs may cause or exacerbate heart failure in patients with HFrEF and should be avoided in this population. The exceptions are amlodipine and felodipine that have less negative inotropic effects compared with other CCBs and appear to be safe in patients with left ventricular systolic dysfunction.[41,42] Finally, there is some evidence that short-acting CCBs (particularly short-acting nifedipine and nicardipine) may increase the risk of cardiovascular events.[43] Therefore, short-acting agents should be avoided in the management of SIHD.

Long-Acting Nitrates Nitrate products are available in both oral and transdermal formulations for chronic use. Commonly used products are listed in Table 7–10. All long-acting nitrate products produce effects within 30 to 60 minutes and are equally effective at preventing the recurrence of angina when used appropriately.

The major limitation of nitrate therapy is the development of tolerance with continuous use. The loss of antianginal effects may occur within the first 24 hours of continuous nitrate therapy.

Table 7–10

Nitrate Formulations and Dosing for Chronic Use

Formulation	Dose
Oral	
Nitroglycerin extended-release capsules	2.5 mg thrice daily initially, with up-titration according to symptoms and tolerance; allow a 10- to 12-hour nitrate-free interval
Isosorbide dinitrate tablets	5–20 mg two to three times daily, with a daily nitrate-free interval of at least 14 hours (eg, dose at 7 AM, noon, and 5 PM)
Isosorbide dinitrate slow-release capsules	40 mg one to two times daily, with a daily nitrate-free interval of at least 18 hours (eg, dose at 8 AM and 2 PM)
Isosorbide mononitrate tablets	5–20 mg twice daily initially, with up-titration according to symptoms and tolerance; doses should be taken 7 hours apart (eg, 8 AM and 3 PM)
Isosorbide mononitrate extended-release tablets	30–120 mg once daily
Transdermal	
Nitroglycerin extended-release film	0.2–0.8 mg/hour, on for 12–14 hours, off for 10–12 hours

Although the cause of tolerance is unclear, several mechanisms have been proposed, including the generation of free radicals that degrade nitric oxide. The most effective method to avoid tolerance and maintain the antianginal efficacy of nitrates is to allow a daily nitrate-free interval of at least 8 to 12 hours. Nitrates do not provide protection from ischemia during the nitrate-free period. Therefore, the nitrate-free interval should occur when the patient is least likely to experience angina, which is generally during the nighttime hours when the patient is sleeping and myocardial oxygen demand is reduced. Thus, it is common to dose long-acting nitrates so that the nitrate-free interval begins in the evening. For example, isosorbide dinitrate is typically dosed on awakening and again 6 to 7 hours later.

Monotherapy with nitrates for the prevention of ischemia should generally be avoided. Reflex increases in sympathetic activity and heart rate, with resultant increases in myocardial oxygen demand, may occur secondary to nitrate-induced venodilation. In addition, patients are unprotected from ischemia during the nitrate-free interval. β-Blockers and CCBs are dosed to provide 24-hour protection from ischemia. KEY CONCEPT Treatment with long-acting nitrates should be added to baseline therapy with either a β-blocker or CCB or a combination of the two. β-Blockers attenuate the increase in sympathetic tone and heart rate that occurs during nitrate therapy. As a result, the combination of β-blockers and nitrates is particularly effective at preventing angina and provides greater protection from ischemia than therapy with either agent alone. Monotherapy with nitrates may be appropriate in patients who have low BP at baseline or who experience symptomatic hypotension with low doses of β-blockers or CCBs.

Common adverse effects of nitrates include postural hypotension, dizziness, flushing, and headache secondary to venodilation. Headache often resolves with continued therapy and may be treated with acetaminophen. Hypotension is generally of no serious consequence. However, in patients with hypertrophic obstructive cardiomyopathy or severe aortic valve stenosis, nitroglycerin may cause serious hypotension and syncope. Therefore, long-acting nitrates are relatively contraindicated in these conditions. Because life-threatening hypotension may occur with concomitant use of nitrates and phosphodiesterase type 5 inhibitors, nitrates should not be used within 24 hours of taking sildenafil or vardenafil or within 48 hours of taking tadalafil. Skin erythema and inflammation may occur with transdermal nitroglycerin administration and may be minimized by rotating the application site.

Ranolazine Ranolazine is an anti-ischemic agent indicated for the management of chronic angina. The mechanism of action is unclear, but it is believed to inhibit the late inward sodium current during the plateau phase of the cardiac action potential. Under ischemic conditions, excess sodium may enter the myocardial cell during systole. The resultant intracellular sodium overload leads to intracellular calcium accumulation (calcium overload) through a sodium/calcium exchange mechanism. Calcium overload results in increases in left ventricular wall tension and MVO_2. By reducing intracellular sodium concentrations in ischemic myocytes, ranolazine decreases intracellular calcium overload, left ventricular wall tension, and MVO_2.

Similar to other antianginal drugs, ranolazine reduces angina and increases exercise capacity but does not reduce incidence of MACE. Ranolazine has minimal effects on heart rate or BP; thus, it may be an option in SIHD patients with low baseline BP or heart rate. Ranolazine is indicated as a first-line treatment for chronic stable angina. However, it is often reserved for patients with angina refractory to other antianginal medications due to its excessive cost. Ranolazine can prolong the QT interval. However, when used at recommended doses, the mean prolongation of QT interval is minimal (2.4 milliseconds [ms]).[44] The risk for QT interval prolongation is elevated in patients with hepatic impairment or taking other medications known to interact with ranolazine or prolong QT interval. Ranolazine should be started at a dose of 500 mg twice daily and increased to 1000 mg twice daily if needed for symptom relief. Higher doses are poorly tolerated and should be avoided. Contraindications to ranolazine are shown in Table 7–11. Common adverse effects with ranolazine include dizziness, constipation, headache, and nausea. Syncope may occur infrequently. Ranolazine is a CYP3A4 substrate, weak CYP2D6 substrate, CYP2D6 inhibitor, organic cation transporter 2 (OCT2) inhibitor, and both an inhibitor and substrate of P-glycoprotein (P-gp). Concomitant use of ranolazine with potent CYP3A4 inhibitors (eg, ketoconazole, clarithromycin, and nelfinavir) or inducers (eg, rifampin) is contraindicated. The use of ranolazine is contraindicated in patients with significant hepatic disease. The ranolazine dose should be limited to 500 mg twice daily when combined with moderate CYP3A4 inhibitors including diltiazem and verapamil. Ranolazine should be used cautiously with P-gp inhibitors (eg, cyclosporine) and substrates (eg, digoxin). The maximum doses of simvastatin (20 mg daily) and metformin (1700 mg daily) are lower during concomitant treatment with ranolazine.

► *Pharmacotherapy with No Benefit or Potentially Harmful Effects*

Hormone Replacement Therapy, Folic Acid, and Antioxidants Current guidelines recommend against the use of hormone replacement therapy (HRT), folic acid, or antioxidants for reducing cardiovascular risk.[1] Early evidence

Table 7–11

Contraindications and Precautions with Ranolazine

Contraindications	Precautions
Liver cirrhosis increases ranolazine plasma concentrations by 30%–80%, resulting in increased risk for QT interval prolongation	Treatment with moderate CYP3A4 inhibitors including diltiazem, verapamil, grapefruit juice, erythromycin, and fluconazole increases ranolazine plasma concentrations (twofold with diltiazem and verapamil)
Treatment with potent CYP3A4 inhibitors (including ketoconazole, clarithromycin, and nelfinavir) increases ranolazine concentrations (3.2-fold with ketoconazole)	Preexisting QT prolongation, history of torsades de pointes, or treatment with other QT-prolonging drugs as QT interval prolongation may occur with ranolazine
Treatment with CYP3A4 inducers (including rifampin, phenobarbital, phenytoin, carbamazepine, and St. John's wort) may significantly decrease the efficacy of ranolazine (by 95% with rifampin)	Treatment with a P-gp inhibitor, such as cyclosporine, may increase ranolazine absorption
	Up to a 50% increase in ranolazine plasma concentration has been observed in renal impairment
	Ranolazine may increase bioavailability of P-gp substrates (increases digoxin plasma concentrations by 1.5-fold)
	Ranolazine may cause reduced metabolism of CYP2D6 substrates
	Ranolazine may increase exposure to drugs transported by OCT2; metformin doses should not exceed 1700 mg/day in patients treated with ranolazine 1000 mg twice daily
	Ranolazine may reduce the metabolism of CYP3A3 substrates; the dose of simvastatin should not exceed 20 mg in patients treated with ranolazine

CYP, cytochrome P450; OCT2, organic cation transporter 2; P-gp, P-glycoprotein.

from observational studies with each of these suggested potential benefit in SIHD. However, no benefit was observed in randomized controlled clinical trials.[45-49] In the case of HRT, there was evidence of harm, with an increased risk of thromboembolic events and breast cancer with HRT in postmenopausal women.[46,47] Clinicians should consider discontinuing HRT therapy in women who suffer an acute coronary event while receiving such therapy.

LO 7

Herbal Supplements Herbal products are widely used for their purported cardiovascular benefits. Examples of such products include danshen, dong quai, feverfew, garlic, hawthorn, and hellebore. However, strong evidence supporting their benefits in cardiovascular disease is generally lacking. Furthermore, the potential for drug interactions and the lack of standardization limits the products' usefulness in clinical practice. Safety with herbal supplements in patients with SIHD is a major concern. Numerous case reports of adverse cardiovascular events led the Food and Drug Administration (FDA) to ban ephedra-containing products (eg, Ma huang) in 2004. However, other herbal supplements with potentially serious adverse cardiovascular effects remain easily accessible. Some herbal supplements, such as feverfew and garlic, may interact with antiplatelet and antithrombotic therapy and increase bleeding risk. Dietary supplements purported to enhance sexual performance may contain phosphodiesterase-like chemicals and increase risk for serious hypotension with nitroglycerin. Other agents may reduce the effectiveness of antianginal medications, such as St. John's wort with ranolazine. Thus, it is important to assess the use of herbal products in patients with SIHD and to counsel patients about the potential for drug interactions and adverse events with herbal therapies.

LO 7

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a specific plan for the management of the patient's stable ischemic heart disease. Your plan should include (a) the goals of therapy, (b) patient-specific nonpharmacologic and pharmacologic interventions to address these goals, and (c) a plan for follow-up to assess drug tolerance and whether the therapeutic goals have been achieved.

Cyclooxygenase-2 Inhibitors and Nonsteroidal Anti-inflammatory Drugs Data suggest that cyclooxygenase-2 (COX-2) inhibitors and nonselective NSAIDs may increase the risk for MI and stroke.[48] The cardiovascular risk with COX-2 inhibitors and NSAIDs may be greatest in patients with a history of, or with risk factors for, cardiovascular disease. The COX-2 inhibitors rofecoxib and valdecoxib were withdrawn from the market because of safety concerns. Product labeling for other COX-2 and nonselective NSAIDs (prescription and over-the-counter) now includes boxed warning about potential adverse cardiovascular effects. The AHA recommends the use of COX-2 inhibitors be limited to low-dose, short-term therapy in patients for whom there is no appropriate alternative.[50] Patients with cardiovascular disease should consult a clinician before using over-the-counter NSAIDs.

LO 7

Special Populations

▶ *Variant Angina*

Vasospasm as the sole etiology of angina (Prinzmetal or variant angina) is relatively uncommon. As a result, treatment options are not well studied. Nevertheless, based on the pharmacology of available drugs, several recommendations can be made. First, β-blockers should be avoided in patients with variant angina because of their potential to worsen vasospasm due to unopposed α-adrenergic receptor stimulation. In contrast, both CCBs and nitrates are effective in relieving vasospasm and are preferred in the management of variant angina. Because nitrates require an 8- to 12-hour nitrate-free interval, their role as monotherapy for prophylaxis of anginal attacks due to vasospasm is limited. However, immediate-release nitroglycerin is effective at terminating acute anginal attacks due to vasospasm. Therefore, all patients diagnosed with variant angina should be prescribed immediate-release nitroglycerin. CCBs are effective for monotherapy of variant angina. Because short-acting CCBs have been associated with increased risk of adverse cardiac events, they should be avoided.[41] Long-acting nitrates may be added to CCB therapy if needed.

LO 7

▶ *Microvascular Angina*

There are limited data on optimal therapy in patients with microvascular disease. Both ACE inhibitors and statins may produce beneficial effects on endothelial function and improve microvascular angina.[6] Short-acting nitrates remain the treatment of choice for relieving acute symptoms, although they may be less effective in microvascular disease. Similar to obstructive CAD, β-blockers are first line to control symptoms of angina in patients with microvascular disease and may be more effective than CCBs and long-acting nitrates in this setting.[4] Ranolazine may also produce favorable antianginal effects for patients with continued symptoms.

LO 7

▶ *Elderly Patients with IHD*

Elderly patients are more likely than younger patients to have other comorbidities that may influence drug selection for the treatment of angina. As a result, polypharmacy is more common in elderly patients, increasing the risk of drug–drug interactions, and perhaps decreasing medication adherence. Additionally, elderly patients are often more susceptible to adverse effects of antianginal therapies, particularly the negative chronotropic and inotropic effects of β-blockers and CCBs. Therefore, drugs should be initiated in low doses with close monitoring of elderly patients with IHD.

LO 7

▶ *Acute Coronary Syndromes*

Management of ACS is discussed in further detail in Chapter 8, "Acute Coronary Syndromes." It is important to educate patients with SIHD on the signs of ACS and steps to take if signs or symptoms occur. Importantly, patients should be instructed to seek emergent care if symptoms of angina last longer than 20 to 30 minutes, do not improve after 5 minutes of using sublingual nitroglycerin, or worsen after 5 minutes of using sublingual nitroglycerin. In patients with a history of ACS, it is crucial to select appropriate pharmacotherapy to prevent recurrent ACS and death. Appropriate pharmacotherapy for patients with a history of ACS includes aspirin (often in combination with a $P2Y_{12}$ inhibitor), ACE inhibitors or ARBs, β-blockers, statins, and sublingual nitroglycerin. In addition, control of cardiovascular risk factors (eg, dyslipidemia, hypertension, and diabetes) with lifestyle modifications and pharmacotherapy is critical.

LO 8

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OUTCOME EVALUATION

Assessing for Drug Effectiveness and Safety

LO 8

- In general, patients with SIHD should have follow-up evaluations every 4 to 12 months.[1] Early in the treatment course (eg, first year), more frequent evaluations (every 4–6 months) are recommended. For reliable patients whose symptoms are stable, less frequent evaluations are recommended after the first year of therapy. The length of the follow-up period may differ based on frequency and severity of symptoms, care coordination with other providers, regional practice patterns, patient preference, and physician availability.

LO 8

- KEY CONCEPT Monitor symptoms of angina at baseline and at each clinic visit for patients with SIHD to assess the effectiveness of antianginal therapy. In particular, assess the frequency and intensity of anginal symptoms.[1] Determining the frequency of sublingual nitroglycerin use is helpful in making this assessment. If angina is occurring with increasing frequency or intensity, adjust antianginal therapy and refer the patient for additional diagnostic testing (eg, coronary angiography) and possibly coronary intervention (eg, PCI or CABG surgery), if indicated.

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- Assess the patient for IHD-related complications, such as heart failure and arrhythmias.[1] The presence of new comorbidities may indicate worsening SIHD requiring additional workup or pharmacologic therapy.
- Routinely monitor hemodynamic parameters to assess drug tolerance. Assess BP at baseline, after drug initiation and after dose titration. BP should be monitored periodically in patients treated with β-blockers, CCBs, nitrates, ACE inhibitors, and/or ARBs. BP reduction may be particularly pronounced after initiation and dose titration of β-blockers that also possess α-blocking effects (eg, labetalol and carvedilol).

LO 8

- Routinely assess adherence to medical therapy and recommended lifestyle changes.
- Because of the potential for postural hypotension, warn patients that dizziness, presyncope, and even syncope may result from abrupt changes in body position during initiation or up-titration of drugs with α-blocking effects.

LO 8

- Closely monitor heart rate in patients treated with drugs that have negative chronotropic effects (eg, β-blockers, verapamil, or diltiazem) or drugs that may cause reflex tachycardia (eg, nitrates or dihydropyridine CCBs). Treatment with β-blockers, verapamil, or diltiazem can usually be continued in patients with asymptomatic bradycardia. However, reduce or discontinue treatment with these agents in patients who develop symptomatic bradycardia or serious conduction abnormalities.

LO 7

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- Regularly assess control of existing risk factors and the presence of new risk factors for SIHD.[1] Routine screening for the presence of metabolic syndrome will help in assessing the control of known major risk factors and identifying new risk factors. If new risk factors are identified and/or the presence of metabolic syndrome is detected, modify the pharmacotherapy regimen, as discussed previously, to control these risk factors and lower the risk of SIHD and IHD-related adverse events.

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- In patients treated with ACE inhibitors and/or ARBs, routinely monitor renal function and potassium levels at baseline, after drug initiation and dose titration, and periodically thereafter. This is particularly important when using these therapies in patients with preexisting renal impairment or diabetes because they may be more susceptible to these adverse events.

Duration of Therapy

LO 7

- Because these therapies reduce the risk for coronary events and death, treatment with antiplatelet (aspirin or clopidogrel), lipid-lowering, and neurohormonal-modifying medications for SIHD is generally lifelong.
- Antianginal therapy with a β-blocker, CCB, and/or nitrate is usually long term.
- A patient with severe symptoms managed with combination antianginal drugs who undergoes successful coronary revascularization may be able to reduce antianginal therapy. However, treatment with at least one agent that improves the balance between myocardial oxygen demand and supply is usually warranted.

Patient Care Process

Collect Information:

- Perform a thorough medication history; identify allergies and intolerances.
- Identify SIHD risk factors. (See Table 7–2.)
- Perform a physical examination; obtain vital signs.
- Collect laboratory and diagnostic information. (See Clinical Presentation and Diagnosis of Ischemic Heart Disease, and Figure 7–4.)

Assess the Information:

- Assess the patient's symptoms. (See Tables 7–3 and 7–4.)
- Determine quality, location, and duration of pain.
- Determine factors that provoke and relieve pain.
- Identify potential noncardiac conditions that can explain the patient's symptoms. (See Table 7–1.)
- Evaluate available laboratory and diagnostic information for SIHD. Do they suggest or confirm SIHD? Was PCI performed? Were there any stents placed and in what setting (ACS or SIHD)?
- Assess the efficacy and safety of the patient's previous SIHD drug regimen, if applicable.
- Identify medications that may interact with antianginal drug therapy.
- Assess adherence to medical therapy and recommended lifestyle modifications.
- Assess for the presence of SIHD-related complications.
- Assess preexisting and newly detected patient-specific risk factors for SIHD. (See Table 7–2 and Figure 7–4.)

Develop a Care Plan:

- Treat modifiable risk factors for SIHD; initiate appropriate lifestyle modifications.
- Treat hypertension, dyslipidemia, and diabetes.
- Initiate and/or modify therapy to prevent MACE. (See Figure 7–5.)
- Initiate and/or modify therapy to treat acute symptoms and prevent chronic angina symptoms. (See Figure 7–5.)

Implement the Care Plan:

- Refer patients with ACS to the hospital. (See Table 7–3.)
- Stress the importance of adherence to the care plan.
- Identify barriers that may affect adherence to the care plan; modify the care plan, if necessary.
- Provide education on the following: consequences of untreated SIHD, lifestyle modifications, medication administration, potential adverse effects, potential drug interactions, signs and symptoms of worsening angina, signs and symptoms of IHD-related complications, and when to seek emergent care.

Follow-up: Monitor and Evaluate:

- Reassess the care plan at least every 4 to 12 months, more often if necessary (eg, first year of therapy, persistent symptoms, intolerance to medical therapy).
- During each subsequent visit, assess control of preexisting risk factors and development of new risk factors, control of angina symptoms, presence of SIHD complications, adherence to the care plan, development of adverse drug reactions, and drug interactions.
- Reevaluate the efficacy and safety of the medical regimen assuring it includes appropriate therapy to prevent MACE and prevent angina symptoms. (See Figures 7–4 and 7–5.)
- Reassess barriers to treatment affecting adherence and modify the care plan, if necessary.

Abbreviations Introduced in This Chapter

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndromes
AHA	American Heart Association
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
AV	Atrioventricular
BMS	Bare metal stent
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCB	Calcium channel blocker
cGMP	Cyclic guanosine monophosphate
CHD	Coronary heart disease
COX-2	Cyclooxygenase-2
CT	Computed tomography
CYP	Cytochrome P450
DES	Drug-eluting stent
DAPT	Dual antiplatelet therapy
EBCT	Electron beam computed tomography
ECG	Electrocardiogram
FDA	Food and Drug Administration
HDL	High-density lipoprotein
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRT	Hormone replacement therapy
HTN	Hypertension
IHD	Ischemic heart disease
IV	Intravenous
LDL	Low-density lipoprotein
MACE	Major adverse cardiac events
MI	Myocardial infarction
MR	Magnetic resonance
MRA	Mineralocorticoid receptor antagonist
Ms	Milliseconds
MVO_2	Myocardial oxygen consumption
NSTEMI	Non–ST-segment elevation myocardial infarction
NSAID	Nonsteroidal anti-inflammatory drug
OCT2	Organic cation transporter 2
PCI	Percutaneous coronary intervention
P-gp	P-glycoprotein
PTCA	Percutaneous transluminal coronary angioplasty
SIHD	Stable ischemic heart disease
STEMI	ST-segment elevation myocardial infarction
TXA_2	Thromboxane A_2
UA	Unstable angina

REFERENCES

1. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60(24):e44–e164.
2. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;64(18):1929–1949.
3. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68(10):1082–1115.
4. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: a report from the American Heart Association. Circulation. 2017;135(10):e146–e603.
5. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–1645.
6. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. Circulation. 2010;121(21):2317–2325.
7. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226–235.
8. Braunwald E, Jones RH, Mark DB, et al. Diagnosing and managing unstable angina. Agency for Health Care Policy and Research. Circulation. 1994;90(1):613–622.
9. Sangareddi V, Chockalingam A, Gnanavelu G, Subramaniam T, Jagannathan V, Elangovan S. Canadian Cardiovascular Society classification of effort angina: an angiographic correlation. Coron Artery Dis. 2004;15(2):111–114.
10. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J. 2003;24(10):946–955.
11. Tzivoni D, Keren A, Meyler S, Khoury Z, Lerer T, Brunel P. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. Cardiovasc Drugs Ther. 1998;12(3):239–244.
12. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation. 2010;121(2):221–229.
13. Kuehn BM. Varenicline gets stronger warnings about psychiatric problems, vehicle crashes. JAMA. 2009;302(8):834.
14. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2960–2984.
15. Chen JT, Wesley R, Shamburek RD, Pucino F, Csako G. Meta-analysis of natural therapies for hyperlipidemia: plant sterols and stanols versus policosanol. Pharmacotherapy. 2005;25(2):171–183.
16. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. Am J Med. 2004;116(10):682–692.
17. Trikalinos TA, Alsheikh-Ali AA, Tatsioni A, Nallamothu BK, Kent DM. Percutaneous coronary interventions for non-acute coronary artery disease: a quantitative 20-year synopsis and a network meta-analysis. Lancet. 2009;373(9667):911–918.

18. Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol. 2015;65(23):2496–2507.
19. Sipahi I, Akay MH, Dagdelen S, Blitz A, Alhan C. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era. JAMA Intern Med. 2014;174(2):223–230.
20. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889–2934.
21. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 13. [Epub ahead of print.]
22. Antithrombotic Trialists Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849–1860.
23. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e637S–e668S.
24. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139–e228.
25. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127(4):e362–e425.
26. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA. 2010;304(16):1821–1830.
27. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA. 2016;315(16):1735–1749.
28. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494–502.
29. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001–2015.
30. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045–1057.
31. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267–1278.
32. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol. 2005;96(5A):24F–33F.
33. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349(20):1893–1906.
34. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. Am J Med. 2003;115(6):473–479.
35. Fox KM, Investigators EUtOrocewPiscAd. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet. 2003;362(9386):782–788.
36. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145–153.
37. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. BMJ. 1999;318(7200):1730–1737.
38. Bangalore S, Steg G, Deedwania P, et al. β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA. 2012;308(13):1340–1349.
39. Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011;58(23):2432–2446.
40. Klein WW, Jackson G, Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a meta-analysis. Coron Artery Dis. 2002;13(8):427–436.
41. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. N Engl J Med. 1996;335(15):1107–1114.
42. Cohn JN, Ziesche S, Smith R, et al. Effect of the calcium antagonist felodipine as supplementary vasodilator therapy in patients with chronic heart failure treated with enalapril: V-HeFT III. Vasodilator-Heart Failure Trial (V-HeFT) Study Group. Circulation. 1997;96(3):856–863.
43. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA. 1997;277(9):739–745.
44. Koren MJ, Crager MR, Sweeney M. Long-term safety of a novel antianginal agent in patients with severe chronic stable angina: the Ranolazine Open Label Experience (ROLE). J Am Coll Cardiol. 2007;49(10):1027–1034.
45. Cook NR, Albert CM, Gaziano JM, et al. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. Arch Intern Med. 2007;167(15):1610–1618.
46. Heiss G, Wallace R, Anderson GL, et al. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. JAMA. 2008;299(9):1036–1045.
47. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280(7):605–613.

48. Marti-Carvajal AJ, Sola I, Lathyris D, Salanti G. Homocysteine lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2009(4):CD006612.
49. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. Lancet. 2003;361(9374): 2017–2023.
50. Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation. 2007;115(12):1634–1642.

8 Acute Coronary Syndromes

Kelly C. Rogers, Shannon W. Finks, and Sarah A. Spinler

LEARNING OBJECTIVES

LO

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

1. Define the role of atherosclerotic plaque, platelets, and the coagulation system in an acute coronary syndrome (ACS).
2. List key electrocardiographic (ECG), biomarker, and clinical features identifying a patient with non–ST-segment elevation (NSTE)–ACS and ST-segment elevation myocardial infarction (STEMI).
3. Devise an initial, early pharmacotherapy treatment and monitoring plan for a patient presenting with either NSTE-ACS or STEMI given patient-specific data.
4. Devise an antithrombotic pharmacotherapy treatment and monitoring plan for a patient with NSTE-ACS or STEMI undergoing percutaneous coronary intervention (PCI) given patient-specific data.
5. Devise an antithrombotic pharmacotherapy treatment and monitoring plan for a patient with NSTE-ACS or STEMI not undergoing PCI given patient-specific data.
6. Develop a pharmacotherapy and risk factor modification treatment plan for secondary prevention of coronary heart disease (CHD) events in a patient following NSTE-ACS or STEMI.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States and one of the major causes of death worldwide. Acute coronary syndromes (ACSs), including **unstable angina** (UA) and **myocardial infarction** (MI), are a form of CHD that comprises the most common cause of CVD death.[1]

LO 1

KEY CONCEPT ACS is primarily caused by rupture of an atherosclerotic plaque with subsequent platelet adherence, activation, aggregation, and the activation of the clotting cascade. Ultimately, a thrombus composed of fibrin and platelets may develop, resulting in incomplete or complete occlusion of a coronary artery.[2] ACS is a spectrum of disease encompassing **ST-segment elevation MI** (STEMI) or **non-ST segment elevation** (NSTE)-ACS, which are classified according to ECG changes and underlying pathophysiology.[3,4] The American Heart Association (AHA), American College of Cardiology (ACC), and American College of Cardiology Foundation (ACCF) recommend strategies or guidelines for ACS patient care for STEMI and NSTE-ACS which includes both UA and non–ST-elevation MI (NSTEMI). In collaboration with the Society for Cardiovascular Angiography and Interventions (SCAI), the ACCF and AHA issue joint guidelines for **percutaneous coronary intervention** (PCI), including PCI in the setting of ACS. These practice guidelines are based on a review of available clinical evidence, have graded recommendations based on evidence and expert opinion, and are updated periodically. These guidelines form the cornerstone for quality care of the ACS patient.[3-5]

EPIDEMIOLOGY

Each year, approximately 695,000 Americans will have a new "coronary attack," defined as a first hospitalization for MI or CHD death, while 325,000 will have a recurrent hospitalization event.[1] The risks of CHD events, such as death, recurrent MI, and stroke, are higher for patients with established CHD and a history of MI than for patients with no known CHD.

The incidence rate of MI in the United States has been decreasing since 2007.[1] In particular, the number of patients presenting with STEMI has significantly decreased (from 133 to 50 cases per 100,000 person-years). Nevertheless, 114,019 Americans died of an MI in 2014. One in seven deaths is secondary to CHD, which is the leading cause of hospitalization in the United States.[1] With median length of hospital stay being 3.2 days, the cost of CHD is high.[6] Estimated direct and indirect costs are more than $199 billion and this figure is expected to double by 2030.[1]

Mortality rates have been declining since the 1990s. Improvements in care that may have contributed to this reduction include greater use of guideline-recommended drugs (eg, aspirin [ASA], β-blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors [statins], $P2Y_{12}$ inhibitors); reductions in the median times for administering fibrinolytics and performing primary PCI; and increased use of early coronary angiography and PCI for high-risk patients with NSTE-ACS.[1] In patients with STEMI, in-hospital death rates are approximately 3% in patients receiving primary PCI, 7% for patients who are treated with fibrinolytics, and 16% for patients who do not receive reperfusion therapy. In patients with NSTEMI, in-hospital mortality is less than 5%. Other than persistent ST-segment changes and troponin, predictors of in-hospital mortality include older age, elevated serum creatinine (SCr), tachycardia, and heart failure (HF).[7]

ETIOLOGY

Endothelial dysfunction, inflammation, and formation of fatty streaks contribute to the formation of atherosclerotic coronary

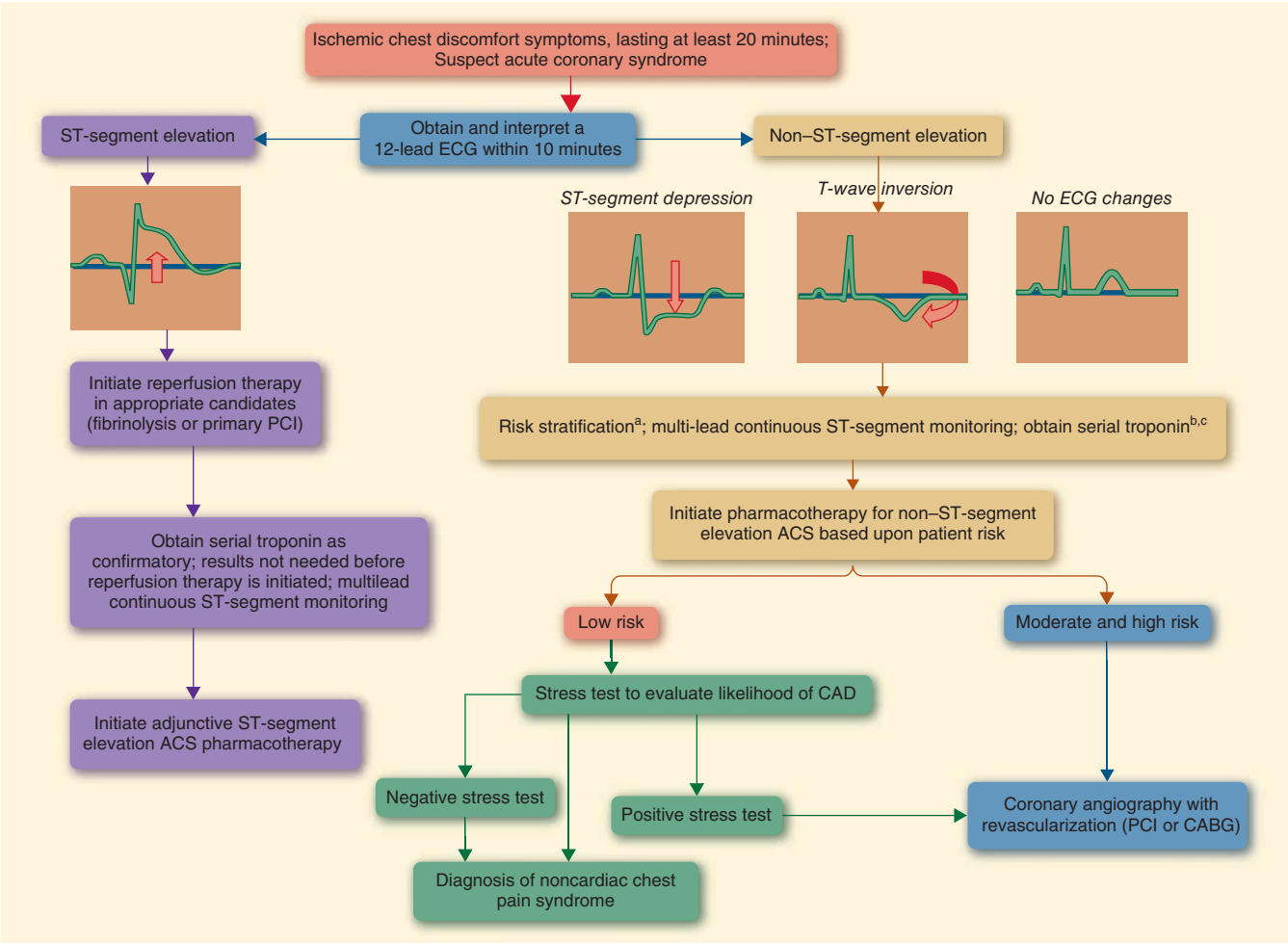

FIGURE 8–1. Evaluation of the acute coronary syndrome patient. [a]As described in Table 8–1. [b]"Positive": Above the myocardial infarction decision limit. [c]"Negative": Below the myocardial infarction decision limit. (ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; ECG, electrocardiogram; PCI, percutaneous coronary intervention.) (Reproduced with permission from: Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:167.)

artery plaques, the underlying cause of coronary artery disease (CAD).[8] KEY CONCEPT The predominant cause of ACS in more than 90% of patients is atheromatous plaque rupture, fissuring, or erosion of an unstable atherosclerotic plaque.[2,8] This is called an MI type 1, which generally occurs in coronary arteries where the stenosis occludes less than 50% of the lumen prior to the event, rather than a more stable 70% to 90% stenosis of the coronary artery.[4,9] Stable stenoses are characteristic of stable angina, are not considered an ACS, and are discussed in Chapter 7. MI type 2 is related to a reduction in myocardial oxygen supply or an increase in myocardial demand in the absence of a coronary artery process. MI type 3 is defined as MI resulting in death without the possibility of measuring biomarkers, while MI types 4 and 5 occur during revascularization procedures.[9]

LO 1

PATHOPHYSIOLOGY

LO 2

The term ACS encompasses all clinical syndromes compatible with acute myocardial ischemia and/or MI resulting from an imbalance between myocardial oxygen demand and supply. In contrast to stable angina, an ACS results primarily from diminished myocardial blood flow secondary to an occlusive or partially occlusive coronary artery thrombus. ACSs are classified according to ECG changes into STEMI or NSTE-ACS (NSTEMI and UA) (Figure 8–1).[3,4] An injury that transects the entire thickness of the myocardial wall results in a STEMI which will result in the release of biomarkers, mainly troponins T or I, from the necrotic myocytes into the bloodstream. An NSTEMI is limited to the subendocardial myocardium and is usually smaller and not as extensive as a STEMI. NSTEMI differs from UA in that ischemia is severe enough to result in the release of troponins. The clinical significance of serum markers is discussed in greater detail in later sections of this chapter.

Plaque Rupture and Clot Formation

LO 1

Plaques that rupture are generally characterized by a soft lipid-rich necrotic core, a thin fibrous cap, adventitial and perivascular inflammation, intraplaque hemorrhage, angiogenesis, and expansive vascular remodeling. The latter explains why these plaques only show minimal luminal obstruction, despite being larger than plaques that characterize stable angina which are associated with more severe luminal narrowing.[2,8] Following plaque rupture, a clot (a partially or completely occlusive thrombus) forms on top of the ruptured plaque. The thrombogenic contents of the plaque are exposed to blood elements. Exposure of collagen

and tissue factor induce platelet adhesion and activation, which promote the release of platelet-derived vasoactive substances, including adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2).[8] These produce vasoconstriction and potentiate platelet activation. Furthermore, during platelet activation, a change in the conformation in the glycoprotein (GP) IIb/IIIa surface receptors of platelets occurs that cross-links platelets to each other through fibrinogen bridges. This is considered the final common pathway of platelet aggregation. Inclusion of platelets gives the clot a white appearance. Simultaneously, the extrinsic coagulation cascade pathway is activated as a result of exposure of blood components to the thrombogenic lipid core and disrupted endothelium, which are rich in tissue factor. This leads to the production of thrombin (factor IIa), which converts fibrinogen to fibrin through enzymatic activity. Fibrin stabilizes the clot and traps red blood cells, which gives the clot a red appearance. Therefore, the clot is composed of cross-linked platelets and fibrin strands.[2,8]

Ventricular Remodeling Following an Acute MI

Ventricular remodeling is a process that occurs in several cardiovascular (CV) conditions including HF and following an MI. It is characterized by left ventricular dilation and reduced pumping function of the left ventricle, leading to cardiac failure.[10] Because HF represents one of the principal causes of morbidity and mortality following an MI, preventing ventricular remodeling is an important therapeutic goal.

Use of ACE inhibitors, ARBs, β-blockers, and aldosterone antagonists can slow down or reverse ventricular remodeling through inhibition of the renin-angiotensin aldosterone system and/or through improvement in hemodynamics (decreasing preload or afterload).[10] These agents also significantly improve survival in ACS patients.

At some point during hospitalization, prior to discharge, patients with a definite ACS should have their left ventricular function (LVF) evaluated.[3,4] The most common way LVF is measured is using an echocardiogram to calculate the patient's left ventricular ejection fraction (LVEF, percent of blood pumped out of the left ventricle with each contraction). LVF is one of the strongest predictors of mortality following MI. Patients with LVEF less than 40% (0.40) are at high risk of death. LVEF is an important factor to consider when contemplating the use of several drugs, such as ACE inhibitors and aldosterone antagonists.

Complications

This chapter focuses on management of the uncomplicated ACS patient. However, it is important for clinicians to recognize complications of an acute MI as these may increase the risk of mortality. The most serious early complication of MI is cardiogenic shock, occurring in approximately 7% of hospitalized patients presenting with STEMI.[11,12] Mortality in cardiogenic shock patients with MI is high, approaching 60%.[12] Other complications that may result from MI are HF, valvular dysfunction, bradycardia, heart block, **pericarditis**, stroke secondary to left ventricular thrombus embolization, venous thromboembolism, left ventricular free wall rupture, and ventricular and atrial tachyarrhythmias.[3] In fact, many patients die, presumably from ventricular fibrillation, prior to reaching the hospital. Patients with ventricular fibrillation or sustained ventricular tachycardia occurring more than 2 days following MI (which are not due to transient and reversible ischemia, reinfarction, or metabolic abnormalities), those with LVEF less than 30% (0.30; measured at least 40 days after STEMI) regardless of symptoms, or those with LVEF less than or equal to 35% (0.35) with New York Heart Association functional classes II to III may experience a mortality benefit against sudden cardiac death from placement of an implantable cardioverter defibrillator (ICD).[3]

CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms and Physical Examination Findings

LO 2

The classic symptom of an ACS is severe new-onset or increasing substernal angina that is at least 20 minutes in duration, most often occurring at rest. The pain may radiate to the shoulder, down the left arm, and to the back or jaw. Associated symptoms include nausea, vomiting, **diaphoresis**, or shortness of breath. Although similar to stable angina, the duration may be longer and the intensity may be greater.[3,4] Elderly, female patients, and diabetics may present with a more atypical presentation, including epigastric pain, shortness of breath, or indigestion symptoms in the absence of chest pain. Patients across the spectrum of ACS can present with symptoms. All health care professionals should review these warning symptoms with patients at high risk for CHD. On physical examination, no specific features are indicative of ACS. Patients with suspected ACS should be referred immediately to an emergency department (ED).

12-Lead ECG

KEY CONCEPT There are key features of a 12-lead ECG that identify and risk-stratify a patient with an ACS. Within 10 minutes of presentation to an ED with symptoms of ischemic chest discomfort, a 12-lead ECG should be obtained and interpreted. If the first ECG is not diagnostic, additional ECGs should be performed every 15 to 30 minutes for the first hour if the patient is still symptomatic and the clinician has a high suspicion of ACS.[4] KEY CONCEPT When possible, an ECG should be performed by emergency medical system providers to reduce the delay until myocardial reperfusion. If available, a prior ECG should be reviewed to identify whether ischemic changes are new or old, with new findings being more indicative of an ACS.

LO 2

Key findings on review of an ECG that indicate myocardial ischemia or infarction are ST-segment elevation (STE), ST-segment depression, and T-wave inversion (see Figure 8–1).[3,4] ST-segment and/or T-wave changes in certain groupings of ECG leads help to identify the location of the coronary artery that is the cause of the ischemia or infarction. In addition, the appearance of a new left bundle-branch block accompanied by chest discomfort is highly specific for acute STEMI. Approximately one-third of patients diagnosed with MI present with STE on their ECG, with the remainder having ST-segment depression, T-wave inversion, or in some instances, no ECG changes.[4] According to the latest guidelines, the diagnosis of STE, in the absence of left bundle-branch block or left ventricular hypertrophy, is a new STE in at least two contiguous leads of greater than or equal to 2 mm in men and greater than or equal to 1.5 mm in women in leads V_2-V_3 and/or of greater than or equal to 1 mm in other leads. Some parts of the heart are more "electrically silent" than others, and myocardial ischemia may not be detected on an ECG. Therefore, it is important to review findings from the ECG in conjunction with biochemical markers of myocardial necrosis, such as troponin I or T, clinical symptoms, and other risk factors for CHD to determine the patient's risk for experiencing a new MI or having other complications.

Clinical Presentation and Diagnosis

General

- The patient is typically in acute distress and may develop or present with acute HF, cardiogenic shock, or cardiac arrest.

Symptoms

- The classic symptom of ACS is substernal chest pain or discomfort. Accompanying symptoms may include radiation of pain to arm, back, or jaw, nausea, vomiting, diaphoresis, anxiety, or shortness of breath.
- Elderly, women, and diabetics are more likely to present with atypical symptoms such as indigestion, epigastric pain, shortness of breath, or anxiety and less likely to present with classic symptoms.

Physical Signs

- There are no "classic" signs for ACS.
- Patients with ACS may present with signs of acute HF, including edema, jugular venous distention, an S_3 sound on auscultation, or pulmonary edema on a chest X-ray.
- Patients may also present with arrhythmias such as tachycardia, bradycardia, or heart block.

Laboratory Tests

- Troponin I or T is measured at presentation and repeated 2 to 3 times at 3- to 6-hour intervals to ascertain heart muscle damage; confirmatory for the diagnosis of an infarction. For patients with NSTE-ACS, an elevated troponin is diagnostic for MI, differentiating NSTEMI from UA. Patients presenting with suspected NSTE-ACS who do not have an MI undergo further diagnostic testing to determine whether they have UA or are not experiencing an ACS.
- Blood chemistry tests are performed with particular attention given to potassium and magnesium, which may affect heart rhythm.
- SCr is measured, and creatinine clearance (CrCl) is used to identify patients who may need dosing adjustments for medications, as well as those who are at high risk of morbidity and mortality.
- Baseline complete blood count (CBC) and coagulation tests (activated partial thromboplastin time [aPTT] and international normalized ratio [INR]) should be obtained because most patients will receive antithrombotic therapy that increases the risk for bleeding.
- Fasting lipid panel within 24 hours.

Other Diagnostic Tests

- The 12-lead ECG is the first step in management. Patients are risk stratified into two groups: STEMI or NSTE-ACS.
- High-risk ACS patients, especially those with STEMI and those with recurrent chest discomfort will undergo coronary angiography via a left heart catheterization and injection of contrast dye into the coronary arteries to determine the presence and extent of coronary artery stenoses with possible PCI.
- During hospitalization, a measurement of LVF, such as an echocardiogram, is performed to identify patients with EF less than or equal to 40% (0.40) who are at high risk of death following hospital discharge.
- Selected low-risk patients may undergo early stress testing.

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Biochemical Markers/Cardiac Enzymes

LO 2

Biochemical markers of myocardial cell death are important for confirming the diagnosis of MI. KEY CONCEPT The diagnosis of MI is confirmed when the following conditions are met in a clinical setting consistent with myocardial ischemia: "Detection of a rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit and with at least one of the following: (a) symptoms of ischemia; (b) ECG changes of new ischemia or development of pathological Q waves; (c) imaging evidence of new loss of viable myocardium; (d) new regional wall motion abnormality; or (e) identification of an intracoronary thrombus by angiography or autopsy."[9] The most recent guidelines indicate that only the use of troponin assays is recommended to assess myocardial necrosis. Typically, troponin levels are obtained at presentation, then 3 to 6 hours later in patients with a high suspicion of MI to identify variations (increase or decrease ≥ 20% if the initial value is increased). In patients with normal troponin levels with an intermediate or high suspicion of ACS, additional levels should be obtained after 6 hours.[4] Troponins are released into the bloodstream approximately 2 to 4 hours after an MI and generally peak around 18 to 24 hours. Troponins can stay elevated for up to two weeks. A single measurement of troponin is not adequate to exclude a diagnosis of MI, as up to 15% of values that were initially below the level of detection (a "negative" test) rise to the level of detection (a "positive" test) in subsequent hours. Additionally, a single "positive" troponin may not be secondary to an MI as elevations can occur in other clinical conditions, such as pulmonary embolus, tachyarrhythmias, pericarditis, myocarditis, and sepsis, which can complicate diagnosis. Measurement of N-terminal pro B-type natriuretic peptide (BNP) may help predict long-term risk of mortality in patients with ACS but does not aid with acute diagnosis.[4]

Risk Stratification

KEY CONCEPT Patient symptoms, past medical history, ECG, and troponins are utilized to stratify patients into low, medium, or high risk of death, MI, or likelihood of failing pharmacotherapy and needing urgent coronary angiography and PCI (Table 8–1). Initial treatment according to risk stratification is depicted in Figure 8–1.[3,4] Patients with STEMI are at the highest risk of death; therefore, immediate reperfusion strategies should be initiated. The ACCF/AHA/SCAI PCI guidelines define a target time to initiate reperfusion treatment as within 30 minutes of first medical contact for fibrinolytics (eg, alteplase, reteplase, and tenecteplase) and within 90 minutes from presentation for primary PCI.[5] The sooner the infarct-related coronary artery is opened, the lower

Table 8–1

Risk Stratification for Acute Coronary Syndromes[4]

TIMI Risk Score for NSTE-ACS

One point is assigned for each of the seven medical history and clinical presentation findings below. The point total is calculated, and the patient is assigned a risk for experiencing the composite endpoint of death, MI, or urgent need for revascularization.

- Age 65 years or older
- Three or more CHD risk factors: smoking, hypercholesterolemia, HTN, DM, family history of premature CHD death/events
- Known CAD (50% or greater stenosis of at least one major coronary artery on coronary angiogram)
- Aspirin use within the past 7 days
- Two or more episodes of chest discomfort within the past 24 hours
- ST-segment depression 0.5 mm or greater
- Positive biochemical marker for infarction

High-Risk	Medium-Risk	Low-Risk
TIMI Risk Score 5–7 points	TIMI Risk Score 3–4 points	TIMI Risk Score 0–2 points

TIMI Risk Score	Mortality, MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 Days
0/1	4.7%
2	8.3%
3	13.2%
4	19.9%
5	26.2%
6/7	40.9%

GRACE Risk Factors for Increased Mortality and the Composite of Death or MI in ACS

Signs and symptoms of HF
Low systolic BP
Elevated heart rate
Older age
Elevated SCr
Baseline risk factors on clinical evaluation: cardiac arrest at admission, ST-segment deviation, elevated troponin
A high-risk patient is defined as a GRACE Risk Score more than 140 points (for in-hospital mortality)
The clinical application tool is available at http://www.outcomes-umassmed.org/grace/

An online calculator for the GRACE Risk Model is available at http://www.outcomes-umassmed.org/GRACE/acs_risk/acs_risk_content.html (Accessed August 28, 2017).

ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; DM, diabetes mellitus; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; HTN, hypertension; MI, myocardial infarction; NSTE, non–ST-segment elevation; SCr, serum creatinine; TIMI, thrombolysis in myocardial infarction.

the mortality and the greater the amount of myocardium that is preserved.[5] Although all patients should be evaluated for reperfusion therapy, not all patients may be eligible. Indications and contraindications for fibrinolytic therapy are described in the treatment section of this chapter. If patients with STEMI are not eligible for reperfusion therapy, additional pharmacotherapy should be initiated in the ED and the patient transferred to a coronary intensive care unit.

Risk-stratification of the patient with NSTE-ACS is more complex because outcomes vary. Patients with a high likelihood of coronary ischemia have a greater risk of adverse cardiac events.[4] Not all patients presenting with suspected NSTE-ACS have CAD. Some are eventually diagnosed with nonischemic chest discomfort. In general, among NSTE-ACS patients, those with ST-segment depression (see Figure 8–1) and/or elevated biomarkers are at higher risk of death or recurrent infarction. Various risk scores are available and should be used to assess the prognosis of patients presenting with NSTE-ACS (see Table 8–1).[4]

Based on this risk assessment, a management strategy is chosen and patients are either treated using: (1) an invasive strategy, which involves coronary angiography in patients classified as high-risk or very high-risk of CV events based on clinical characteristics (eg, high TIMI [Thrombolysis in Myocardial Infarction] score), or (2) an ischemia-guided strategy in which patients initially receive medication therapy alone and will undergo an invasive evaluation only if they fail medical therapy (eg, continued ischemia despite optimal medical treatment) or have objective evidence of ischemia on noninvasive stress testing.[4] The ischemia-guided strategy is generally reserved for patients stratified as low-risk. The timing of the diagnostic angiography in moderate- to high-risk patients is generally guided by the short-term risk of the patients, with the invasive strategy of early coronary angiography preferred in very-high and high-risk individuals.[4]

TREATMENT

Desired Outcomes

Short-term desired outcomes in a patient with ACS are: (a) early restoration of blood flow to the infarct-related artery to prevent infarct expansion (in the case of MI) or prevent complete occlusion and MI (in UA); (b) prevention of death and other MI complications; (c) prevention of coronary artery reocclusion; (d) relief of ischemic chest discomfort; and (e) resolution of ST-segment and T-wave changes on the ECG.

Long-term desired outcomes are control of CV risk factors, prevention of additional CV events, including reinfarction, stroke, and HF, and improvement in quality of life.

General Approach to Treatment

Selecting evidence-based therapies described in the guidelines for patients without contraindications results in lower mortality.[3,4] General treatment measures for all STEMI and high- and intermediate-risk NSTE-ACS patients include admission to hospital, oxygen administration (if oxygen saturation is low, < 90% [0.90] or respiratory distress), continuous multilead ST-segment monitoring for arrhythmias and ischemia, frequent measurement of vital signs, bed rest for 12 hours in hemodynamically stable patients, avoidance of the Valsalva maneuver (prescribe stool softeners routinely), and pain relief (Figures 8–2 and 8–3).[3,4]

Because risk varies and resources are limited, it is important to triage and treat patients according to their risk category. Initial approaches to treatment of STEMI and NSTE-ACS patients are outlined in Figures 8–2 and 8–3. Patients with STE are at high risk of death, and efforts to reestablish coronary perfusion as well as adjunctive pharmacotherapy should be initiated immediately (see Figure 8–2). Features identifying low-, moderate-, and high-risk NSTE-ACS patients are described in Table 8–1 and treatment efforts are outlined in Figure 8–3.[4]

Patient Encounter 1, Part 1

A 62-year-old, 87-kg (191-lb) Hispanic male developed substernal chest squeezing and left arm tingling while raking leaves. When it was not relieved by rest, his wife called 911. Local paramedics arrived and ST-segment elevation was found on 12-lead ECG. He was given a total of three 0.4 mg sublingual nitroglycerin tablets by mouth over three successive doses, 325 mg ASA by mouth, and morphine 2-mg IV push without relief of discomfort upon transport to the emergency department (ED). He was taken to a facility with a cardiac catheterization laboratory with the intent of performing primary PCI.

PMH: Hypertension (HTN) for 7 years; dyslipidemia for 7 years; diabetes mellitus (DM) type 2 for 5 years; chronic kidney disease (CKD) for 2 years

FH: Mother with stroke at age 65 years; father with myocardial infarction at age 55 years; siblings with HTN and DM

SH: Nonsmoker, never smoked

Allergies: NKDA

Meds: Lisinopril 20 mg by mouth once daily; amlodipine 10 mg by mouth once daily; ASA 81 mg by mouth once daily; rosuvastatin 5 mg by mouth once daily

ROS: substernal chest discomfort

PE:

HEENT: Normocephalic atraumatic

CV: Regular rate and rhythm; S_1, S_2, no S_3, no S_4; no murmurs or rubs

VS: BP 140/90 mm Hg; HR 88 beats/min; T 37°C (98.6°F)

Lungs: Fine crackles at the lower bases

Abd: Nontender, nondistended

GI: Normal bowel sounds

GU: Stool guaiac negative

Exts: No bruits, No peripheral edema, pulses 2+, femoral pulses present, good range of motion

Neuro: Alert and oriented × 3, cranial nerves intact

Labs: Sodium 139 mEq/L (mmol/L), potassium 3.7 mEq/L (mmol/L), chloride 103 mEq/L (mmol/L), bicarbonate 21 mEq/L (mmol/L), SCr 1.6 mg/dL (141 µmol/L), glucose 155 mg/dL (8.6 mmol/L), WBC 9.9 × 10^3/mm^3 (9.9 × 10^9/L), hemoglobin 14.7 g/dL (147 g/L or 9.12 mmol/L), hematocrit 43% (0.43), platelets 220 × 10^3/mm^3 (220 × 10^9/L), troponin I 4.8 ng/mL (4800 ng/L), oxygen saturation 96% (0.96) on room air, N-terminal proBNP 500 pg/mL (59 pmol/L)

ECG: Normal sinus rhythm, PR 0.16 seconds, QRS 0.08 seconds, QTc 0.38 seconds, 2-mm ST-segment elevation in 2 or more contiguous anterior leads

CXR: No active disease

Echo: Anterior wall dyskinesis, LVEF 40% (0.40)

What information is suggestive of acute MI?

Are any complications of MI present?

Reperfusion Strategies for ACS

▶ *Reperfusion Strategies for STEMIs*

KEY CONCEPT Early reperfusion therapy with primary PCI of the infarct artery within 90 minutes from the time of hospital presentation is the reperfusion treatment of choice for patients with STEMI who present within 12 hours of symptom onset (see Figure 8–2).[3] Patients may not often recognize the importance of seeking immediate medical care for a variety of reasons, which include self-treatment and preconception regarding the importance or presentation of a heart attack. Thus, education to patients and their families about the symptoms of ACS is paramount to reduce delays in reperfusion.

For primary PCI in STEMI, the patient is taken from the ED to the cardiac catheterization laboratory and undergoes coronary angiography with either balloon angioplasty or, preferably, placement of a bare metal or drug-eluting intracoronary stent in the artery associated with the infarct.[5] Results of biochemical marker tests do not need to be available when the decision to proceed to primary PCI is made. Findings from a meta-analysis of trials comparing fibrinolysis with primary PCI indicate a lower mortality rate with primary PCI.[13] One reason for the superiority of primary PCI compared with fibrinolysis is that more than 90% of occluded infarct-related coronary arteries are opened with primary PCI compared with fewer than 60% with fibrinolytics.[3,5] In addition, intracranial hemorrhage (ICH) and major bleeding risks from primary PCI are lower than the risks of severe bleeding events following fibrinolysis.[14] An invasive strategy of primary PCI is generally preferred in patients presenting to institutions with skilled interventional cardiologists and a catheterization laboratory immediately available, those in cardiogenic shock, those with contraindications to fibrinolytics, and those with continuing symptoms 12 to 24 hours after symptom onset.[3] Current guidelines indicate that the time from first medical contact-to-device should be less than or equal to 90 minutes, with every effort made to ensure the time to reperfusion is as short as possible.[3]

Patients presenting to facilities that do not have interventional cardiology services can be transferred when a protocol that minimizes delays has been established between institutions and if primary PCI can be performed within the first 120 minutes of first medical contact.[3,14] Immediate transfer to a PCI-capable facility is recommended for patients who develop cardiogenic shock or acute severe HF, irrespective of the timing of presentation. PCI during hospitalization for STEMI, or transfer to a PCI-capable hospital, is also appropriate in those in whom fibrinolysis is not successful and those with persistent rest ischemia or signs of ischemia on stress testing following MI.[3,5]

▶ *Fibrinolytic Therapy for STEMI*

LO 3

Administration of a fibrinolytic agent is indicated in patients with STEMI who present to the hospital within 12 hours of the onset of chest discomfort, who are initially seen at a non-PCI-capable hospital and who have an anticipated time from first medical contact-to-device greater than 120 minutes if transferred to a PCI capable hospital (see Figure 8–2).[3] The reduction in mortality with fibrinolysis is greatest with early administration and diminishes after 12 hours. The use of fibrinolytics between

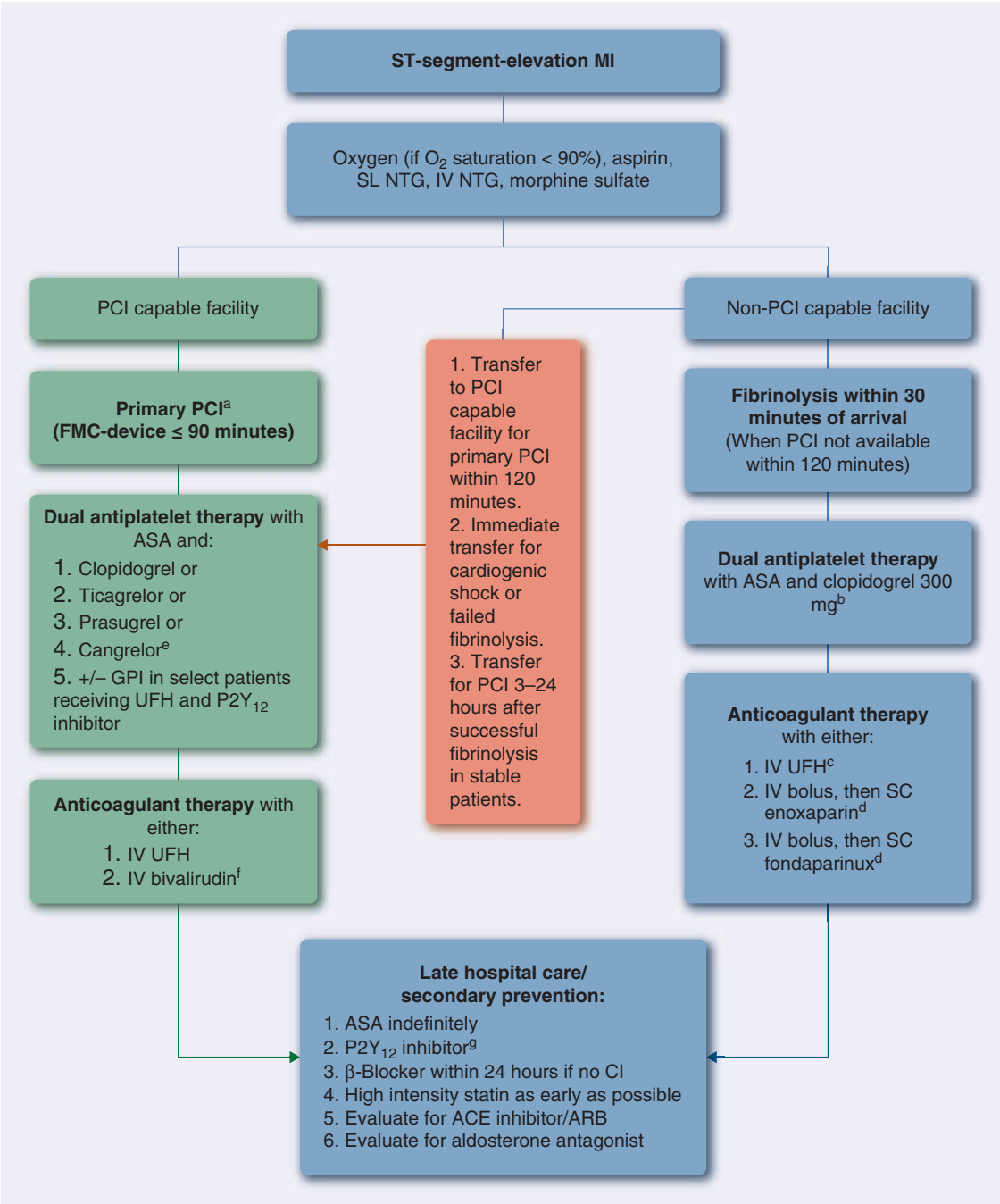

FIGURE 8–2. Initial pharmacotherapy for ST-segment elevation myocardial infarction. See Table 8–3 for dosing recommendations and contraindications to specific therapies. [a]Options after coronary angiography also include medical management alone or coronary artery bypass graft surgery. [b]Clopidogrel preferred $P2Y_{12}$ when fibrinolytic therapy is utilized. No loading dose recommended if age older than 75 years. [c]Given for up to 48 hours or until revascularization. [d]Given for the duration of hospitalization, up to 8 days or until revascularization. [e]For use as adjunct therapy during PCI only. Administer ticagrelor at any time prior to or during the cangrelor infusion. Administer prasugrel or clopidogrel after the cangrelor infusion. [f]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin (bolus plus infusion). [g]In patients with STEMI receiving a fibrinolytic or who do not receive reperfusion therapy, administer clopidogrel for at least 14 days and ideally up to 1 year. (ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; CI, contraindication; FMC, first medical contact; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; MI, myocardial infarction; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin.)

12 and 24 hours after symptom onset should be limited to patients with ongoing ischemia. Fibrinolytic therapy is preferred over primary PCI when there is no cardiac catheterization laboratory in a hospital and the delay from first medical contact-to-device would exceed 120 minutes if the patient was transferred to a PCI-capable hospital.[3] Guidelines recommend that the fibrinolytic agent be administered within 30 minutes of arrival.[3] All hospitals should have protocols addressing

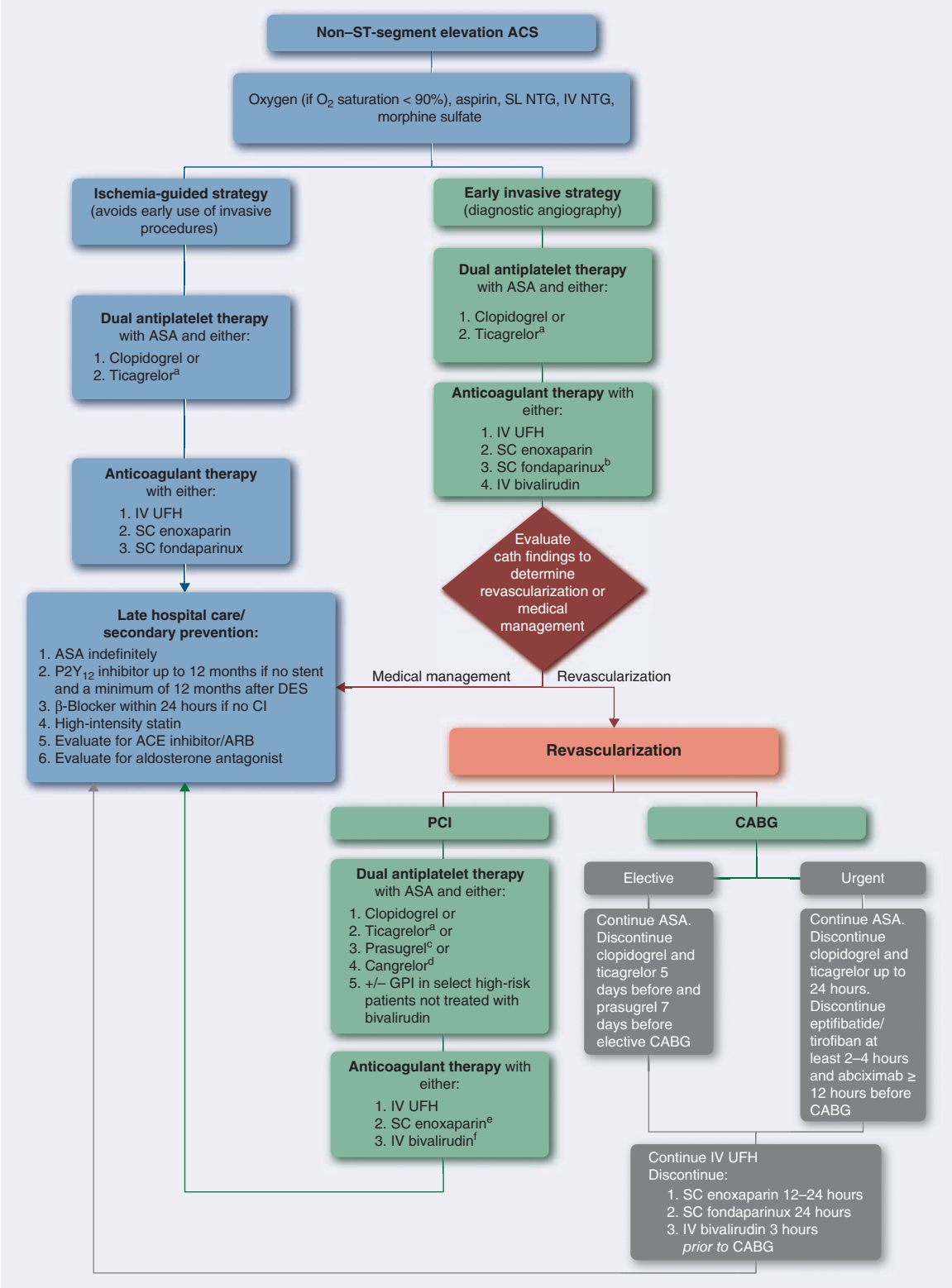

FIGURE 8–3. Initial pharmacotherapy for non–ST-segment elevation (NSTE) ACS. See Table 8–3 for dosing recommendations and contraindications to specific therapies. [a]Reasonable to choose ticagrelor over clopidogrel for maintenance $P2Y_{12}$ for NSTE-ACS patients treated with an early invasive or ischemia-guided strategy. [b]Not to be used as the sole anticoagulant during PCI. Give additional UFH 85 units/kg IV without GPI and 60 units/kg IV with GPI. [c]Reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ for NSTE-ACS patients undergoing PCI who are not at high risk for bleeding. Do not use if prior history of stroke/transient ischemic attack (TIA), age older than 75 years, or body weight less than or equal to 60 kg (132 lb). [d]Adjunct agent to be used during PCI only. Administer ticagrelor at any time prior to or during the cangrelor infusion. Administer prasugrel or clopidogrel after the cangrelor infusion. [e]May require IV supplemental dose of enoxaparin; see Table 8–3. [f]If pretreated with UFH, stop UFH infusion for 30 minutes prior to administration of bivalirudin bolus plus infusion. (ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; ASA, aspirin; CABG, coronary artery bypass graft; CI, contraindication; DES, drug-eluting stent; GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; NTG, nitroglycerin; PCI, percutaneous coronary intervention; SC, subcutaneous; SL, sublingual; UFH, unfractionated heparin).

Table 8–2

Indications and Contraindications to Fibrinolytic Therapy for Management of ST-Segment Elevation Myocardial Infarction[3]

Indications

1. Ischemic chest discomfort at least 20 minutes in duration but 12 hours or less since symptom onset
   and
   ST-segment elevation of at least two contiguous leads of ≥ 2 mm in men and ≥ 1.5 mm in women in leads V_2-V_3 and/or of ≥ 1 mm in other leads, or new or presumed new left bundle-branch block
2. Ongoing ischemic chest discomfort at least 20 minutes in duration 12–24 hours since symptom onset
   and
   ST-segment elevation of at least two contiguous leads of ≥ 2 mm in men and ≥ 1.5 mm in women in leads V_2-V_3 and/or of ≥ 1 mm in other leads

Absolute Contraindications

- Active internal bleeding (not including menses)
- Previous intracranial hemorrhage at any time; ischemic stroke within 3 months (except acute ischemic stroke within 4.5 hours)
- Known intracranial neoplasm
- Known structural cerebral vascular lesion (eg, arteriovenous malformation)
- Suspected aortic dissection
- Significant closed head or facial trauma within 3 months
- Intracranial or intraspinal surgery within 2 months
- Severe uncontrolled hypertension (unresponsive to emergency therapy)
- For streptokinase, prior treatment within the previous 6 months

Modified with permission from: Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:177.

fibrinolysis eligibility, dosing, and monitoring. Indications and contraindications for fibrinolysis are listed in Table 8–2.[3] It is not necessary to obtain the results of biochemical markers before initiating fibrinolytic therapy.

Because administration of fibrinolytics results in clot lysis, patients who are at high risk of major bleeding (including ICH) presenting with an absolute contraindication should not receive fibrinolytic therapy; primary PCI is preferred.

Generally, a more fibrin-specific agent such as alteplase, reteplase, or tenecteplase is preferred over a non-fibrin-specific agent such as streptokinase.[3] Fibrin-specific fibrinolytics open a greater percentage of infarcted arteries. In a large clinical trial, administration of alteplase resulted in a 1% absolute reduction in mortality and cost about $30,000 per year of life saved compared with streptokinase.[15] Other trials compared alteplase with reteplase and alteplase with tenecteplase and found similar mortality between agents.[16,17] Therefore, either alteplase, reteplase, or tenecteplase is acceptable as a first-line agent. ICH and major bleeding are the most serious side effects of fibrinolytic agents. The risk of ICH is higher with fibrin-specific agents than with streptokinase.[18] However, the risk of systemic bleeding other than ICH is higher with streptokinase than with other more fibrin-specific agents and was higher with alteplase versus tenecteplase in one study.[3,16,18]

Fibrinolytic therapy is not indicated and should not be used in patients with NSTE-ACS because increased mortality has been reported with these agents compared with controls in clinical trials.[3]

Patient Encounter 1, Part 2

Identify your acute treatment goals for this patient with STEMI.

What adjunctive pharmacotherapy should be administered in the emergency department prior to proceeding to the cardiac catheterization laboratory?

What additional pharmacotherapy should be initiated on the first day of this patient's hospitalization following successful PCI/intracoronary stenting?

▶ *Early Invasive Therapy for NSTE-ACS*

KEY CONCEPT Clinical practice guidelines recommend coronary angiography followed by either PCI or coronary artery bypass graft (CABG) surgery revascularization as an early treatment (early invasive strategy) for patients with NSTE-ACS at an elevated risk for death or MI, including those with a high-risk score (see Table 8–1) or patients with refractory angina, hemodynamic instability or electrical instability (see Figure 8–3).[4,5] Several clinical trials support an "invasive" interventional strategy with early angiography and PCI or CABG versus an ischemia-guided approach, whereby coronary angiography with revascularization is reserved for patients with symptoms refractory to pharmacotherapy and patients with signs of ischemia on stress testing.[4,19] An early invasive approach results in a long-term reduction in the rates of CV death or MI, with the largest absolute effect seen in higher-risk patients.[4] Several studies have also shown less angina, fewer hospitalizations, and improved quality of life with an invasive strategy.[4]

LO 4

All patients undergoing PCI should receive ASA therapy indefinitely. A $P2Y_{12}$ inhibitor antiplatelet (clopidogrel, prasugrel, or ticagrelor) should be administered concomitantly with ASA for at least 12 months following PCI for a patient with ACS (Table 8–3).[3,4,20] A longer duration of $P2Y_{12}$ inhibitor therapy may be considered for select patients with a low-bleeding risk receiving a drug-eluting stent (DES) because the risk of stent thrombosis is greater upon cessation of dual antiplatelet therapy (DAPT).[3,4] This is because although DES reduce the rate of smooth muscle cell growth that causes stent restenosis, they induce a delay in endothelial cell regrowth at the site of the stent (re-epithelialization in arterial lumen) that places the patient at higher risk of thrombotic events following PCI, especially stent thrombosis. This explains why DAPT may be beneficial for a longer period of time following PCI with a DES when compared to patients receiving a bare metal stent (BMS). Nevertheless, recent trials have provided uncertain evidence regarding the benefit of continuing DAPT beyond 12 months for patients with an ACS, while the risk of bleeding persists.[21] Until data from larger trials evaluating the need for an extended duration (> 12 months) of $P2Y_{12}$ inhibitor therapy following PCI are available, the preferred duration of $P2Y_{12}$ therapy is at least a year regardless of whether a patient with NSTE-ACS or STEMI receives a stent.[4]

Ischemia-Guided Therapy for NSTE-ACS and STEMI

For patients with NSTE-ACS, an initial ischemia-guided strategy is recommended for patients with a low-risk score, normal

Table 8–3

Evidence-Based Pharmacotherapy for ST-Segment Elevation Myocardial Infarction and Non–ST-Segment Elevation Acute Coronary Syndrome[3,4,20]

Drug	Clinical Condition and Guideline Recommendations[a]	Contraindications[b]	Dose and Duration of Therapy
Aspirin	STEMI, class I recommendation for all patients. NSTE-ACS, class I recommendation for all patients.	Hypersensitivity, active bleeding, severe bleeding risk.	162–325 mg orally once on hospital day 1. 81–325 mg once daily orally starting hospital day 2 and continued indefinitely in all patients. Aspirin dose of 81 mg is preferred. Limit dose to < 100 mg if using ticagrelor.
Clopidogrel	NSTE-ACS, class I recommendation added to aspirin. STEMI, class I recommendation added to aspirin. PCI in STEMI and NSTE-ACS, class I recommendation. In patients with aspirin allergy, class I recommendation.	Hypersensitivity, active bleeding, severe bleeding risk.	300- to 600-mg oral loading dose on hospital day 1 followed by a maintenance dose of 75 mg once daily starting on hospital day 2 in patients with NSTE-ACS. 300-mg oral loading dose followed by 75 mg orally daily in patients receiving a fibrinolytic or who do not receive reperfusion therapy with a STEMI; avoid loading dose in patients ≥ 75 years. 600-mg (class I recommendation) loading dose before or when PCI performed (unless within 24 hours of fibrinolytic therapy, a dose of 300 mg should be given). Discontinue at least 5 days before CABG surgery if bleeding risk outweighs benefit (class I recommendation). Administer indefinitely in patients with aspirin allergy (class I recommendation). Continue for at least 12 months (class I recommendation) and possibly beyond 12 months (class IIb recommendation) in patients with ACS managed with PCI/stent. In patients with NSTE-ACS treated medically, administer for up to 12 months (class I recommendation). In patients receiving a fibrinolytic or who do not receive reperfusion therapy, administer for at least 14 days (class I recommendation) and ideally up to 12 months. Genetic testing might be considered to identify patients at high risk of poor response (class IIb recommendation). In these patients, an alternative $P2Y_{12}$ inhibitor might be considered (class IIb recommendation). The routine use of genetic testing is not recommended (class III recommendation).
Prasugrel	PCI in STE and NSTE-ACS, added to aspirin, class I recommendation. Class IIa as preference over clopidogrel for those not at high risk of bleeding and do not have a history of stroke/TIA.	Active bleeding, prior stroke or TIA.	Initiate in patients with known coronary artery anatomy only (so as to avoid use in patients needing CABG surgery; class I recommendation). Give no later than 1 hour after PCI. Patients who have history of prior stroke/TIA, are 75 years of age or more, or weigh < 60 kg (132 lb) have higher risk of bleeding and there's no added benefit compared with clopidogrel. 60-mg oral loading dose followed by 10 mg once daily for patients weighing 60 kg (132 lb) or more. Consider 5 mg once daily in patients weighing < 60 kg (132 lb) (based on limited data). Discontinue at least 7 days prior to CABG surgery if bleeding risk outweighs benefit (class I recommendation). Continue for at least 12 months (class I recommendation) and possibly beyond 12 months (class IIb recommendation) in patients with ACS managed with PCI/stent.
Ticagrelor	PCI in STEMI and NSTE-ACS, added to aspirin, class I recommendation. Class IIa as preference over clopidogrel.	Active bleeding.	180-mg (class I recommendation) oral loading dose in patients undergoing PCI or ischemia-guided management, followed by 90 mg twice daily for at least 12 months (class I recommendation) and possibly beyond 12 months (class IIb recommendation) in patients with ACS managed with PCI/stent. Current data are too limited to recommend use in patients with STEMI not undergoing primary PCI. Discontinue at least 5 days prior to CABG surgery if bleeding risk outweighs benefit (class I recommendation).
Cangrelor	PCI-adjunct in patients not treated with oral $P2Y_{12}$ inhibitor or GPI.	Active bleeding.	30 mcg/kg IV bolus initiated prior to PCI followed by 4 mcg/kg/min IV infusion for duration of PCI or 2 hours, whichever is longer. To maintain platelet inhibition after infusion, initiate oral $P2Y_{12}$ agent as follows: ticagrelor 180 mg at any time during or immediately after infusion; prasugrel 60 mg or clopidogrel 600 mg immediately after discontinuation of infusion. Do not administer prasugrel or clopidogrel during infusion of cangrelor. There is no antiplatelet effect of cangrelor 1 hour after discontinuation of infusion.

Unfractionated heparin	STEMI, class I recommendation in patients undergoing PCI and for those patients treated with fibrinolytics. NSTE-ACS, class I recommendation in combination with antiplatelet therapy for ischemia-guided or early invasive approach PCI, class I recommendation (NSTE-ACS and STEMI).	Active bleeding, history of heparin-induced thrombocytopenia, severe bleeding risk, recent stroke.	For STEMI with fibrinolytics, administer an initial 60-units/kg IV bolus (maximum 4000 units) heparin followed by a constant IV infusion at 12-units/kg/hour (maximum 1000 units/hour). Titrate to therapeutic aPTT. For STEMI primary PCI, administer 50- to 70-units/kg IV bolus if a GPI planned; 70–100 units/kg IV bolus if no GPI planned and supplement with IV bolus doses to maintain target ACT. For NSTE-ACS, administer 60-units/kg IV bolus (maximum 4000 units) followed by a constant IV infusion at 12 units/kg/hour (maximum 1000 units/hour). Titrated to maintain an aPTT of 1.5–2.0 times control (approximately 50–70 seconds) for STEMI with fibrinolytics and for NSTE-ACS. Titrated to ACT of 250–350 seconds for primary PCI without a GPI and 200–250 seconds in patients given a concomitant GPI. The first aPTT should be measured at 4–6 hours for NSTE-ACS and STEMI in patients not treated with fibrinolytics or undergoing primary PCI. The first aPTT should be measured at 3 hours in patients with STEMI who are treated with fibrinolytics. Continue for 48 hours or until revascularization.
Enoxaparin	STEMI class I recommendation in patients receiving fibrinolytics. NSTE-ACS, class I recommendation in combination with aspirin for ischemia-guided or early invasive strategy. For PCI, class IIa recommendation as an alternative to UFH in patients with NSTE-ACS.	Active bleeding, history of heparin-induced thrombocytopenia, severe bleeding risk, recent stroke, avoid enoxaparin if CrCl < 15 mL/min (0.25 mL/s), avoid if CABG surgery planned.	Enoxaparin 1 mg/kg SC every 12 hours for patients (CrCl ≥ 30 mL/min [0.50 mL/s]). Enoxaparin 1 mg/kg SC every 24 hours (CrCl 15–29 mL/min [0.25–0.49 mL/s]). For all patients undergoing PCI following initiation of SC enoxaparin for NSTE-ACS or STEMI, a supplemental 0.3-mg/kg IV dose of enoxaparin should be administered at the time of PCI if the last dose of SC enoxaparin was given 8–12 hours prior to PCI or received < 2 therapeutic SC doses. For patients with STEMI receiving fibrinolytics: • Age < 75 years: Administer enoxaparin 30-mg IV bolus followed in 15 minutes by 1 mg/kg. • SC every 12 hours (first two doses administer maximum of 100 mg for patients weighing > 100 kg). • Age ≥ 75 years: Administer enoxaparin 0.75-mg/kg SC every 12 hours (first two doses administer maximum of 75 mg). • Continue throughout hospitalization, up to 8 days, or until revascularization. Continue for duration of hospitalization for NSTE-ACS or until revascularization. Discontinue at least 12–24 hours before CABG surgery.
Bivalirudin	NSTE-ACS class I recommendation for invasive strategy. PCI in STEMI (class I recommendation).	Active bleeding, severe bleeding risk.	For NSTE-ACS, administer 0.1 mg/kg IV bolus followed by 0.25-mg/kg/hour infusion. For PCI in NSTE-ACS, administer a second bolus of 0.5 mg/kg IV and increase infusion rate to 1.75 mg/kg/hour. For PCI in STEMI, administer 0.75-mg/kg IV bolus followed by 1.75-mg/kg/hour infusion. If prior UFH given, discontinue UFH and wait 30 minutes before initiating bivalirudin. Adjust dose of infusion to 1 mg/kg/hr when CrCl < 30 mL/min (0.50 mL/s). Discontinue at end of PCI or continue at 0.25 mg/kg/hour if prolonged anticoagulation necessary. Lower bleeding rates are mitigated when administered with a GPI. Clopidogrel should be administered at least 6 hours before if a GPI is not used. Discontinue at least 3 hours prior to CABG surgery.
Fondaparinux	STEMI class I recommendation receiving fibrinolytics. NSTE-ACS class I recommendation for ischemia-guided or early invasive strategy. Class III as sole agent in PCI.	Active bleeding, severe bleeding risk, SCr ≥ 3.0 mg/dL (265 µmol/L) or CrCl < 30 mL/min (0.50 mL/s).	For STEMI, 2.5-mg IV bolus followed by 2.5-mg SC once daily starting on hospital day 2. For NSTE-ACS, 2.5-mg SC once daily. Continue throughout hospitalization, up to 8 days, or until revascularization. For PCI, give additional doses of either UFH or bivalirudin as recommended above. Discontinue at least 24 hours prior to CABG surgery.

(*Continued*)

Table 8–3

Evidence-Based Pharmacotherapy for ST-Segment Elevation Myocardial Infarction and Non–ST-Segment Elevation Acute Coronary Syndrome[3,4,20] (*Continued*)

Drug	Clinical Condition and Guideline Recommendations[a]	Contraindications[b]	Dose and Duration of Therapy
Fibrinolytic therapy	STEMI, class I recommendation for patients presenting within 12 hours following the onset of symptoms, class IIa in patients presenting between 12 and 24 hours following the onset of symptoms with continuing signs of ischemia. NSTE-ACS, class III recommendation.	Any prior ICH, known structural cerebrovascular lesions such as an arterial venous malformation, known intracranial malignant neoplasm, ischemic stroke within 3 months, active bleeding (excluding menses) or known bleeding diathesis, significant closed head or facial trauma within 3 months, severe uncontrolled HTN unresponsive to treatment.	Streptokinase: 1.5 MU IV over 60 minutes. Alteplase: 15-mg IV bolus followed by 0.75 mg/kg IV over 30 minutes (maximum 50 mg) followed by 0.5 mg/kg (max 35 mg) over 60 minutes (maximum dose 100 mg). Reteplase: 10 units IV × 2, 30 minutes apart. Tenecteplase: • < 60 kg (132 lb), 30-mg IV bolus • 60–69.9 kg (132–153 lb), 35-mg IV bolus • 70–80 kg (154–176 lb), 40-mg IV bolus
Glycoprotein IIb/IIIa receptor inhibitors	NSTE-ACS PCI, class I recommendation for abciximab, high-bolus dose tirofiban or double-bolus eptifibatide at the time of PCI in high-risk patients already receiving aspirin and not adequately pretreated with a $P2Y_{12}$ inhibitor and not receiving bivalirudin as the anticoagulant; class IIa at the time of PCI for high-risk patients already receiving aspirin and pretreated with a $P2Y_{12}$ inhibitor and receiving UFH; class IIb for early invasive strategies in high-risk patients already receiving DAPT; eptifibatide or tirofiban preferred. STEMI primary PCI, class IIa recommendation for abciximab, high-bolus dose tirofiban or double-bolus eptifibatide in patients receiving UFH; IIb for administration of upstream GPI when PCI is intended; IIb for intracoronary abciximab injection in select patients during PCI.	Active bleeding, thrombocytopenia, prior stroke, renal dialysis (eptifibatide).	**Drug** / **Dose** / **Dosing Adjustment for CKD** Abciximab: 0.25-mg/kg IV bolus followed by 0.125 mcg/kg/min (maximum 10-mcg/min) for 12 hours. None Eptifibatide: 180-mcg/kg IV bolus × 2, 10 minutes apart with an infusion of 2 mcg/kg/min for 18–24 hours after PCI. Reduce maintenance infusion to 1 mcg/kg/min for CrCl < 50 mL/min (0.83 mL/s); contraindicated if patient dependent on dialysis. Patients weighing 121 kg (267 lb) or more should receive a maximum infusion rate of 22.6 mg per bolus and a maximum rate of 15 mg/hour. Tirofiban: 25-mcg/kg IV bolus followed by an infusion of 0.15 mcg/kg/min for up to 18 hours. Reduce maintenance infusion to 0.075 mcg/kg/min for patients with CrCl ≤ 60 mL/min (1.0 mL/s).

Nitroglycerin	STEMI and NSTE-ACS, class I recommendation in patients with ongoing ischemic discomfort, control of HTN, or management of HF.	Hypotension, sildenafil, avanafil, tadalafil, or vardenafil are all contraindicated with nitrates.	0.4-mg SL, repeated every 5 minutes × 3 doses then assess need for IV infusion. 5- to 10-mcg/min IV infusion titrated up to 75–100 mcg/min until relief of symptoms or limiting side effects (headache) with a systolic BP < 90 mm Hg or > 30% below starting mean arterial pressure levels if significant HTN is present. Topical patches or oral nitrates are acceptable alternatives for patients without ongoing or refractory symptoms. Discontinue IV infusion after 24–48 hours.
β-Blockers[c]	STEMI and NSTE-ACS, class I recommendation for oral β-blockers in all patients without contraindications in the first 24 hours, class IIa for IV β-blockers in STEMI patients with HTN or those with ongoing ischemia. Class III for IV β-blockers in patients with risk factors for shock.	PR ECG interval > 0.24 seconds, second-degree or third-degree atrioventricular heart block, heart rate < 60 beats/min, systolic BP < 90 mm Hg, shock, left ventricular failure with decompensated HF, severe reactive airway disease.	Metoprolol 5-mg slow IV push (over 1–2 minutes), repeated every 5 min for a total of 15 mg followed in 1–2 hours by 25–50 mg orally every 6 hours; if a very conservative regimen is desired, initial doses can be reduced to 1–2 mg. Atenolol 5-mg IV dose followed in 5 minutes by a second 5-mg IV dose for a total of 10 mg followed in 1–2 hours by 50–100 mg orally once daily. Alternatively, initial IV therapy can be omitted and treatment started with oral dosing. For dosing of carvedilol, metoprolol succinate, and bisoprolol in patients with systolic HF, please refer to Chapter 6. Continue oral β-blocker for 3 years and possibly indefinitely.
Calcium channel blockers	NSTE-ACS class I recommendation for patients with ongoing ischemia or vasospasm who are already taking adequate doses of nitrates and β-blockers or in patients with contraindications or intolerance to β-blockers (diltiazem or verapamil preferred during initial presentation if EF > 40% [0.40]). NSTE-ACS, class IIb recommendation for diltiazem for patients with AMI.	Pulmonary edema, evidence of left ventricular dysfunction, systolic BP < 100 mm Hg, PR ECG segment to > 0.24 seconds second- or third-degree atrioventricular heart block for verapamil or diltiazem, pulse rate < 60 beats/min for diltiazem or verapamil.	Diltiazem 120–360 mg sustained release orally once daily. Verapamil 180–480 mg sustained release orally once daily. Amlodipine 5–10 mg orally once daily. Continue as indicated to manage angina, HTN, or arrhythmias.

ACE inhibitors	NSTE-ACS and STEMI, class I recommendation for patients with HF, left ventricular dysfunction and EF < 40% (0.40), DM, HTN, or stable CKD in the absence of contraindications. Consider in all patients with CAD (class I recommendation, class IIb in low-risk patients). Indicated indefinitely for all patients with EF < 40% (0.40) (class I recommendation).	Systolic BP < 100 mm Hg, history of intolerance to an ACE inhibitor, bilateral renal artery stenosis, serum potassium > 5.5 mEq/L (mmol/L), acute renal failure, pregnancy.	**Drug**	**Initial Dose (mg)**	**Target Dose (mg)**
			Captopril	6.25–12.5	50 twice daily orally to 50 three times daily
			Enalapril	2.5–5.0	10 twice daily orally
			Lisinopril	2.5–5.0	10–20 once daily orally
			Ramipril	1.25–2.5	5 twice daily or 10 once daily orally
			Trandolapril	1.0	4 once daily orally
Angiotensin receptor blockers	NSTEMI and STEMI, class I recommendation in patients with HF or left ventricular EF < 40% (0.40) and intolerant of an ACE inhibitor, class IIa recommendation in patients with clinical signs of HF or EF < 40% (0.40) and no documentation of ACE inhibitor intolerance. Class I in other ACE inhibitor–intolerant patients with HTN.	Systolic BP < 100 mm Hg, bilateral renal artery stenosis, serum potassium > 5.5 mEq/L (mmol/L), acute renal failure, pregnancy.	**Drug**	**Initial Dose (mg)**	**Target Dose (mg)**
			Candesartan	4–8	32 once daily orally
			Valsartan	40	160 twice daily orally
			Losartan	12.5–25	150 daily
			Continue indefinitely.		

(*Continued*)

Table 8–3

Evidence-Based Pharmacotherapy for ST-Segment Elevation Myocardial Infarction and Non–ST-Segment Elevation Acute Coronary Syndrome[3,4,20] (*Continued*)

Drug	Clinical Condition and Guideline Recommendations[a]	Contraindications[b]	Dose and Duration of Therapy
Aldosterone antagonists	NSTEMI and STEMI class I recommendation in patients with EF ≤ 40% (0.40) and either DM or HF who are already receiving an ACE inhibitor and β-blocker.	Hypotension, hyperkalemia, serum potassium > 5.0 mEq/L (mmol/L), SCr ≥ 2.5 mg/dL (221 µmol/L) for men and ≥ 2.0 mg/dL (177 µmol/L) for women and/or CrCl ≤ 30 mL/min (0.50 mL/s) for spironolactone; SCr ≥ 2.0 mg/dL (177 µmol/L) for men or 1.8 mg/dL (159 µmol/L) for women or CrCl ≤ 50 mL/min (0.83 mL/s) for eplerenone.	**Drug** / **Initial Dose (mg)** / **Target Dose (mg)** Eplerenone / 25 / 50 once daily orally Spironolactone / 12.5 / 25–50 once daily orally Continue indefinitely.
Morphine sulfate	STEMI and NSTE-ACS class IIb recommendation for patients whose chest pain persists despite treatment with maximally tolerated anti-anginal drugs.	Hypotension, respiratory depression, confusion, obtundation.	1- to 5-mg IV bolus dose. May be repeated every 5–30 minutes as needed to relieve symptoms and maintain patient comfort.
Statins	NSTE-ACS and STEMI class I recommendation to initiate or continue high-intensity statin therapy during early hospital care.	Caution with use of fibrate and statin-specific drug interactions.	Atorvastatin 40–80 mg daily. Rosuvastatin 20–40 mg daily.

[a]Class I recommendations are conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II recommendations are those conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa recommendations, the weight of the evidence/opinion is in favor of usefulness/efficacy. Class IIb recommendations are those for which usefulness/efficacy is less well established by evidence/opinion. Class III recommendations are those where the procedure or treatment is not useful and may be harmful.

[b]Allergy or prior intolerance is a contraindication for all categories of drugs listed in this chart.

[c]Choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance due to existing pulmonary disease, especially asthma, selection should favor a short-acting agent, such as metoprolol, or the ultra short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (eg, 2.5-mg IV metoprolol, 12.5-mg oral metoprolol, or 25-mcg/kg/min esmolol as initial doses) rather than complete avoidance of β-blocker therapy.

ACE, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ACT, activated clotting time; AMI, acute myocardial infarction; aPTT, activated partial thromboplastin time; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CrCl, creatinine clearance; DM, diabetes mellitus; ECG, electrocardiogram; EF, ejection fraction; GPI, glycoprotein IIb/IIIa inhibitor; HF, heart failure; HTN, hypertension; ICH, intracranial hemorrhage; IV, intravenous; NSTE, non–ST-segment elevation; PCI, percutaneous coronary intervention; SC, subcutaneous; SCr, serum creatinine; SL, sublingual; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; UFH, unfractionated heparin.

Modified with permission from Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:173–176.

ECGs, and negative troponin tests who are without recurrence of chest discomfort (see Figure 8–3).[4] An ischemia-guided strategy may also be the preferred approach in patients with extensive comorbidities in which the cumulative risks of comorbidities plus revascularization would outweigh the potential benefits of revascularization.

Stress testing (see Figure 8–1) is indicated in patients with NSTE-ACS when an initial ischemia-guided strategy is selected and for patients with STEMI where primary PCI was not performed and who do not have high-risk clinical characteristics for which earlier coronary angiography would be warranted.[3,4] Following the stress test, patients experiencing recurrent ischemia or symptoms despite optimal medical treatment or who are considered high-risk (see Table 8–1) should undergo left heart catheterization with coronary angiography and revascularization as indicated.[3,4] Patients with NSTE-ACS at low risk for recurrent CHD events following stress testing should be given ASA indefinitely and either clopidogrel or ticagrelor for up to 12 months following hospital discharge in addition to other secondary preventive pharmacotherapy described later in this chapter.[4] Patients with STEMI at low risk for recurrent CHD events should receive ASA indefinitely and clopidogrel for at least 14 days and up to 12 months in addition to other secondary preventive pharmacotherapy (see Figure 8–2).[3]

Early Pharmacologic Therapy for ACS

LO 3

Pharmacotherapy for early treatment of ACS is outlined in Figures 8–2 and 8–3 and Tables 8–2 and 8–3.[3-5] KEY CONCEPT According to ACC/ACCF/AHA STEMI and NSTE ACS practice guidelines, additional pharmacotherapy that all patients should receive within the first day of hospitalization, and preferably in the ED, are intranasal oxygen (if oxygen saturation is low), sublingual (SL) nitroglycerin (NTG), ASA, a $P2Y_{12}$ inhibitor (agent dependent on reperfusion strategy), and anticoagulation (agent dependent on reperfusion strategy). A GP IIb/IIIa inhibitor (GPI) may be administered with unfractionated heparin (UFH) for patients with STEMI undergoing primary PCI. High-risk patients with NSTE-ACS should proceed to early angiography (within 24 hours) and select high-risk patients may receive a GPI. Intravenous (IV) NTG may be given in select patients still experiencing pain despite SL NTG. It is reasonable to administer morphine to patients with refractory angina as an analgesic and a venodilator that lowers preload. Oral β-blockers should be initiated within the first day in patients without cardiogenic shock or other contraindications.[3,4] ACE inhibitors (or ARB in ACE inhibitor-intolerant patients) should be initiated in select patients during hospitalization with ACS.[3] High-intensity statin therapy should be initiated or continued during hospitalization in all patients without contraindications. Dosing and contraindications for SL and IV NTG, ASA, clopidogrel, β-blockers, ACE inhibitors, statins, anticoagulants, and fibrinolytics are listed in Table 8–3.[3,4,20]

► *Nitrates*

Nitrates promote the release of nitric oxide from the endothelium, which results in venous and arterial vasodilation. Venodilation lowers preload and myocardial oxygen demand. Arterial vasodilation may lower blood pressure (BP), thus reducing myocardial oxygen demand. Arterial vasodilation also relieves coronary artery vasospasm, dilating coronary arteries to improve myocardial blood flow and oxygenation. Randomized clinical trials failed to show a mortality benefit for IV nitrate therapy followed by oral nitrate therapy in acute MI.[4]

Patient Encounter 2, Part 1

A 56-year-old, 81-kg (178-lb) man presents to the ED by ambulance complaining of 5 hours of intermittent chest pressure while working at his office desk. His symptoms were not relieved with two antacid tablets. Local paramedics were called who gave the patient a total of three 0.4 mg sublingual nitroglycerin tablets over three successive doses and 325 mg ASA by mouth without relief of chest discomfort. The patient is transferred to the hospital where an early invasive strategy is chosen.

PMH: Dyslipidemia for 2 years

FH: Father died after myocardial infarction at age 65; mother and brother alive with HTN and dyslipidemia

SH: Nonsmoker

Allergies: NKDA

Meds: Atorvastatin 80 mg by mouth once daily at bedtime

ROS: Chest pressure

PE:

HEENT: Normocephalic atraumatic

CV: Regular rate and rhythm; S_1, S_2, no S_3, no S_4; no murmurs or rubs

VS: BP 138/88 mm Hg; HR 86 beats/min; T 37°C (98.6°F)

Lungs: Clear to auscultation and percussion

Abd: Nontender, nondistended

GI: Normal bowel sounds

GU: Stool guaiac negative

Exts: No bruits, no peripheral edema, pulses 2+, femoral pulses present, good range of motion

Neuro: Alert and oriented × 3, cranial nerves intact

Labs: Sodium 131 mEq/L (mmol/L), potassium 4.0 mEq/L (mmol/L), chloride 103 mEq/L (mmol/L), bicarbonate 23 mEq/L (mmol/L), SCr 0.8 mg/dL (71 µmol/L), glucose 88 mg/dL (4.9 mmol/L), WBC 4.9 × 10^3/mm^3 (4.9 × 10^9/L), hemoglobin 14.7 g/dL (147 g/L or 9.12 mmol/L), hematocrit 42% (0.42), platelets 226 × 10^3/mm^3 (226 × 10^9/L), troponin I 0.8 ng/mL (800 ng/L), oxygen saturation 99% (0.99) on room air, BNP 8600 pg/mL (2485 pmol/L)

ECG: Normal sinus rhythm, PR 0.16 seconds, QRS 0.08 seconds, QTc 0.38 seconds, 1-mm ST-segment depression in inferior leads

CXR: Normal

Echo: Inferior wall dyskinesis, LVEF 55% (0.55)

What type of ACS is this?

What information is suggestive of acute MI?

LO 3

In patients presenting with ACS, one SL NTG tablet should be administered every 5 minutes for up to three doses to relieve myocardial ischemia, unless contraindicated. IV NTG may be initiated in patients who have persistent ischemia, HF, or uncontrolled high BP in the absence of contraindications.[3,4] IV NTG is typically continued until revascularization is performed or for approximately 24 hours following ischemia relief.

The most significant adverse effects of nitrates are tachycardia, flushing, headache, and hypotension. Nitrate administration is contraindicated in patients who have received oral phosphodiesterase-5 inhibitors, such as sildenafil and vardenafil, within the past 24 hours, and tadalafil within the past 48 hours (see Table 8–3).[4]

▶ *Aspirin*

LO 3 ASA is the preferred antiplatelet agent in the treatment of ACS.[3,4] The antiplatelet effects of ASA are mediated by inhibiting the synthesis of TXA_2 through an irreversible inhibition of platelet cyclooxygenase-1.

In patients receiving fibrinolytics, ASA reduces mortality, and its effects are additive to fibrinolysis alone.[22] In patients undergoing PCI, ASA prevents acute thrombotic occlusion during the procedure. Additionally, in patients undergoing PCI, ASA, in addition to a $P2Y_{12}$ inhibitor, reduces the risk of stent thrombosis. ASA reduces the risk of death or MI by approximately 50% compared with no antiplatelet therapy in patients with NSTE-ACS.[22] Therefore, ASA remains the cornerstone of early treatment for all ACSs.

LO 3 In patients experiencing an ACS, an initial dose of at least 162 mg nonenteric-coated ASA is recommended to achieve a rapid platelet inhibition. Current guidelines for STEMI and NSTE-ACS recommend an initial ASA dose of 162 to 325 mg (see Table 8–3).[3,4] This first dose can be chewed to achieve high blood concentrations and platelet inhibition rapidly. Current data suggest that although an initial dose of 162 to 325 mg is required, long-term therapy with doses of 75 to 150 mg daily are as effective as higher doses. Therefore, a daily maintenance dose of 81 to 162 mg is generally preferred in most patients with ACS, including those patients also receiving a $P2Y_{12}$ inhibitor, to inhibit the 10% of the total platelet pool that is regenerated daily.[3,4,22] In patients receiving ticagrelor, the recommended maintenance dose of ASA is 81 mg.[4] ASA should be continued indefinitely following either STEMI or NSTE-ACS.[3,4]

The most frequent side effects of ASA are dyspepsia and nausea. Patients should be counseled about the risk of bleeding, especially gastrointestinal (GI) bleeding, with ASA (see Table 8–3).[22] Nonsteroidal anti-inflammatory agents other than ASA, as well as cyclooxygenase-2 (COX-2) selective anti-inflammatory agents, are contraindicated and should be discontinued at the time of ACS secondary to increased risk of death, reinfarction, HF, and myocardial rupture.[3,4]

▶ *Platelet $P2Y_{12}$ Inhibitors*

Clopidogrel, prasugrel, ticagrelor, and cangrelor block the $P2Y_{12}$ receptor, a subtype of ADP receptor, on platelets which prevents the binding of ADP to the receptor and subsequent expression of platelet GP IIb/IIIa receptors, and reduces platelet activation and aggregation. Both clopidogrel and prasugrel are thienopyridines and prodrugs that are converted to an active metabolite by a variety of cytochrome P-450 (CYP) isoenzymes, the most critical appearing to be CYP2C19 for clopidogrel (Table 8–4).[22] Both of these agents bind irreversibly to $P2Y_{12}$ receptors. Ticagrelor, which is not a thienopyridine, is a reversible, noncompetitive $P2Y_{12}$ receptor inhibitor. Ticagrelor's parent compound has antiplatelet effects and is also metabolized primarily by CYP3A4 to an active metabolite producing its antiplatelet effects. Cangrelor is the only intravenous $P2Y_{12}$ inhibitor approved as an adjunct to PCI in patients not receiving prior oral $P2Y_{12}$ inhibitors or planned GPIs to reduce the risk of periprocedural MI, revascularization, and stent thrombosis. Currently, there are no US guideline recommendations describing the role of cangrelor in ACS.

Both prasugrel and ticagrelor are more potent ADP inhibitors than clopidogrel. Prasugrel has the fewest significant drug–drug interactions of the oral agents. Moderate and strong inhibitors of CYP2C19 reduce the production of clopidogrel's active metabolite and consequently its antiplatelet effect, whereas strong inhibitors of CYP3A reduce ticagrelor's concentration. Cangrelor is an active drug that undergoes rapid dephosphorylation in the circulation and has no drug–drug interactions involving the CYP system. A more detailed discussion of the drug interactions with clopidogrel and proton pump inhibitors (PPIs) may be found in Chapter 7, "Stable Ischemic Heart Disease."

Genetic variations in the gene coding for *CYP2C19* significantly modulate the antiplatelet effects of clopidogrel. Specifically, carriers of reduced-function allele (ie, *2 or *3) are not able to convert clopidogrel to its active metabolite to the extent of carriers of the wild-type allele. This results in decreased antiplatelet effects, which could translate into higher rates of CV events, especially stent thrombosis and periprocedural MI.[22,23] The efficacy of prasugrel and ticagrelor is not associated with *CYP2C19* genotype.[3,4,22] Hence, ticagrelor or prasugrel may theoretically be considered preferred agents in carriers of *CYP2C19* reduced function alleles.[24] Nevertheless, in the absence of a large randomized trial demonstrating the benefit of such genotype-based approach, the most recent clinical practice guidelines of the ACC/AHA/SCAI have not endorsed routine genotyping to guide the prescription of $P2Y_{12}$ inhibitors.[3,4] Ongoing clinical trials should clarify the benefits of genotype-guided use of $P2Y_{12}$ receptor inhibitors.

LO 3 LO 4 Administration of a $P2Y_{12}$ receptor inhibitor, in addition to ASA, is recommended for all patients with ACS.[3,4] For patients with STEMI undergoing primary PCI, clopidogrel, prasugrel, ticagrelor, or cangrelor in addition to ASA, should be administered to prevent subacute stent thrombosis and long-term CV events (see Table 8–3 and Figure 8–2).[3-5] Although the most recent PCI and STEMI guidelines give no preference for any of the oral agents over the others, the NSTE-ACS guidelines indicate that ticagrelor may be preferred over clopidogrel for patients treated with either an ischemia-guided or early invasive approach, and both ticagrelor and prasugrel may be preferred over clopidogrel post PCI if patients are not at high risk of bleeding.[3-5] Cangrelor is only administered intravenously as an adjunct agent during PCI; an oral $P2Y_{12}$ agent must be initiated after PCI if cangrelor is used (see Table 8–4).

LO 4 LO 5 A large randomized double-blind study demonstrated that compared to clopidogrel, the addition of prasugrel to ASA for patients undergoing PCI significantly reduced the risk of CV death or MI by 19% (9.9% vs 12.1%), as well as MI and stent thrombosis, but increased the risk of major bleeding (not ICH) by 32% (2.4% vs 1.8%).[25] Patients with a history of prior stroke or transient ischemic attack (TIA) had an increased risk of ICH and net harm from prasugrel; therefore, prior stroke or TIA are contraindications to prasugrel. Patients 75 years and older as well as those weighing less than 60 kg (132 lb) are at increased risk of bleeding with prasugrel compared with clopidogrel and received no net clinical benefit from prasugrel.[25]

In a large randomized clinical trial, ticagrelor significantly reduced the rate of vascular death at 1 year by 22% (4.0% vs 5.1%), MI (5.8% vs 6.9%), and stent thrombosis (1.3% vs 1.9%) compared with clopidogrel.[26] There was no difference in the rate

Table 8–4

Clinical Considerations When Choosing a $P2Y_{12}$ Receptor Inhibitor[3-5,20]

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Pharmacologic class	Thienopyridine	Thienopyridine	Cyclopentyl triazolopyrimidine	Stabilized ATP analog
ADP receptor binding	Irreversible	Irreversible	Reversible	Reversible
Pharmacokinetics	Prodrug Converted twice to active metabolite primarily through CYP 2C19 Elimination half-life of active metabolite is approximately 30 minutes after a 75-mg dose Excretion is 50% urinary and 46% fecal	Prodrug Converted to active metabolite through CYP 3A4 and 2B6 Median elimination half-life of the active metabolite approximately 7.4 hours Excretion is primarily urinary (approximately 70%); fecal excretion < 30%	Active moiety Converted to active metabolite through CYP 3A4/5 Median elimination half-life of the parent compound is approximately 7 hours and active metabolite approximately 9 hours Excretion is primarily metabolism (84%); fecal excretion 58%, urinary excretion (26%)	Active drug Independent of hepatic function; rapidly dephosphorylzed to inactive metabolite Plasma half-life of 5–10 minutes; elimination half-life of 3–6 minutes Excretion is 58% renal and 35% fecal (presumed biliary)
	No dose adjustment necessary in CKD	Not recommended when eGFR < 15 mL/min/1.73 m^2	Not recommended when eGFR < 15 mL/min/1.73 m^2	No dose adjustment necessary in CKD
Dosing	300–600 mg loading dose; 75 mg daily	60 mg loading dose; 10 mg daily	180 mg loading dose; 90 mg twice daily. After 12 months, can use 60 mg twice daily in patients at low risk for bleeding	30 mcg/kg bolus; 4 mcg/kg/min IV infusion continued for at least 2 hours or the duration of PCI, whichever is longer
Onset of loading dose effect	Peak platelet inhibition occurs within 2 hours after 600 mg load and 6 hours after oral 300 mg load	Peak platelet inhibition reached within 1–1.5 hours after oral 60 mg load	Peak platelet inhibition within 1 hour after oral 180 mg load	Peak platelet inhibition within 2 minutes after 30 mcg/kg bolus
Duration of effect	3–10 days	7–10 days	3–5 days	1–2 hours
Drug and disease considerations	Genetic polymorphisms may influence efficacy Enhanced bleeding with NSAIDs; avoid use Enhanced bleeding with warfarin; monitor carefully for bleeding; target INR to 2.0–2.5 for most indications Avoid use with moderate or strong CYP2C19 inhibitors (omeprazole, esomeprazole, chloramphenicol, cimetidine, efavirenz, etravirine felbamate, fluoxetine, fluconazole, fluvoxamine, isoniazid, oxcarbazepine, ketoconazole, voriconazole); select alternative non-interacting $P2Y_{12}$ inhibitor or alternative non-interacting drug	Enhanced bleeding with warfarin and NSAIDs, avoid use	Enhanced bleeding with warfarin and NSAIDs Use aspirin doses < 100 mg daily Avoid use with strong CYP3A inhibitors (atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ketoconazole, ritonavir, saquinavir, telithromycin, voriconazole) Avoid use with potent CYP3A inducers (carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin) Avoid simvastatin and lovastatin doses > 40 mg daily (ticagrelor inhibits CYP3A4 and increases statin concentration) Monitor digoxin serum concentrations with any change in ticagrelor dose (ticagrelor inhibits P-glycoprotein) Unique side-effects including dyspnea and bradycardia	Do not administer clopidogrel or prasugrel prior to the discontinuation of cangrelor infusion Ticagrelor may be given at any time during cangrelor infusion or immediately after the discontinuation of cangrelor infusion

(*Continued*)

Table 8–4

Clinical Considerations When Choosing a $P2Y_{12}$ Receptor Inhibitor[3-5,20] (*Continued*)

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Contraindications	Any active pathological bleeding	Any active pathological bleeding; any history of TIA/stroke	Any active pathological bleeding; ICH or severe hepatic disease	Significant active bleeding or hypersensitivity
Surgery hold time	5 days for elective surgery; 24 hours for urgent	7 days	5 days for elective surgery; 24 hours for urgent	1 hour
NSTE-ACS indication	May be used regardless of treatment strategy; additional non-ACS indications	Reasonable over clopidogrel in patients treated with PCI who are not at high risk for bleeding and who have no history of stroke/TIA	Reasonable over clopidogrel for NSTE-ACS patients treated with invasive or ischemia-guided approach	No US guideline recommendation; may be considered in $P2Y_{12}$ inhibitor–naïve patients undergoing PCI
STEMI indication	Preferred when fibrinolytics used	Superior to clopidogrel in STEMI or in other high-risk patients like DM; not studied in patients receiving fibrinolytic therapy	Superior to clopidogrel; not studied in patients receiving fibrinolytic therapy	No US guideline recommendation; may be considered in $P2Y_{12}$ inhibitor–naïve patients undergoing PCI
Risk benefit considerations	Gold standard for reducing CV death and stent thrombosis compared to placebo Consider alternative if documented clopidogrel ineffectiveness (ie, poor metabolism, stent thrombosis during clopidogrel therapy)	Superior to clopidogrel with a significant increase in bleeding risk (driven mainly by reductions in MI and stent thrombosis); no clinical benefit when age ≥ 75 years or weight < 60 kg (132 lb); Net harm in patients with history of TIA or stroke	Superior to clopidogrel with modest increase in major non-CABG related bleeding; associated with an all-cause mortality reduction; consider compliance with twice daily dosing	Demonstrated better efficacy than post-PCI clopidogrel with minor increases in bleeding Has potential use as a bridge to CABG surgery in high-risk patients

ACS, acute coronary syndrome; ADP, adenosine diphosphate; ATP, adenosine triphosphate; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CV, cardiovascular; CYP, cytochrome P-450; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ICH, intracranial hemorrhage; INR, international normalized ratio; IV, intravenous; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

From Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:179–180, with permission.

of total stroke. Although no increase in study-defined major bleeding was noted with ticagrelor, the frequency of non-CABG major bleeding was increased compared with clopidogrel (4.5% vs 3.8%). Therefore, both of the more potent $P2Y_{12}$ inhibitors are more efficacious than clopidogrel but are also associated with an increased risk of bleeding. Patients with diabetes mellitus (DM) or those with STEMI appear to have a greater ischemic benefit with prasugrel and ticagrelor without an increase in major bleeding compared to clopidogrel.[27-30] No large randomized trial has directly compared ticagrelor to prasugrel. Figures 8–2 and 8–3 and Table 8–4 outline the role of antiplatelets and anticoagulants in ACS.[3,4]

LO 4 A clopidogrel loading dose of 600 mg is recommended over administration of 300 mg for patients undergoing PCI. A systematic review and meta-analysis of randomized and nonrandomized trials in more than 25,000 patients demonstrated a reduction in CV ischemic events with a loading dose of 600 mg compared with 300 mg in patients undergoing PCI.[31] Although a modest benefit of using a 7-day course of clopidogrel 150 mg compared to 75 mg daily has been suggested, it is also associated with a higher risk of major bleeding.[32] Thus, routine use of such dosing is not recommended in current clinical guidelines.[3,4]

LO 5 In STEMI patients receiving fibrinolysis, early therapy with clopidogrel 75 mg once daily administered during hospitalization and up to 28 days (mean: 14 days) reduced mortality and reinfarction without increasing the risk of major bleeding.[22] In adult patients 75 years or younger receiving fibrinolytics, a 300-mg loading dose (omit the load in those older than 75) of clopidogrel followed by 75 mg daily is recommended.[3] Clopidogrel should be continued for at least 14 days (and up to 1 year in the absence of bleeding) for patients presenting with STEMI who undergo reperfusion therapy with fibrinolysis.[3] Although prasugrel and ticagrelor are recommended in the setting of STEMI and primary PCI, no studies have evaluated their use in conjunction with fibrinolytics.

For patients with NSTE-ACS with an initial ischemia-guided approach, either clopidogrel (a 300- or 600-mg loading dose followed by 75 mg daily) or ticagrelor can be used (ticagrelor preferred). If an invasive management strategy is selected, either clopidogrel or ticagrelor can be used (ticagrelor may be preferred) either prehospital or in the ED. Following PCI, in patients not already treated with a $P2Y_{12}$ inhibitor, either clopidogrel, prasugrel, or ticagrelor can be used (in patients not at high risk of bleeding, ticagrelor and prasugrel may be preferred) and should

LO 4

be initiated within 1 hour following PCI. As in primary PCI for STEMI patients, cangrelor may be used in patients who have not received an oral $P2Y_{12}$ agent prior as an adjunct to PCI with an oral $P2Y_{12}$ agent initiated after cangrelor is discontinued. Specific dosing and contraindications of the $P2Y_{12}$ inhibitors are described in Tables 8–3 and 8–4.[3,4,22]

The recommended duration of $P2Y_{12}$ inhibitors for a patient undergoing PCI for ACS, either STEMI or NSTE-ACS, is at least 12 months for patients receiving either a BMS or DES.[3,4,20,22] The benefit of prolonging treatment beyond 12 months is uncertain. Trials evaluating the need for an extended duration greater than 12 months in patients with or without ACS undergoing PCI demonstrate a reduction in ischemic endpoints but an increased risk of bleeding.[20] For patients who are treated using an ischemia-guided approach, $P2Y_{12}$ inhibitors should be given for up to 12 months. Discontinuation of the $P2Y_{12}$ agent after 6 months may be considered for patients with ACS treated with a DES who have a high risk of bleeding.[20]

Nonadherence to $P2Y_{12}$ inhibitors is a major risk factor for stent thrombosis; therefore, the likelihood of compliance with DAPT (ASA and an oral $P2Y_{12}$ inhibitor) should be assessed prior to angiography.[5] The use of a BMS over a DES should be considered in patients who are anticipated to be nonadherent to 12 months of DAPT.[5] Adherence to twice-daily ticagrelor should also be a consideration.

To minimize the risk of CV events, elective noncardiac surgery should be delayed 4 to 6 weeks after angioplasty or BMS implantation, or 12 months after DES implantation if the discontinuation of the $P2Y_{12}$ inhibitor is required. If elective CABG surgery is planned, clopidogrel and ticagrelor should be withheld preferably for 5 days, and prasugrel at least 7 days, and cangrelor for 1 hour to reduce the risk of postoperative bleeding, unless the need for revascularization outweighs the bleeding risk. If urgent CABG is necessary, discontinue clopidogrel and ticagrelor up to 24 hours to reduce the risk of major bleeding.[4,5]

Although a variety of blood tests can assess functional platelet aggregation inhibition to $P2Y_{12}$ inhibitors, especially clopidogrel, there is no one gold standard test. Moreover, their benefit to personalize antiplatelet regimens has not been demonstrated. Therefore, the most recent practice guidelines do not recommend routine platelet aggregation testing to determine $P2Y_{12}$ inhibitor strategy.[3-5]

LO 4 LO 5 Bleeding should be carefully monitored when using $P2Y_{12}$ inhibitors.[25-27] Rarely, thrombotic thrombocytopenic purpura (TTP) has been reported with clopidogrel.[33] In addition, the use of ticagrelor is associated with dyspnea and, rarely, ventricular pauses and bradyarrhythmias. Small non-clinically significant increases in SCr and serum uric acid have also been reported with ticagrelor.[26]

▶ *Glycoprotein IIb/IIIa Receptor Inhibitors*

GP IIb/IIIa receptor inhibitors block the final common pathway of platelet aggregation, namely cross-linking of platelets by fibrinogen bridges between the GP IIb and IIIa receptors on the platelet surface. In patients with STEMI undergoing primary PCI who are treated with UFH, abciximab, eptifibatide, or tirofiban may be administered on an individual basis.[3,5] Investigations of GPIs precede the widespread use of oral DAPT and thus their benefit in modern settings is not as clear. Their use appears most appropriate and beneficial in patients who are not adequately treated with a $P2Y_{12}$ receptor antagonist or in those with a large thrombus burden. Routine use of a GPI is not recommended in patients who have received fibrinolytics or bivalirudin secondary to increased bleeding risk. For patients treated with bivalirudin as the anticoagulant, GPIs should only be used in select cases as clinically indicated. These agents should not be administered for medical management of patients with STEMI who will not be undergoing PCI.[3]

The role of GPIs in NSTE-ACS has diminished since $P2Y_{12}$ inhibitors are used earlier in therapy, and bivalirudin is commonly selected as the anticoagulant in patients receiving an early intervention approach. Current evidence indicates no benefit of routine use of GPIs in patients treated with an ischemia-guided approach because the bleeding risk exceeds the benefit.[4] Nevertheless, in select patients treated with an LO 5 ischemia-guided approach who experience recurrent ischemia (chest discomfort and ECG changes), HF, or arrhythmias after initial medical therapy necessitating a change in strategy to angiography and revascularization, a GPI may be added to ASA prior to the angiogram, particularly if the patient is (1) not adequately treated with clopidogrel or ticagrelor and (2) not treated with bivalirudin.

LO 4 In patients who undergo an early invasive strategy and are adequately treated with clopidogrel or ticagrelor, routine upstream (prior to coronary angiography) administration of a GPI is not recommended, although eptifibatide or tirofiban may be considered in select high-risk patients (eg, troponin positive). Indeed clinical trials have shown that eptifibatide (added to ASA and clopidogrel) prior to angiography and PCI (ie, "upstream" use) in NSTE-ACS does not reduce ischemic events and increases bleeding risk.[4,34] LO 4 In patients undergoing PCI, a GPI (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) should be used in patients presenting with high-risk features who are not adequately pretreated with clopidogrel or ticagrelor (and who are not treated with bivalirudin as the anticoagulant), and may be considered in select individuals adequately pretreated with clopidogrel.[4]

Dosing and contraindications for GPIs are described in Table 8–3.[3,4] LO 4 LO 5 Bleeding is the most significant adverse effect associated with administration of GPIs; therefore, they should not be administered to patients with a prior history of hemorrhagic stroke or recent ischemic stroke. The risk of bleeding is increased in patients with CKD. Eptifibatide is contraindicated in patients dependent on dialysis and requires a 50% reduced infusion rate in patients with CrCl less than 50 mL/min (0.83 mL/s).[3] The rate of tirofiban infusion should also be halved in patients with CrCl less than or equal to 60 mL/min (1.0 mL/s).[3] No dosage adjustment for renal function is necessary for abciximab. An immune-mediated thrombocytopenia occurs in approximately 5% of patients with abciximab and less than 1% of patients receiving eptifibatide or tirofiban.[35]

▶ *Anticoagulants*

LO 3 LO 4 All patients should receive an anticoagulant in addition to DAPT regardless of ACS type or initial treatment strategy. Options for anticoagulant therapy are outlined in Figures 8–2 and 8–3.[3,4] For patients with STEMI undergoing primary PCI, either UFH or bivalirudin is preferred.[3] Bivalirudin monotherapy reduces CV and overall mortality while minimizing bleeding compared to UFH plus a GPI. However, direct head-to-head comparisons of monotherapy with UFH and bivalirudin have not shown this bleeding advantage.[36-38] Anticoagulant therapy is generally discontinued after primary PCI unless a compelling reason to continue exists. When fibrinolytic therapy is utilized in STEMI, LO 5 anticoagulation with either UFH, enoxaparin, or fondaparinux are administered concomitantly. In this case, anticoagulant

therapy should be maintained for a minimum of 48 hours (for UFH) and preferably for the duration of the hospitalization (with enoxaparin and fondaparinux) up to 8 days after fibrinolysis or until reperfusion is performed to support patency and prevent reocclusion of the affected artery.[3] Enoxaparin dosing is adjusted for body weight and renal function, and when administered in combination with fibrinolysis, it has special dosing requirements for older patients and those weighing more than 100 kg (220 lb) (see Table 8–3).

The choice of anticoagulant for a patient with NSTE-ACS is guided by risk stratification and initial treatment strategy, either an early invasive approach with coronary angiography and PCI or an ischemia-guided strategy with angiography in select patients guided by relief of symptoms and stress testing (see Figure 8–3). For patients treated by an early invasive strategy, UFH, enoxaparin, fondaparinux, or bivalirudin are options.[4] These same anticoagulants are continued after angiography if the decision is made to revascularize with PCI with one exception. Fondaparinux should not be used as the sole anticoagulant during PCI due to an increased risk of catheter-related thrombosis. Additional heparin must be administered during PCI if fondaparinux was initially chosen for anticoagulation. Clinical trials with bivalirudin have demonstrated similar efficacy in preventing CV ischemic events with a lower bleeding rate compared to UFH or enoxaparin plus a GPI in moderate- and high-risk patients with NSTE-ACS undergoing an early invasive strategy.[22] Use of enoxaparin during PCI is considered reasonable in patients treated with upstream subcutaneous enoxaparin. Dosing considerations for initial treatment and during PCI are outlined in Table 8–3.[4]

In NSTE-ACS patients in whom an initial ischemia-guided strategy is planned, enoxaparin, UFH, or low-dose fondaparinux is recommended.[4] Bivalirudin has not been studied as initial therapy in this setting. When added to ASA, UFH and low-molecular-weight heparins (LMWHs) reduce the frequency of death or MI in patients presenting with NSTE-ACS compared with control/placebo in patients primarily managed with an ischemia-guided strategy.[4,22] Compared with enoxaparin, fondaparinux showed similar ischemic outcomes with a lower bleeding rate in patients with NSTE-ACS primarily managed with an ischemia-guided strategy and may be preferred in patients at high risk for bleeding.[22] However, if fondaparinux is chosen for a patient who subsequently undergoes angiography and PCI, it should be administered in combination with UFH to avoid catheter thrombosis.[4] Guideline-recommended dosing and contraindications are described in Table 8–3.

UFH is preferred following angiography in patients proceeding to CABG during the same hospitalization because it has a short duration of action following discontinuation. Because enoxaparin is eliminated renally and patients with renal insufficiency generally have been excluded from clinical trials, UFH should be considered for patients with CrCl rates of less than 30 mL/min (0.50 mL/s) based on total patient body weight using the Cockroft–Gault equation.[4] Although recommendations for dosing adjustment of enoxaparin in patients with CrCl between 10 and 30 mL/min (0.17 and 0.50 mL/s) are listed in the product manufacturer's label, the safety and efficacy of enoxaparin in this patient population remain vastly understudied. Administration of enoxaparin should be avoided in dialysis patients with ACS. While the duration of bivalirudin infusion is generally short (several hours only), few patients with significant renal impairment have been included in clinical trials. Dose adjustments for bivalirudin in patients with CrCl less than 30 mL/min (0.50 mL/s) or on hemodialysis is recommended. Patients with SCr greater than 3.0 mg/dL (265 μmol/L) were excluded from ACS trials with fondaparinux. Fondaparinux is contraindicated in patients with CrCl less than 30 mL/min (0.50 mL/s).[4]

UFH is monitored and the dose adjusted to a target aPTT or antifactor Xa levels, whereas the dose of enoxaparin is based on actual body weight without routine monitoring of antifactor Xa levels. Some experts recommend antifactor Xa monitoring for LMWHs (eg, enoxaparin, fondaparinux) in patients with renal impairment during prolonged courses of administration of more than several days. No monitoring of coagulation is recommended for bivalirudin and fondaparinux.

Besides bleeding, the most serious adverse effect of UFH and enoxaparin is **heparin-induced thrombocytopenia**. ACS registry data indicate the frequency of heparin-induced thrombocytopenia is rare (< 0.5%).[11] Bivalirudin would be the preferred anticoagulant for patients with a history of heparin-induced thrombocytopenia undergoing PCI.[5]

► *β-Blockers*

Oral β-blockers should be administered early in the care of patients with an ACS and continued for at least 3 years in patients with normal LVF.[3,4,39] In ACS, the benefit of β-blockers results mainly from the competitive blockade of β_1-adrenergic receptors located on the myocardium. β_1-Blockade produces a reduction in heart rate, myocardial contractility, and BP, decreasing myocardial oxygen demand. In addition, the reduction in heart rate increases diastolic time, thus improving ventricular filling and coronary artery perfusion. As a result of these effects, β-blockers reduce the risk for recurrent ischemia, infarct size, risk of reinfarction, and occurrence of ventricular arrhythmias in the hours and days following MI.[3,4]

The role of early β-blocker therapy in reducing MI mortality was established in the 1970s and 1980s before routine use of early reperfusion therapy. Data in the reperfusion era are derived mainly from a large clinical trial that suggests IV initiation followed by oral β-blockers early in the course of MI is associated with a lower risk of reinfarction or ventricular fibrillation. However, there may be an early risk of cardiogenic shock in patients presenting with advanced age (> 70 years), heart rate greater than 100 beats/min, systolic BP less than 120 mm Hg, or late presentation.[4,40] Therefore, initiation of β-blockers (oral preferred) should be limited to patients who are hemodynamically stable, not at increased risk for cardiogenic shock, and without signs or symptoms of acute HF. Careful assessment for any contraindications to β-blockers should be performed following initiation and prior to any dose titration. The most serious side effects of β-blocker administration early in ACS are hypotension, acute HF, bradycardia, and heart block.[3,4]

Patients already taking β-blockers can continue taking them. Patients with contraindications to their use in the first 24 hours of presentation should be reevaluated and treated with β-blockers at a later time if they become eligible. In patients presenting with acute HF, use of β-blockers should be delayed until they are stabilized. Initiation of β-blockers may be attempted before hospital discharge in most patients following resolution of acute HF. Patients with HF secondary to reduced LVF should receive one of three β-blockers: bisoprolol, sustained-release metoprolol succinate, or carvedilol.[3,4]

► *Additional Therapies*

Oral ACE inhibitors have been shown to decrease nonfatal and fatal major CV events.[3,4] The benefit of ACE inhibitors in patients with MI most likely comes from their ability to prevent cardiac

remodeling and ultimately development of HF. The largest reduction in mortality is observed in patients with left ventricular dysfunction (low LVEF) or HF symptoms. Early initiation (within 24 hours) of an oral ACE inhibitor is recommended as benefit can be seen as early as 24 hours post MI, especially in patients with high-risk features such as HF, low LVEF, or STEMI in the anterior location.[3,4] However, these agents should be used cautiously in the first 24 hours to avoid renal dysfunction or hypotension.[4] The use of IV ACE inhibitors is not recommended because mortality may be increased. Administration of ACE inhibitors should be continued indefinitely in those patients without contraindications with LVEF less than 40% (0.40) and in those with HTN, stable CKD, or DM.[4,39]

To accurately assess baseline low-density lipoprotein (LDL), it is recommended to obtain a fasting lipid panel within 24 hours in patients presenting with an ACS.[41] The administration of high-intensity statins prior to PCI may reduce the risk of periprocedural MI, and hence statins should be initiated as early as possible in ACS.[5] Additionally, statins reduce the risk of CV death, recurrent MI, stroke, and the need for revascularization when initiated early in the treatment of ACS.[3,4,41] Although the primary effect of statins is to decrease LDL cholesterol, statins are believed to produce many non-lipid-lowering or "pleiotropic" effects such as anti-inflammatory and antithrombotic properties. Based on current evidence, the most recent guidelines for the treatment of cholesterol in adults recommend that patients who experience an ACS should receive high-intensity statin therapy (atorvastatin 40–80 mg daily; rosuvastatin 20–40 mg daily) if they are less than or equal to 75 years of age, and moderate-intensity statin therapy (eg, atorvastatin 10–20 mg; pravastatin 40–80 mg; rosuvastatin 5–10 mg; simvastatin 20–40 mg) if they are older than 75 years or not a candidate for high-intensity statins because of contraindications, at risk for statin intolerance, or have a history of statin-associated adverse drug reactions. Select patients older than 75 years may be candidates for high-intensity therapy to lower LDL cholesterol. High- and moderate-intensity statins defined as daily statin doses required to reduce LDL cholesterol greater than or equal to 50% and 30% to 49%, respectively.[42] Thus, in the absence of contraindications and depending on age, moderate- to high-intensity statin therapy should be initiated early during hospitalization to all patients experiencing ACS.[3,4]

▶ *Calcium Channel Blockers*

Calcium channel blockers in the setting of ACS are used for relief of continued ischemia despite β-blocker and nitrate therapy, vasospastic angina, additional need for BP lowering (ie, amlodipine), or in patients with contraindications to β-blockers. Data suggest little benefit on clinical outcomes beyond symptom relief for calcium channel blockers in the setting of ACS especially in patients with reduced LVEF.[3,4] Therefore, calcium channel blockers should be avoided in the acute management of ACS unless there is a clear symptomatic need or contraindication to β-blockers. Agent selection is based on presenting heart rate and left ventricular dysfunction (diltiazem and verapamil are contraindicated in patients with bradycardia, heart block, or reduced LVEF). Immediate-release nifedipine should be avoided because it has demonstrated reflex sympathetic activation, tachycardia, and worsened myocardial ischemia.[3,4] Dosing and contraindications are described in Table 8–3.

Secondary Prevention Following MI

The long-term goals following ACS are to: (a) control modifiable CHD risk factors; (b) prevent the development of HF; (c) prevent new or recurrent MI and stroke; (d) prevent death, including sudden cardiac death; and (e) prevent stent thrombosis following PCI. Pharmacotherapy, which has been proven to decrease mortality, HF, reinfarction, stroke, and stent thrombosis should be initiated prior to hospital discharge for secondary prevention.

KEY CONCEPT Secondary prevention guidelines suggest that following MI, all patients should receive long-term treatment with ASA, a β-blocker, an ACE inhibitor, and a statin for secondary prevention of death, stroke, or recurrent infarction.[39] A $P2Y_{12}$ inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients with NSTE-ACS receiving an ischemia-guided treatment strategy.[3-5,20] Clopidogrel should be continued for at least 14 days and ideally up to 1 year in patients with STEMI receiving thrombolytics. Other $P2Y_{12}$ inhibitors have not been studied in combination with thrombolytics; however, prasugrel may be an alternative to clopidogrel in patients who undergo delayed PCI after thrombolytics.[3] An ARB and an aldosterone antagonist should be given to select patients. Dosing and contraindications of medication therapy are described in detail in Table 8–3. For all patients with ACS, treatment and control of modifiable risk factors such as HTN, dyslipidemia, obesity, smoking, and DM are essential.[3,4,39] Patients should receive proper counseling and education, both verbal and written, regarding these treatments and recommendations prior to discharge. At follow-up appointments, medication reconciliation and dose optimization improve drug adherence.[43] Use of ICDs for the prevention of sudden cardiac death following MI in patients with reduced LVF and nonsustained ventricular arrhythmias is discussed in more detail in Chapter 9, "Arrhythmias."

▶ *Aspirin*

ASA decreases the risk of death, recurrent infarction, and stroke following MI. All patients should receive daily ASA 81 to 162 mg indefinitely; those patients with a contraindication to ASA should receive clopidogrel.[3,4,39] The risk of major bleeding from chronic ASA therapy is approximately 2% and is dose related. Higher doses of ASA, 160 to 325 mg, are not more effective than ASA doses of 75 to 81 mg but have higher rates of bleeding.[44] Therefore, the guidelines recommend 81 mg daily as a preferred strategy in ACS patients with or without PCI.[3,4]

▶ *$P2Y_{12}$ Inhibitors*

For patients with either STEMI or NSTE-ACS, clopidogrel decreases the risk of CV events and stent thrombosis compared with placebo. Compared with clopidogrel, either prasugrel or ticagrelor lowers the risk of CV death, MI, or stroke by an additional 20% to 30% depending on the patient population studied. The frequency of stent thrombosis following PCI is also lower with prasugrel or ticagrelor compared with clopidogrel. However, the rate of bleeding not related to CABG surgery

Patient Encounter 2, Part 2

Is reperfusion therapy with fibrinolysis indicated at this time for this patient?

What adjunctive pharmacotherapy should be administered to this patient in the emergency department?

What additional pharmacotherapy should be initiated on the first day of this patient's hospitalization following successful reperfusion with PCI?

is higher with both prasugrel and ticagrelor compared with clopidogrel.[25,26]

LO 6 The ACC/AHA Dual Antiplatelet Therapy Focused Update recommends continuation of a $P2Y_{12}$ inhibitor for at least 12 months following PCI for ACS.[20] Continuation of $P2Y_{12}$ inhibitors longer than 12 months may be considered in patients who have not experienced any bleeding episodes and are not at high risk for bleeding.[20] For patients with STEMI receiving thrombolytics, clopidogrel should be continued for at least 14 days and ideally up to 1 year.[3] For NSTE-ACS patients who do not receive a coronary stent, clopidogrel or ticagrelor should be continued up to 1 year.[4,20]

Bleeding is an inherent risk with long-term DAPT. In fact, oral antiplatelet agents are the third leading cause of adverse drug reaction–associated hospital admissions after ED visits among seniors.[45] Therefore, patients should be counseled on the risks and sites of potential bleeding and should be told to seek medical care immediately if significant bleeding is noticed. Some patients who are at increased risk of GI bleeding may benefit from the addition of a PPI.[20,46]

► β-Blockers, Nitrates, and Calcium Channel Blockers

LO 6 Current treatment guidelines recommend that following an ACS, patients with normal LVF should receive a β-blocker for at least 3 years, indefinitely for those with reduced LVF, and may be considered longer if needed for the treatment of HTN or angina.[3,4,39,47] Overwhelming data support the use of β-blockers in patients with a previous MI to improve long-term survival. Currently, there are no data to support the superiority of one β-blocker over another in the absence of HF with reduced LVF.

Although β-blockers should be avoided in patients with decompensated HF from left ventricular systolic dysfunction complicating an MI, clinical trial data suggest it is safe to initiate β-blockers prior to hospital discharge in these patients once HF symptoms have resolved.[3,4] In patients who cannot tolerate or have a contraindication to a β-blocker, a calcium channel blocker can be used to prevent anginal symptoms but nondihydropyridines should not be used in patients with reduced LVF.[3,4]

Chronic long-acting nitrate therapy has not been shown to reduce CHD events following MI and is not indicated in ACS patients who have undergone revascularization, unless the patient has stable ischemic heart disease, refractory angina, coronary vasospasms, or significant coronary stenoses that were not revascularized. All patients should be prescribed short-acting SL NTG tablets or spray to relieve any anginal symptoms when necessary and instructed on its use.[3,4] If ischemic chest discomfort persists for more than 5 minutes after the first dose, the patient should be instructed to contact emergency medical services. Nitrates should not be administered to patients with hypotension or who have recently received a phosphodiesterase inhibitor (see Table 8–3).[3,4,48]

► ACE Inhibitors and ARBs

ACE inhibitors reduce mortality, decrease reinfarction, and prevent the development of HF with recent ACS, especially in those with reduced LVF.[3,4,39] Additional trials suggest that most patients with CAD, not just ACS or HF patients, benefit from ACE inhibitors. Therefore, ACE inhibitors should be considered in all patients (eg, those with HTN, DM, or stable CKD) following an ACS in the absence of a contraindication.

Besides hypotension, the most frequent adverse reaction to an ACE inhibitor is cough, which may occur in up to 30% of patients. Patients who cannot tolerate an ACE inhibitor may be prescribed an ARB. Other, less common but more serious adverse effects of ACE inhibitors and ARBs include acute renal failure, hyperkalemia, and angioedema.[3,39]

► Aldosterone Antagonists

LO 6 Aldosterone plays an important role in HF and in MI because it promotes vascular and myocardial fibrosis, endothelial dysfunction, HTN, left ventricular hypertrophy, sodium retention, potassium and magnesium loss, and arrhythmias. Aldosterone antagonists have been shown to attenuate these adverse effects and reduce mortality in patients who are already receiving an ACE inhibitor (or ARB) and β-blocker and have an LVEF less than or equal to 40% (0.40) and either HF symptoms or DM.[3,4]

Eplerenone and spironolactone are aldosterone antagonists that block the mineralocorticoid receptor. In contrast to spironolactone, eplerenone has no effect on the progesterone or androgen receptor, thereby minimizing the risk of gynecomastia, sexual dysfunction, and menstrual irregularities. In a large clinical trial, eplerenone significantly reduced mortality as well as hospitalization for HF in post–MI patients with an LVEF less than 40% (0.40) and symptoms of HF at any time during hospitalization.[49]

LO 6 The risk of hyperkalemia increases with the use of aldosterone antagonists when added to an ACE inhibitor or ARB. Therefore, patients with serum potassium concentrations greater than 5.0 mmol/L (mEq/L) should not receive these agents. Specific contraindications for spironolactone include SCr greater than or equal to 2.5 mg/dL (221 μmol/L) for men or 2.0 mg/dL (177 μmol/L) for women, or CrCl less than or equal to 30 mL/min (0.50 mL/s). Contraindications for eplerenone include SCr greater than or equal to 2.0 mg/dL (177 μmol/L) for men or 1.8 mg/dL (159 μmol/L) for women, or CrCl less than or equal to 50 mL/min (0.83 mL/s). Currently, there are no data to support that eplerenone is superior or preferred to spironolactone unless a patient has experienced gynecomastia, breast pain, or impotence while receiving spironolactone.

► Lipid-Lowering Agents

LO 6 Following MI, statins reduce total mortality, CV mortality, need for revascularization, and stroke. According to practice guidelines, all patients who have experienced ACS should receive high-intensity statin therapy provided that no contraindications exist.[4,42] Indeed, results from landmark clinical trials have unequivocally demonstrated the value of statins in secondary prevention. High-intensity statin therapy, which typically lowers LDL cholesterol by 50% or greater, is preferred because of the greatest reduction in outcomes. The current evidence indicates that higher-dose statin therapy, such as atorvastatin 40 to 80 mg daily and rosuvastatin 10 to 20 mg daily, produces a greater reduction in CV events such as MI, ischemic stroke, and revascularization than less intensive statin regimens (such as simvastatin 20–40 mg daily). Moderate intensity statin therapy is recommended for those who are 75 years of age or older if high-intensity therapy is not tolerated, or in those who have a high risk for statin-associated adverse effects such as those with drug–drug interactions.[4,42]

In patients for whom a 50% reduction of LDL cholesterol is not achieved by statin therapy alone (or, in whom LDL cholesterol remains ≥ 70 mg/dL [1.81 mmol/L]), nonstatin therapy may be added to the statin for therapy intensification. An expert consensus statement supports the addition of either ezetimibe or

a proprotein convertase subtilisin/kexin type (PCSK9) inhibitor to statin therapy in very high-risk patients after considering desired LDL reduction, potential for additional CV risk reduction, adverse events or drug–drug interactions, and patient preference.[41] Based on randomized data, ezetimibe added to statin therapy after ACS produced a modest benefit (~10% reduction) on CV outcomes.[41] Both evolocumab and alirocumab (PCSK9 inhibitors) have also demonstrated improved CV outcomes in patients with atherosclerotic cardiovascular disease (ASCVD) added to maximal statin therapy with or without ezetimibe.

▶ *Other Modifiable Risk Factors*

LO 6

Smoking cessation, managing HTN, weight loss, exercise, and glucose control for patients with DM, in addition to treatment of dyslipidemia, are important treatments for secondary prevention of CHD events.[39] Referral to a comprehensive CV risk reduction program for cardiac rehabilitation is recommended.[3,39] HTN should be strictly controlled according to published guidelines.[47] Patients who are overweight, hypertensive, or who require cholesterol lowering should be educated on the importance of regular exercise, healthy eating habits, and reaching and maintaining an ideal weight. Moderate-intensity aerobic exercise for at least 40 minutes, 3 to 4 days per week is recommended. Because patients with DM have up to a fourfold increased mortality risk compared with patients without DM, the importance of blood glucose control, as well as other CHD risk factor modifications, cannot be overstated.[39] Finally, influenza vaccination is recommended in all patients with CV disease. Additionally, vaccination with the 13- and 23-valent pneumococcal polysaccharide vaccines is recommended in those 65 years and older, as well as all high-risk individuals presenting with CV disease.[4,39]

LO 6

In patients who require treatment for musculoskeletal pain, a stepped-care approach should be taken in the selection of treatment. Acetaminophen, tramadol, and nonacetylated salicylates are preferred. Use of small doses of narcotics for short periods can be added if the aforementioned are not adequate to relieve the patient.[4] If these agents are insufficient, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered, and should be used at the lowest effective dose and for the shortest possible time. Existing evidence suggests that naproxen may have the lowest risk to induce CV ischemic events, but the quality of the evidence available limits the definitiveness of assessment of its safety, particularly when it is used for long term. Importantly, all NSAIDs increase the risk of HF. If NSAIDs are used in combination with antiplatelets, a PPI should be added to reduce risk of GI bleeding.[46]

Patient Encounter 2, Part 3

The patient undergoes coronary angiography and is found to have a 95% stenosis in his right coronary artery. PCI is performed and a drug-eluting stent is placed without complications.

Identify the long-term treatment goals for this patient.

What additional pharmacotherapy should be initiated prior to hospital discharge?

Create a care plan for this patient for hospital discharge that includes pharmacotherapy, desired treatment outcomes, and monitoring for efficacy and adverse effects.

OUTCOME EVALUATION

LO 3 LO 4 LO 5

- KEY CONCEPT To determine the efficacy of nonpharmacologic and pharmacotherapy for both STEMI and NSTE-ACS, monitor patients for: (a) relief of ischemic discomfort; (b) return of ECG changes to baseline; and (c) absence or resolution of HF signs and symptoms.
- Monitoring parameters for recognition and prevention of adverse effects from ACS pharmacotherapy are described in Table 8–5. KEY CONCEPT In general, the most common adverse reactions from ACS therapies are hypotension and bleeding. To treat bleeding and hypotension, discontinue the offending agent(s) until symptoms resolve. Severe bleeding resulting in

Table 8–5

Therapeutic Drug Monitoring of Pharmacotherapy for Acute Coronary Syndromes

Drug	Adverse Effects	Monitoring
Aspirin	Dyspepsia, bleeding, gastritis	Clinical signs of bleeding[a]; GI upset; baseline and every 6 months: Hgb, HCT, platelet count
Clopidogrel and prasugrel	Bleeding, diarrhea, rash, TTP (rare)	Clinical signs of bleeding[a]; baseline and every 6 months: Hgb, HCT, platelet count
Ticagrelor	Bleeding, dyspnea, diarrhea, rash, elevated SCr, elevated serum uric acid	Clinical signs of bleeding[a]; baseline and every 6 months: Hgb, HCT, platelet count
Unfractionated heparin	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding[a]; baseline aPTT, INR, Hgb, HCT, and platelet count; ACT during cardiac catheterization; aPTT every 6 hours until target then every 24 hours; daily Hgb, HCT, and platelet count
Enoxaparin	Bleeding, heparin-induced thrombocytopenia	Clinical signs of bleeding[a]; baseline SCr, aPTT, INR, Hgb, HCT, and platelet count; daily SCr, Hgb, HCT, and platelet count
Fondaparinux	Bleeding	Clinical signs of bleeding[a]; baseline SCr, aPTT, INR, Hgb, HCT, and platelet count; daily SCr, Hgb, HCT, and platelet count
Bivalirudin	Bleeding	Clinical signs of bleeding[a]; baseline SCr, aPTT, INR, Hgb, HCT, and platelet count
Fibrinolytics	Bleeding, especially ICH	Clinical signs of bleeding[a]; baseline aPTT, INR, Hgb, HCT, and platelet count; mental status every 2 hours for signs of ICH; daily Hgb, HCT, and platelet count

(*Continued*)

Table 8–5

Therapeutic Drug Monitoring of Pharmacotherapy for Acute Coronary Syndromes (*Continued*)

Drug	Adverse Effects	Monitoring
GPIs	Bleeding, acute profound thrombocytopenia	Clinical signs of bleeding[a]; baseline SCr (for eptifibatide and tirofiban), Hgb, HCT, and platelet count; platelet count at 4 hours after initiation; daily Hgb, HCT, and platelet count (and SCr for eptifibatide and tirofiban)
IV nitrates	Hypotension, flushing, headache, tachycardia	BP and HR every 2 hours
β-Blockers	Hypotension, bradycardia, heart block, bronchospasm, acute HF, fatigue, depression, sexual dysfunction	BP, RR, HR, 12-lead ECG, and clinical signs of HF every 5 minutes with bolus IV dosing; BP, RR, HR, and clinical signs of HF every shift with oral therapy, then BP and HR every 6 months following hospital discharge
Diltiazem and verapamil	Hypotension, bradycardia, heart block, HF, constipation, gingival hyperplasia	BP and HR every shift with oral therapy, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
Amlodipine	Hypotension, dependent peripheral edema, gingival hyperplasia	BP every shift with oral therapy, then every 6 months following hospital discharge; dental examination and teeth cleaning every 6 months
ACE inhibitors and ARBs	Hypotension, cough (with ACE inhibitors), hyperkalemia, prerenal azotemia, acute renal failure, angioedema (ACE inhibitors more so than ARBs)	BP every 4 hours × 3 for first dose, then every shift with oral therapy, then once every 6 months following hospital discharge; baseline SCr and potassium; daily SCr and potassium while hospitalized, then every 6 months (or 1–2 weeks after each outpatient dose titration); closer monitoring required in patients receiving spironolactone or eplerenone or if renal insufficiency; counsel patient on symptoms of angioedema including throat, tongue, and facial swelling
Aldosterone antagonists	Hypotension, hyperkalemia, increased SCr	BP and HR every shift with oral therapy, then once every 6 months; SCr and serum potassium concentration at baseline then at 48 hours, at 7 days, monthly for 3 months, then every 3 months thereafter
Morphine	Hypotension, respiratory depression	BP and RR 5 minutes after each bolus dose and resolution of pain
Statins	GI upset, myopathy, hepatotoxicity	Liver function tests at baseline. Lipid panel for adherence. CK if indicated. Only repeat if patients present with sign/symptoms of liver failure or muscle symptoms; counsel patient on myalgia; consider CK at baseline if adding a fibrate or niacin

[a]Clinical signs of bleeding include bloody stools, melena, hematuria, hematemesis, bruising, and oozing from arterial or venous puncture sites.

ACE, angiotensin-converting enzyme; ACT, activated clotting time; aPTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; BP, blood pressure; CK, creatine kinase; ECG, electrocardiogram; GI, gastrointestinal; GPI, glycoprotein IIb/IIIa inhibitor; HCT, hematocrit; HF, heart failure; Hgb, hemoglobin; HR, heart rate; ICH, intracranial hemorrhage; INR, international normalized ratio; IV, intravenous; RR, respiratory rate; SCr, serum creatinine; TTP, thrombotic thrombocytopenic purpura.

Modified with permission from Rogers KC, de Denus S, Finks SW, Spinler SA. Acute coronary syndromes. In: DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:188.

Patient Care Process

Collect Information:

- Perform a medication history (including prescriptions, over-the-counter medications, and dietary supplements). Identify whether the patient has any drug allergies or is experiencing side effects from therapy.
- Review the medical history to identify possible causes of ACS (eg, HTN, hyperlipidemia).
- Review the medical history and physical assessment findings, specifically
  - Possible causes and risk factors for ACS (eg, tobacco use, HTN, hyperlipidemia)
  - Family history of premature ASCVD
  - Patient's description of chest pain, precipitating causes, other symptoms, and what may have relieved the chest pain
  - Results of the 12-lead ECG which should be performed and interpreted within 10 minutes (see Figure 8–1)
  - Serial cardiac troponin levels at presentation and 3–6 hours after symptom onset. (See Figure 8–1 and Clinical Presentation and Diagnosis textbox). Serial troponin measurements are not necessary if the patient is experiencing a STEMI (see Figure 8–1)
  - Vital signs (eg, BP and HR) to determine need for appropriate treatment

(*Continued*)

Patient Care Process (*Continued*)

- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Risk stratify the patient using available risk calculators for those with NSTE-ACS (see Table 8–1).
- If the patient is diagnosed with ACS, determine what pharmacotherapy is indicated.
- For STEMI patients in non-PCI facilities, assess for contraindications for fibrinolytic therapy if patient cannot be transferred and undergo PCI within 120 minutes.
- If patient is already receiving pharmacotherapy for ACS, assess efficacy and safety. Are there any significant drug interactions? Document existing contraindications and adverse events to medications (eg, aspirin, $P2Y_{12}$ inhibitors, β-blockers, ACE inhibitors, or aldosterone antagonists) in the medical record.
- Determine whether recommended agents are included on the institution's formulary.
- Discuss prescription coverage with the patient to determine any barriers to paying for medications.
- Talk with patient and assess refill history, if available, to determine medication adherence and to identify any barriers to adherence.
- Review relevant laboratory tests (eg, electrolytes, lipids, renal function, CBC).

Develop a Care Plan:

- Use risk stratification to select site of care, antithrombotic therapies, and invasive management for patients with NSTE-ACS (see Figure 8–3).
- Choose appropriate initial therapy and antithrombotic therapy for patients presenting with STEMI based on reperfusion strategy chosen (see Figure 8–2).
- Assess for potential contraindications for antiplatelet (active bleeding, history of TIA/stroke, renal function) and anticoagulant therapies (SCr, hemoglobin/hematocrit, platelet function). See Table 8–3.
- Initiate ACE inhibitors (or ARBs) and aldosterone antagonists as appropriate before discharge.
- Initiate prescription of PPI therapy as appropriate for those requiring triple therapy with aspirin, a $P2Y_{12}$ receptor inhibitor, and a vitamin K antagonist.
- Assess for appropriate vaccinations prior to discharge.

Implement the Care Plan:

- Verify orders for anti-ischemic (nitroglycerin [NTG], β-blockers), antiplatelet (aspirin), and analgesic (morphine) medications where appropriate early in care.
- Initiate appropriate antiplatelet and anticoagulant medications based on ACS type (STEMI vs NSTE-ACS) and strategy chosen (early invasive vs ischemia guided) (see Figures 8–2 and 8–3). If a patient has received fondaparinux and is going to the catheterization or cath laboratory, ensure that additional anticoagulation with UFH is given at time of intervention (see Figure 8–3).
- Review renal function and baseline coagulation tests (aPTT, platelets) to make appropriate dosing adjustments in antiplatelet and anticoagulant therapies given during early ACS.
- Appropriately adjust all medications based on renal function (see Table 8–3).
- Monitor for signs and symptoms of bleeding during hospitalization and prior to discharge.
- Ensure all patients without contraindications receive oral β-blockers, preferably within the first 24 hours.
- Patients with initial contraindications to β-blockers in the first 24 hours should be reevaluated for therapy prior to discharge.
- Ensure all patients receive aspirin and statins at discharge and continue indefinitely as long as no contraindication exists.
- Educate patient on discharge prescriptions for DAPT (with aspirin 81 mg plus a $P2Y_{12}$ inhibitor), which should be given for 12 months after ACS regardless of stenting. Also, discuss with the patient the importance of DAPT (especially in the patient receiving a stent).
- Ensure patients receive a prescription for SL NTG at the time of discharge with verbal and written instructions for use.
- Continue anti-ischemic medications at discharge in those with recurrent symptoms or in patients who do not undergo revascularization.
- Discontinue NSAIDs and select COX-2 inhibitor agents taken prior to ACS.
- Educate patients about appropriate cholesterol management, BP goals, smoking cessation, and lifestyle management with easily understandable and culturally sensitive verbal and written instructions.
- Address musculoskeletal pain control prior to discharge.
- Refer all patients to a comprehensive CV rehabilitation program.

Follow-up: Monitor and Evaluate:

- Follow-up within 2 weeks to assess angina symptoms and interventional success if applicable.
- Review medical history and physical examination findings, laboratory tests, and results of other diagnostic workup.
- Discuss adherence with medications and discover if the patient is experiencing any adverse events from medications.

hypotension secondary to hypovolemia may require blood transfusion.

LO 6

- Because poor medication adherence of secondary prevention medications following MI leads to worsened CV outcomes, patients should receive medication counseling (including counseling prior to hospital discharge) and be monitored for medication persistence.[3,4,43] Counseling should include assessment of health literacy level, assessment of barriers to adherence, assessment of access to medications, written and verbal instructions about the purpose of each medication, changes to previous medication regimen, optimal time to take each medication, new allergies or medication intolerances, need for timely prescription fill after discharge, anticipated duration of therapy, consequences of nonadherence, common and/or serious adverse reactions that may develop, drug–drug and drug–food interactions, and an assessment of instruction understanding.

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Abbreviations Introduced in This Chapter

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADP	Adenosine diphosphate
AHA	American Heart Association
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ASA	Aspirin
ASCVD	Atherosclerotic cardiovascular disease
BNP	B-type natriuretic peptide
BMS	Bare metal stent
BP	Blood pressure
CABG	Coronary artery bypass graft (surgery)
CAD	Coronary artery disease
CBC	Complete blood count
CHD	Coronary heart disease
CKD	Chronic kidney disease
COX-2	Cyclooxygenase-2
CrCl	Creatinine clearance
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P-450
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
DM	Diabetes mellitus
ECG	Electrocardiogram
ED	Emergency department
GI	Gastrointestinal
GP	Glycoprotein
GPI	Glycoprotein IIb/IIIa inhibitor
HF	Heart failure
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HTN	Hypertension
ICD	Implantable cardioverter defibrillator
ICH	Intracranial hemorrhage
INR	International normalized ratio
IV	Intravenous
LDL	Low-density lipoprotein
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
LVF	Left ventricular function
MI	Myocardial infarction
NSAID	Nonsteroidal anti-inflammatory drug
NSTE	Non–ST-segment elevation
NSTEMI	Non–ST-elevation myocardial infarction
NTG	Nitroglycerin
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type
PPI	Proton pump inhibitor
SCAI	Society for Cardiovascular Angiography and Interventions
SCr	Serum creatinine
SL	Sublingual
STE	ST-segment elevation
STEMI	ST-segment elevation myocardial infarction
TIA	Transient ischemic attack
TIMI	Thrombolysis in myocardial infarction
TTP	Thrombotic thrombocytopenic purpura
TXA_2	Thromboxane A_2
UA	Unstable angina
UFH	Unfractionated heparin

REFERENCES

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135:e146–e603.
2. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. Circ Res. 2014;114:1852–1866.
3. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61:e78–e140.
4. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64:e139–e228.
5. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol. 2011;58:e44–e122.
6. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation. 2013;127:e6–e245.
7. Chin CT, Chen AY, Wang TY, et al. Risk adjustment for in-hospital mortality of contemporary patients with acute myocardial infarction: the acute coronary treatment and intervention outcomes network (ACTION) registry-get with the guidelines (GWTG) acute myocardial infarction mortality model and risk score. Am Heart J. 2011;161:113–22.e2.
8. Borissoff JI, Spronk HM, ten Cate H. The hemostatic system as a modulator of atherosclerosis. New Engl J Med. 2011;364:1746–1760.
9. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60:1581–1598.
10. Gajarsa JJ, Kloner RA. Left ventricular remodeling in the post-infarction heart: a review of cellular, molecular mechanisms, and therapeutic modalities. Heart Fail Rev. 2011;16:13–21.
11. Goodman SG, Huang W, Yan AT, et al. The expanded Global Registry of Acute Coronary Events: baseline characteristics,

management practices, and hospital outcomes of patients with acute coronary syndromes. Am Heart J. 2009;158:193–201. e1–e5.
12. Awad HH, Anderson FA, Jr., Gore JM, Goodman SG, Goldberg RJ. Cardiogenic shock complicating acute coronary syndromes: insights from the Global Registry of Acute Coronary Events. Am Heart J. 2012;163:963–971.
13. Huynh T, Perron S, O'Loughlin J, et al. Comparison of primary percutaneous coronary intervention and fibrinolytic therapy in ST-segment-elevation myocardial infarction: bayesian hierarchical meta-analyses of randomized controlled trials and observational studies. Circulation. 2009;119:3101–3109.
14. Bagai A, Dangas GD, Stone GW, Granger CB. Reperfusion strategies in acute coronary syndromes. Circ Res. 2014;114:1918–1928.
15. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. New Engl J Med. 1995;332:1418–1424.
16. Van De Werf F, Adgey J, Ardissino D, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet. 1999;354:716–722.
17. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. New Engl J Med. 1997;337:1118–1123.
18. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet. 1994;343:311–322.
19. Hoenig MR, Aroney CN, Scott IA. Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. Cochrane Database Syst Rev. 2010;(3):Cd004815.
20. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68:1082–1115.
21. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. New Engl J Med. 2014;371:2155–2166.
22. Bhatt DL, Hulot JS, Moliterno DJ, Harrington RA. Antiplatelet and anticoagulation therapy for acute coronary syndromes. Circ Res. 2014;114:1929–1943.
23. Sofi F, Giusti B, Marcucci R, Gori AM, Abbate R, Gensini GF. Cytochrome P450 2C19*2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. Pharmacogenomics J. 2011;11:199–206.
24. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clin Pharmacol Ther. 2013;94:317–323.
25. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. New Engl J Med. 2007;357:2001–2015.
26. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New Engl J Med. 2009;361:1045–1057.
27. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009;373:723–731.
28. Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation. 2008;118:1626–1636.
29. James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2010;31:3006–3016.
30. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. Lancet. 2010;376:1320–1328.
31. Siller-Matula JM, Huber K, Christ G, et al. Impact of clopidogrel loading dose on clinical outcome in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Heart. 2011;97:98–105.
32. Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet. 2010;376:1233–1243.
33. Mangalpally KK, Kleiman NS. The safety of clopidogrel. Expert Opin Drug Saf. 2011;10:85–95.
34. Giugliano RP, White JA, Bode C, et al. Early versus delayed, provisional eptifibatide in acute coronary syndromes. New Engl J Med. 2009;360:2176–2190.
35. Dasgupta H, Blankenship JC, Wood GC, Frey CM, Demko SL, Menapace FJ. Thrombocytopenia complicating treatment with intravenous glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis. Am Heart J. 2000;140:206–211.
36. Stone GW, Witzenbichler B, Guagliumi G, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet. 2011;377:2193–2204.
37. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet. 2014;384:1849–1858.
38. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. Lancet. 2014;384:599–606.
39. Smith SC, Jr., Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011;58:2432–2446.
40. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366:1622–1632.
41. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2016;68:92–125.
42. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889–2934.

43. Ho PM, Lambert-Kerzner A, Carey EP, et al. Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. JAMA Intern Med. 2014;174:186–193.
44. Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. Am J Cardiol. 2005;95:1218–1222.
45. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. New Engl J Med. 2011;365:2002–2012.
46. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Circulation. 2010;122:2619–2633.
47. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13. [Epub ahead of print.]
48. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;60:e44–e164.
49. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New Engl J Med. 2003;348:1309–1321.

9 Arrhythmias

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LEARNING OBJECTIVES

LO

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

1. Describe the phases of cardiac action potential, compare and contrast cardiac myocyte ion currents corresponding to each phase, and explain the relationship between the cardiac action potential and the electrocardiogram (ECG).
2. Describe the modified Vaughan Williams classification of antiarrhythmic drugs, and compare and contrast the effects of available antiarrhythmic drugs on ventricular conduction velocity, refractory period, automaticity, and inhibition of ion flux through specific myocyte ion channels.
3. Compare and contrast risk factors for and features, mechanisms, etiologies, symptoms, and goals of therapy of (a) sinus bradycardia, (b) atrioventricular (AV) block, (c) atrial fibrillation (AF), (d) paroxysmal supraventricular tachycardia (PSVT), (e) premature ventricular complexes (PVCs), (f) ventricular tachycardia (VT, including torsades de pointes [TdP]), and (g) ventricular fibrillation (VF).
4. Compare and contrast appropriate treatment options for sinus bradycardia and AV block.
5. Compare and contrast mechanisms of action of drugs used for ventricular rate control, conversion to sinus rhythm and maintenance of sinus rhythm in patients with AF.
6. Compare and contrast the advantages and disadvantages of warfarin and the non-vitamin K antagonist oral anticoagulants (NOACs) for prevention of stroke and systemic embolism in patients with AF.
7. Discuss nonpharmacologic methods for termination of PSVT, compare and contrast mechanisms of action of drugs used for acute termination of PSVT, and compare and contrast appropriate treatment options for long-term prevention of PSVT recurrence.
8. Describe the role of drug therapy for management of asymptomatic and symptomatic PVCs.
9. Compare and contrast mechanisms of action of drugs used for treatment of acute episodes of VT, and describe options and indications for nonpharmacologic treatment of VT and VF.
10. Design individualized drug therapy treatment plans for patients with (a) sinus bradycardia, (b) AV block, (c) AF, (d) PSVT, (e) PVCs, (f) VT (including TdP), and (g) VF.

NORMAL AND ABNORMAL CARDIAC CONDUCTION AND ELECTROPHYSIOLOGY

The heart functions via mechanical and electrical activity. Mechanical activity refers to atrial and ventricular contraction, the mechanism by which blood is delivered to tissues. When deoxygenated blood returns to the heart via venous circulation, the blood enters the right atrium. Right atrial contraction and right ventricular pressure changes result in delivery of blood to the right ventricle through the tricuspid valve. Right ventricular contraction pumps blood through the pulmonic valve and through the pulmonary arteries to the lungs, where blood becomes oxygenated. The oxygenated blood then flows through the pulmonary veins into the left atrium. Left atrial contraction and left ventricle (LV) pressure changes result in delivery of blood through the mitral valve into the LV, contraction of which results in pumping of blood through the aortic valve and to the tissues of the body.

Mechanical activity is stimulated by the electrical activity of the heart. The heart possesses an intrinsic electrical conduction system (Figure 9–1). Normal myocardial contraction cannot occur without normal function of the heart's electrical conduction system. Depolarization of the atria results in atrial contraction, and ventricular depolarization produces ventricular contraction. Perturbation of the heart's electrical conduction system may result in dysfunctional atrial and/or ventricular contraction and may reduce cardiac output.

Cardiac Conduction System

The sinoatrial (SA) node (frequently referred to as the sinus node), located in the upper portion of the right atrium, normally serves as the pacemaker of the heart and generates the electrical impulses that subsequently result in atrial and ventricular depolarization (see Figure 9–1). The sinus node serves as the heart's dominant pacemaker because it has the greatest degree of automaticity,

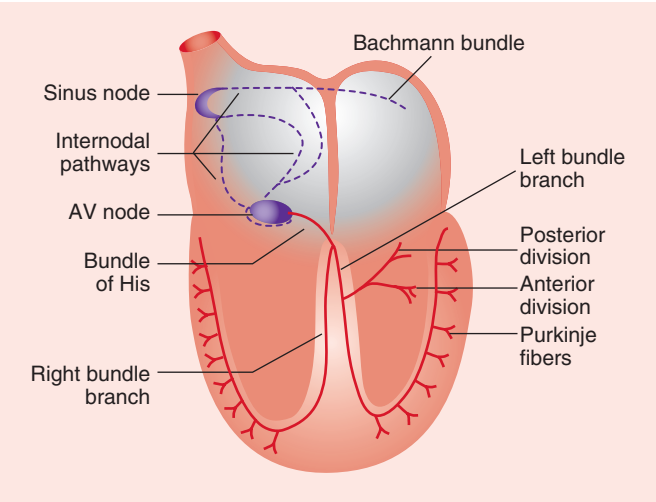

FIGURE 9–1. The cardiac conduction system. (AV, atrioventricular.)

defined as the ability of a cardiac fiber or tissue to initiate depolarizations spontaneously. In adults at rest, the normal intrinsic depolarization rate of the sinus node is 60 to 100 per minute. Other cardiac fibers also possess the property of automaticity, but normally the intrinsic depolarization rates are slower than that of the sinus node. For example, the normal depolarization rate of the atrioventricular (AV) node and ventricular tissue are 40 to 60 per minute and 30 to 40 per minute, respectively. Therefore, as a result of greater automaticity, the sinus node normally serves as the pacemaker of the heart. However, if the sinus node fails to generate depolarizations at a rate faster than that of the AV node, the AV node may take over as the pacemaker. If both the sinus node and AV node fail to generate depolarizations at a rate more than 30 to 40 per minute, ventricular tissue may take over.

Following initiation of the electrical impulse from the sinus node, the impulse travels through internodal pathways of the specialized atrial conduction system and the Bachmann bundle. The atrial conducting fibers do not traverse the entire breadth of the left and right atria; upon excitation via the internodal pathways and the Bachmann bundle, atrial depolarization spreads as a wave, conceptually similar to that which occurs upon throwing a pebble into water. As the impulse is conducted across the atria, each depolarized cell depolarizes the surrounding connected cells, until both atria have been completely depolarized. Atrial contraction follows normal atrial depolarization.

Following atrial depolarization, impulses are conducted through the AV node, located in the lower right atrium (see Figure 9–1). The impulse then enters the bundle of His and is conducted through the ventricular conduction system, consisting of the left and right bundle branches. The LV requires a larger conduction system than the right ventricle due to its larger mass; therefore, the left bundle branch bifurcates into the left anterior and posterior divisions (also known as "fascicles"). The bundle branches further divide into the **Purkinje fibers** through which impulse conduction results in ventricular depolarization, initiating ventricular contraction.

Ventricular Action Potential

LO 1

Ventricular **action potential** is depicted in **Figure 9–2**. Ventricular myocyte resting membrane potential is –70 to –90 mV, due to the function of the sodium–potassium adenosine triphosphatase (ATPase) pump, which maintains relatively high extracellular sodium concentrations and low extracellular potassium concentrations. During each action potential cycle, the membrane potential slowly increases due to a slow influx of sodium into the cell, raising the threshold to –60 to –80 mV. When the membrane potential reaches this threshold, the fast

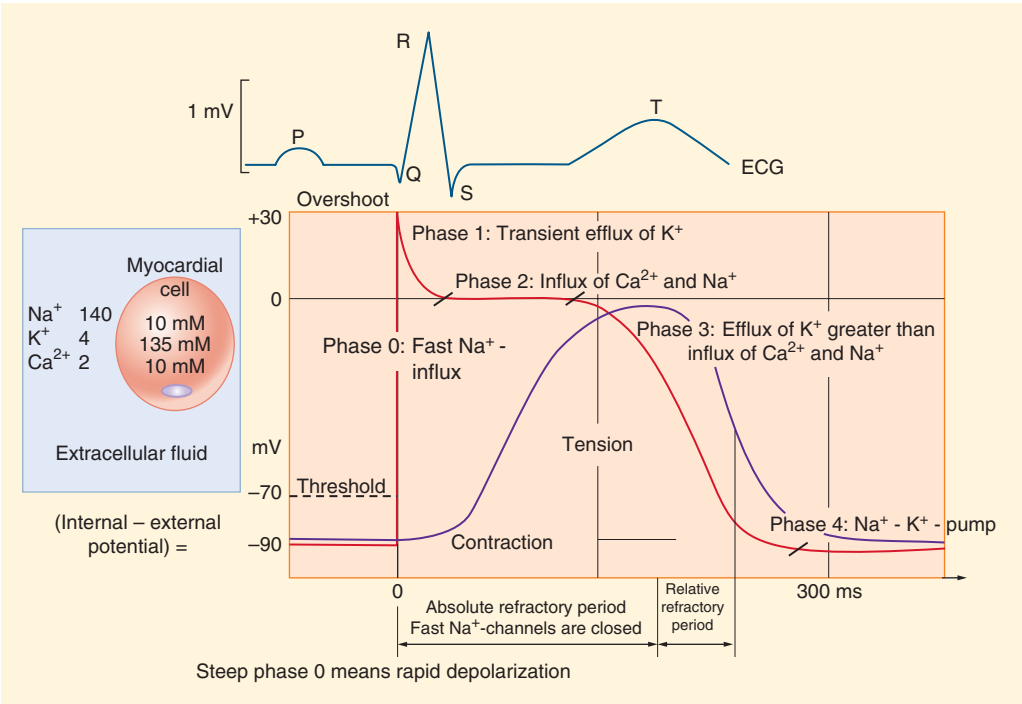

FIGURE 9–2. The ventricular action potential depicting the flow of specific ions responsible for each phase. The phases of the action potential that correspond to the absolute and relative refractory periods are portrayed, and the relationship between phases of the action potential and the ECG are shown. The red line represents the ventricular action potential and the purple line represents ventricular contraction. (Ca, calcium; K, potassium; Na, sodium.)

sodium channels open, allowing rapid entry of sodium ions into the cell. This rapid influx of positive ions creates a vertical upstroke of the action potential, which reaches 20 to 30 mV. This is phase 0, representing ventricular depolarization. At this point, the fast sodium channels become inactivated, and ventricular repolarization begins, consisting of phases 1 through 3. Phase 1 repolarization occurs primarily as a result of an efflux of potassium ions. During phase 2, potassium ions continue to exit the cell, but the membrane potential is balanced by an influx of calcium and sodium ions, transported through slow calcium and slow sodium channels, resulting in a plateau. During phase 3, the efflux of potassium ions greatly exceeds calcium and sodium influx, resulting in the major component of ventricular repolarization. During phase 4, sodium ions gradually enter the cell, increasing the threshold again to −60 to −80 mV and initiating another action potential. Understanding the ion fluxes responsible for each phase of the action potential facilitates understanding of the effects of specific drugs. For example, drugs that primarily inhibit ion flux through sodium channels influence phase 0 (ventricular depolarization), whereas drugs that primarily inhibit ion flux through potassium channels influence the repolarization phases, particularly phase 3.

Electrocardiogram

LO 1

The electrocardiogram (ECG) is a noninvasive means of measuring the heart's electrical activity. The relationship between the ventricular action potential and the ECG is depicted in Figure 9–2. The P wave on the ECG represents atrial depolarization (not depicted in Figure 9–2, which shows only the ventricular action potential). Phase 0 of the action potential corresponds to the QRS complex, which therefore is a noninvasive representation of ventricular depolarization. The T wave on the ECG corresponds to phase 3 ventricular repolarization. The interval from the beginning of the Q wave to the end of the T wave, known as the QT interval, is used as a noninvasive marker of ventricular repolarization time. Atrial repolarization is not visible on the ECG because it occurs during ventricular depolarization and is obscured by the QRS complex.

Several ECG intervals and durations are measured routinely. The PR interval represents the time of impulse conduction from the atria to the ventricles through the AV node; normal PR interval in adults is 0.12 to 0.2 seconds (120–200 ms). The QRS duration represents the time required for ventricular depolarization, which is normally 0.08 to 0.12 seconds (80–120 ms) in adults. The QT interval, measuring 0.32 to 0.4 seconds (320–400 ms), represents the time required for ventricular repolarization. The QT interval varies with heart rate—the faster the heart rate, the shorter the QT interval, and vice versa. Therefore, the QT interval is corrected for heart rate using the Bazett formula:

$$QTc = \frac{QT}{\sqrt{RR}}$$

where QTc is the QT interval corrected for heart rate, and RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds (ie, the heart rate, expressed in different terminology). Normal QTc interval in adults is 0.36 to 0.47 seconds (360–470 ms) in men and 0.36 to 0.48 seconds (360–480 ms) in women.[1]

Refractory Periods

After an impulse is initiated and conducted, there is a period during which cells and fibers cannot be depolarized again, which is referred to as the absolute refractory period (see Figure 9–2) and corresponds to phases 1, 2, and approximately one-third of phase 3 repolarization. The absolute refractory period also corresponds to the period from the Q wave to approximately the first half of the T wave on the ECG (see Figure 9–2). During this period, if there is a premature stimulus for an electrical impulse, this impulse cannot be conducted because the tissue is absolutely refractory to conduction. However, there is a period following the absolute refractory period during which a premature electrical stimulus can be conducted and is often conducted abnormally, which is called the relative refractory period, corresponding roughly to the latter two-thirds of phase 3 repolarization on the action potential and to the latter half of the T wave on the ECG. The relative refractory period is also sometimes referred to as the "vulnerable period." If a premature electrical stimulus is initiated during the relative refractory period, it can be conducted abnormally, potentially resulting in an arrhythmia.

Mechanisms of Cardiac Arrhythmias

KEY CONCEPT Cardiac arrhythmias are caused by (a) abnormal impulse initiation, (b) abnormal impulse conduction, or (c) both.

▶ *Abnormal Impulse Initiation*

Abnormal initiation of electrical impulses occurs due to abnormal automaticity. A decrease in sinus node automaticity results in a reduced rate of impulse generation and a slow heart rate (sinus bradycardia). Conversely, an increase in sinus node automaticity results in an increased rate of impulse generation and a rapid heart rate (sinus tachycardia). If other cardiac fibers become abnormally automatic, such that the rate of spontaneous impulse initiation exceeds that of the sinus node, or premature impulses are generated, other tachyarrhythmias may occur. Many cardiac fibers possess the capability for automaticity, including atrial tissue, the AV node, the Purkinje fibers, and ventricular muscle. In addition, fibers with the capability of initiating and conducting electrical impulses are present in left atrial myocardial sleeves that extend into the pulmonary veins. Abnormal atrial automaticity may result in premature atrial depolarizations or may precipitate atrial tachycardia or atrial fibrillation (AF); abnormal AV nodal automaticity may result in "junctional tachycardia" (so named because the AV node is also sometimes referred to as the AV junction). Abnormal automaticity originating from the pulmonary veins is a precipitant of AF. In addition, abnormal automaticity in the ventricles may result in premature ventricular complexes (PVCs) or may precipitate ventricular tachycardia (VT) or ventricular fibrillation (VF).

Automaticity of cardiac fibers is controlled in part by activity of the sympathetic and parasympathetic nervous systems. Enhanced sympathetic nervous system activity may result in increased automaticity of the sinus node or other automatic cardiac fibers. Enhanced parasympathetic nervous system activity suppresses automaticity, while inhibition of parasympathetic nervous system activity increases automaticity. Other factors may lead to increases in automaticity of extra-sinus node tissues, including hypoxia, atrial or ventricular stretch (such as following long-standing hypertension or during and after development of heart failure [HF]), and electrolyte abnormalities such as hypokalemia or hypomagnesemia.

▶ *Abnormal Impulse Conduction*

The mechanism of abnormal impulse conduction is referred to as reentry. Reentry is often triggered as a result of an abnormal premature electrical impulse (abnormal automaticity); therefore, in these situations, the mechanism of the arrhythmia is both

abnormal impulse formation (automaticity) and abnormal impulse conduction (reentry). For reentry to occur, three conditions must be present. There must be: (a) at least two pathways down which an electrical impulse may travel (which is the case in most cardiac fibers); (b) a "unidirectional block" in one of the conduction pathways (this "unidirectional block" reflects prolonged refractoriness in this pathway, or increased "dispersion of refractoriness," defined as substantial variation in refractory periods between cardiac fibers); and (c) slowing of the velocity of impulse conduction down the other conduction pathway.

The process of reentry is depicted in Figure 9–3.[2] Normally, when a premature impulse is initiated, it cannot be conducted in either direction down either pathway because the tissue is in its absolute refractory period from the previous impulse. A premature impulse may be conducted down both pathways if it is only slightly premature and arrives after the tissue is no longer refractory. However, when refractoriness is prolonged down one of the pathways, a precisely timed premature beat may be conducted down one pathway but cannot be conducted in either direction in the pathway with prolonged refractoriness because the tissue is still in its absolute refractory period.[2] Refractoriness may be prolonged to a greater degree in one pathway than in the other as a result of increased dispersion of repolarization. When the third condition for reentry is present, the impulse traveling forward down the other pathway still cannot be conducted. However, because the impulse in one pathway is traveling more slowly than normal, by the time it circles around and travels upward along the other pathway, sufficient time has passed so the pathway is no longer in its absolute refractory period, and now the impulse may travel upward in that pathway. In other words, the electrical impulse "reenters" a previously stimulated pathway in the reverse (retrograde) direction. This results in circular movement of electrical impulses; as the impulse travels in this circular fashion, it depolarizes each cell around it, and if the impulse is traveling at a rate faster than the intrinsic rate of the sinus node, a tachycardia occurs. Reentry may occur in numerous tissues, including the atria, the AV node, and the ventricles.

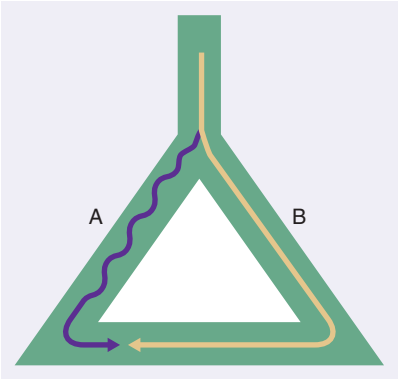

FIGURE 9–3. The process of initiation of reentry. There are two pathways for impulse conduction, slowed impulse conduction down pathway A and a longer refractory period in pathway B. A precisely timed premature impulse initiates reentry; the premature impulse cannot be conducted down pathway B because the tissue is still in the absolute refractory period from the previous, normal impulse. However, because of dispersion of refractoriness (ie, different refractory periods down the two pathways), the impulse can be conducted down pathway A. Because conduction down pathway A is slowed, by the time the impulse reaches pathway B in a retrograde direction, the impulse can be conducted retrogradely up the pathway because the pathway is now beyond its refractory period from the previous impulse. This creates reentry, in which the impulse continuously and repeatedly travels in a circular fashion around the loop.

Prolonged refractoriness and/or slowed impulse conduction velocity may be present in cardiac tissues for a variety of reasons. Myocardial ischemia may alter ventricular refractory periods or impulse conduction velocity, facilitating ventricular reentry. In patients with past myocardial infarction (MI), the infarcted myocardium is dead and cannot conduct impulses. However, there is typically a border zone of tissue that is damaged and in which refractory periods and conduction velocity are aberrant, facilitating ventricular reentry. In patients with left atrial or LV hypertrophy as a result of hypertension, refractory periods and conduction velocity are often perturbed. In patients with HF with reduced ejection fraction (HFrEF), ventricular refractoriness and conduction velocity are often altered due to LV hypertrophy, collagen deposition, and other anatomical and structural changes.

Vaughan Williams Classification of Antiarrhythmic Drugs

LO 2

The modified Vaughan Williams classification of antiarrhythmic drugs is presented in Table 9–1.[3-5] This classification is based on the effects of drugs on ventricular conduction velocity, repolarization/refractoriness, and automaticity. Class I drugs inhibit ventricular automaticity and decrease conduction velocity. However, due to differences in the potency of the drugs to reduce conduction velocity, the class I drugs are subdivided into classes IA, IB, and IC. The class IC drugs have the greatest potency for slowing ventricular conduction, class IA drugs have intermediate potency, and class IB drugs have the lowest potency, with minimal effects on conduction velocity at normal heart rates. Class II drugs are the adrenergic β-receptor inhibitors (β-blockers), class III drugs are those that delay ventricular repolarization and prolong refractoriness, and class IV drugs are the nondihydropyridine calcium channel blockers (CCBs) diltiazem and verapamil.

The Vaughan Williams classification of antiarrhythmic drugs has notable limitations. The classification is based on the effects of drugs on normal, rather than diseased, myocardium. In addition, many of the drugs may be placed into more than one class. For example, the class IA drugs prolong repolarization/refractoriness, either via the parent drug[6] or an active metabolite,[7] and therefore may also be placed in class III. Sotalol is also a β-blocker and therefore fits into class II. Amiodarone inhibits sodium and potassium conductance, is a noncompetitive inhibitor of β-receptors, and inhibits calcium channels, and therefore may be placed into any of the four classes. For this reason, drugs within each class cannot be considered interchangeable. Nonetheless, despite attempts to develop mechanism-based classifications that better distinguish the actions of antiarrhythmic drugs, the Vaughan Williams classification continues to be widely used because of its simplicity.

CARDIAC ARRHYTHMIAS

Arrhythmias are classified into two broad categories: supraventricular (those occurring above the ventricles) and ventricular (those occurring in the ventricles). Names of specific arrhythmias are generally composed of two words, the first of which indicates the location of the electrophysiological abnormality resulting in the arrhythmia (sinus node, AV node,

Table 9–1

Vaughan Williams Classification of Antiarrhythmic Agents[a,3-5]

Class	Drug	Conduction Velocity[b]	Repolarization/Refractoriness[b]	Automaticity[b]
IA	Quinidine Procainamide Disopyramide	↓	↑	↓
IB	Lidocaine Mexiletine	0/↓	↓/0	↓
IC	Flecainide Propafenone	↓↓	0	↓
II	β-Blockers[c] Acebutolol Atenolol Betaxolol Bisoprolol Carteolol Carvedilol[d] Esmolol Labetalol[d] Metoprolol Nadolol Nebivolol Penbutolol Pindolol Propranolol Timolol	0	0	0
III	Amiodarone[e] Dofetilide Dronedarone[e] Ibutilide Sotalol	0	↑	0
IV	CCBs[c] Diltiazem Verapamil	0	0	0

[a]Adenosine and digoxin are agents used for the management of arrhythmias that do not fit into the Vaughan Williams classification.

[b]In ventricular tissue only; effects may differ in atria, sinus node, or atrioventricular node.

[c]Slow conduction, prolong refractory period, and reduce automaticity in sinoatrial node and atrioventricular node tissue but generally not in the ventricles.

[d]Combined α- and β-blocker.

[e]Amiodarone and dronedarone also slow conduction velocity and inhibit automaticity.

CCB, calcium channel blocker; ↑, increase/prolong; ↓, decrease; 0, no effect; 0/↓, does not change or may decrease: ↓/0, decreases or does not change.

atrial, or ventricular), and the second describes the arrhythmia as abnormally slow (bradycardia) or fast (tachycardia), or the type of arrhythmia (block, fibrillation, or flutter).

SUPRAVENTRICULAR ARRHYTHMIAS

Sinus Bradycardia

Sinus bradycardia is defined by a sinus rate less than 60 beats/min.[8]

► *Epidemiology and Etiology*

LO 3

Many individuals, particularly those who engage in regular vigorous exercise, have resting heart rates less than 60 beats/min. For those individuals, sinus bradycardia is normal and healthy, and does not require evaluation or treatment. However, some people develop symptomatic sinus node dysfunction. In the absence of correctable underlying causes, idiopathic sinus node dysfunction is referred to as sick sinus syndrome. The prevalence of sick sinus syndrome is approximately 1 in 600 individuals older than 65 years, while the incidence is about 0.8 per 1000 person-years of follow-up.[9] The incidence of sick sinus syndrome increases with advancing age and is higher in white versus black individuals.[9] Sinus node dysfunction accounts for roughly 50% of all pacemaker implantations in the United States,[9] and may also manifest as the bradycardia-tachycardia syndrome (also known as tachy-brady syndrome) characterized by alternating periods of supraventricular tachyarrhythmias and bradycardia.[8]

LO 3

Sick sinus syndrome leading to sinus bradycardia may be caused by degenerative changes in the sinus node that occur with advancing age. However, there are other possible etiologies of sinus bradycardia including drugs (Table 9–2).[8,10]

► *Pathophysiology*

LO 3

Sick sinus syndrome leading to sinus bradycardia occurs as a result of fibrotic tissue in the sinus node, which replaces normal sinus node tissue.[8]

Table 9–2

Etiologies of Sinus Bradycardia[8,10]

Idiopathic ("sick sinus syndrome")
Myocardial ischemia
Carotid sinus hypersensitivity
Neurocardiac syncope
Electrolyte abnormalities: hypokalemia or hyperkalemia
Hypothyroidism
Hypothermia
Amyloidosis
Sarcoidosis
Systemic lupus erythematosus
Scleroderma
Sleep apnea
Drugs:

- Adenosine
- Amiodarone
- β-Blockers
- Cisplatin
- Citalopram
- Clonidine
- Cocaine
- Dexmedetomidine
- Digoxin
- Diltiazem
- Dipyridamole
- Disopyramide
- Donepezil
- Dronedarone
- Fingolimod
- Flecainide
- Fluoxetine
- Halothane
- Isradipine
- Ivabradine
- Ketamine
- Neostigmine
- Nicardipine
- Nitroglycerin
- Paclitaxel
- Pregabalin
- Propafenone
- Propofol
- Remifentanil
- Sotalol
- Succinylcholine
- Thalidomide
- Verapamil

Clinical Presentation and Diagnosis of Sinus Bradycardia

Symptoms

LO 3

- Many patients are asymptomatic, particularly those with normal resting heart rates less than 60 beats/min as a result of physical fitness due to regular exercise
- Susceptible patients may develop symptoms, depending on the degree of heart rate lowering
- Symptoms include dizziness, fatigue, light-headedness, syncope, chest pain (in patients with underlying coronary artery disease [CAD]), and shortness of breath and other symptoms of HF (in patients with underlying LV dysfunction)

Diagnosis

- Cannot be made on the basis of symptoms alone because the symptoms of all bradyarrhythmias are similar
- History of present illness, presenting symptoms, and 12-lead ECG that reveals sinus bradycardia
- Assess possible correctable etiologies, including myocardial ischemia, serum potassium concentration (for hyperkalemia), thyroid function tests (for hypothyroidism)
- Determine whether patient is taking any drugs known to cause sinus bradycardia. If the patient is currently taking digoxin, determine the serum digoxin concentration and ascertain whether it is supratherapeutic (> 2 ng/mL [2.6 nmol/L])

▶ *Treatment*

LO 3

Desired Outcomes Desired outcomes of treatment are to restore normal heart rate and alleviate patient symptoms.

Pharmacologic Therapy KEY CONCEPT Treatment of sinus bradycardia is only necessary in patients who become symptomatic. If the patient is taking any medication(s) that may cause symptomatic sinus bradycardia, they should be discontinued whenever possible. If the patient remains in sinus bradycardia after drug discontinuation and after five half-lives of the drug(s) have elapsed, then drug(s) can usually be excluded as the etiology. In certain circumstances, however, discontinuation may be undesirable, even if the drug may be the cause of symptomatic sinus bradycardia. For example, if the patient has a history of MI or HFrEF, discontinuation of a β-blocker may be necessary in the short term but undesirable long term because β-blockers reduce mortality and prolong life in patients with these diseases, and benefits of therapy outweigh risks associated with sinus bradycardia. In this situation, clinicians and patients may elect to implant a permanent pacemaker to allow continuation of therapy with β-blockers.

LO 4 LO 10

KEY CONCEPT Acute treatment of the symptomatic and/or hemodynamically unstable patient with sinus bradycardia includes administration of the anticholinergic drug atropine, which should be given in doses of 0.5 mg intravenous (IV) every 3 to 5 minutes to a maximum recommended total dose of 3 mg.[11] Atropine is generally used as a method of achieving acute symptom control while awaiting placement of a transcutaneous or transvenous pacemaker. Where necessary, transcutaneous pacing can be initiated during atropine administration. Atropine should be used cautiously in patients with myocardial ischemia or MI because increasing heart rate and myocardial oxygen demand may aggravate ischemia or extend the infarct.

In patients with hemodynamically unstable sinus bradycardia unresponsive to atropine, transcutaneous pacing may be initiated. In patients with hemodynamically unstable or severely symptomatic sinus bradycardia unresponsive to atropine and in whom temporary or transvenous pacing is not available or is ineffective, or while awaiting placement of a pacemaker, dopamine (2–10 mcg/kg/min, titrate to response), epinephrine (2–10 mcg/min, titrate to response), or isoproterenol (2–10 mcg/min, titrate to response) may be administered to increase heart rate.[11]

In patients with sinus bradycardia due to underlying correctable disorders (such as electrolyte abnormalities or hypothyroidism), management consists of correcting those disorders.

LO 4

Nonpharmacologic Therapy Long-term management of patients with sick sinus syndrome requires implantation of a permanent pacemaker.[8]

▶ *Outcome Evaluation*

- Monitor heart rate and alleviation of symptoms.
- Monitor for adverse effects of medications such as atropine (dry mouth, mydriasis, urinary retention, and tachycardia).

AV Block

LO 3

AV block occurs when conduction of electrical impulses through the AV node is impaired to varying degrees. AV block is classified into three categories. First-degree (1°) AV block is defined simply as prolongation of the PR interval to greater than 0.2 seconds. During 1° AV block, all impulses initiated by the sinus node resulting in atrial depolarization are conducted through the AV

node; the abnormality is simply that the impulses are conducted more slowly than normal, resulting in prolongation of the PR interval.[12] Second-degree (2°) AV block is further distinguished into two types: Mobitz type I (also known as Wenckebach) and Mobitz type II. In both types, some of the impulses initiated by the sinus node are not conducted through the AV node. This often occurs in a regular pattern; for example, there may be absence of AV nodal conduction of every third or fourth impulse. During third-degree (3°) AV block, also referred to as "complete heart block," none of the impulses generated by the sinus node are conducted through the AV node. This results in AV dissociation, during which the atria continue to depolarize normally as a result of normal impulses initiated by the sinus node; however, the ventricles initiate their own depolarizations because no sinus node-generated impulses are conducted to the ventricles. Therefore, on the ECG, there is no relationship (dissociation) between the P waves and the QRS complexes.

▶ *Epidemiology and Etiology*

LO 3

Overall incidence of AV block is unknown. AV block may be caused by degenerative changes in the AV node. In addition, there are many other possible etiologies of AV block including drugs (Table 9–3).[8,10,12]

▶ *Pathophysiology*

1° AV block is due to inhibition of conduction within the upper portion of the node.[12] Mobitz type I 2° AV block results from inhibition of conduction further down within the node.[8,12] Mobitz type II 2° AV block is caused by inhibition of conduction within or below the level of the bundle of His.[8,12] 3° AV block may be a result of inhibition of conduction either within the AV node or within the bundle of His or the His-Purkinje system.[8,12] AV block may occur as a result of age-related AV node degeneration.

Table 9–3

Etiologies of Atrioventricular (AV) Block[8,10,12]

Idiopathic degeneration of the AV node
Myocardial ischemia or infarction
Neurocardiac syncope
Carotid sinus hypersensitivity
Electrolyte abnormalities: hypokalemia or hyperkalemia
Hypothyroidism
Hypothermia
Infectious diseases: Chagas disease or endocarditis
Amyloidosis
Sarcoidosis
Systemic lupus erythematosus
Scleroderma
Sleep apnea
Drugs:
- Adenosine
- Amiodarone
- β-Blockers
- Bupivacaine
- Carbamazepine
- Chloroquine
- Digoxin
- Diltiazem
- Dronedarone
- Fingolimod
- Flecainide
- Hydroxychloroquine
- Paclitaxel
- Phenylpropanolamine
- Propafenone
- Propofol
- Sotalol
- Thioridazine
- Tricyclic antidepressants
- Verapamil

Clinical Presentation and Diagnosis of AV Block

LO 3

Symptoms

- 1° AV block is rarely symptomatic because it rarely results in bradycardia
- 2° AV block may cause bradycardia because not all impulses generated by the sinus node are conducted through the AV node to the ventricles
- In 3° AV block, or complete heart block, the heart rate is often 30 to 40 beats/min, resulting in symptoms
- Symptoms consist of dizziness, fatigue, light-headedness, syncope, chest pain (in patients with underlying CAD), and shortness of breath and other symptoms of HF (in patients with underlying HF)

Diagnosis

- Made on the basis of patient presentation, including history of present illness and presenting symptoms, as well as a 12-lead ECG that reveals AV block
- Assess potentially correctable etiologies, including myocardial ischemia, serum potassium concentration (for hyperkalemia), and thyroid function tests (for hypothyroidism)
- Determine whether the patient is taking any drugs known to cause AV block
- If the patient is currently taking digoxin, determine the serum digoxin concentration and ascertain whether it is supratherapeutic (> 2 ng/mL [2.6 nmol/L])

▶ *Treatment*

LO 3

Desired Outcomes Desired outcomes of treatment are to restore normal sinus rhythm and alleviate patient symptoms.

Pharmacologic Therapy KEY CONCEPT Treatment of 1° AV block is rarely necessary because symptoms rarely occur. However, the ECGs of patients with 1° AV block should be monitored to assess the possibility of progression to 2° or 3° block, which requires treatment because bradycardia often results in symptoms. If the patient is taking any medication(s) that may cause AV block, the drug(s) should be discontinued whenever possible. If the patient's rhythm still exhibits AV block after discontinuing the medication(s) and after five half-lives of the drug(s) have elapsed, then drug(s) can usually be excluded as the etiology. However, in certain circumstances, discontinuation of a medication that is inducing AV block may be undesirable. For example, if the patient has a history of MI or HFrEF, discontinuation of a β-blocker is undesirable, as the benefits of therapy outweigh risks associated with AV block. In these patients, clinicians and patients may elect to implant a permanent pacemaker to allow the patient to continue β-blocker therapy.

LO 4 LO 10

KEY CONCEPT Acute treatment of patients with 2° or 3° AV block consists primarily of administration of atropine, which may be administered in the same doses as recommended for management of sinus bradycardia. In patients with hemodynamically unstable or severely symptomatic AV block that is unresponsive to atropine and in whom temporary or transvenous pacing is not available or is ineffective, epinephrine (2–10 mcg/min, titrate to response) and/or dopamine (2–10 mcg/kg/min) may be administered.[11]

In patients with 2° or 3° AV block due to underlying correctable disorders (such as electrolyte abnormalities or hypothyroidism), management consists of correcting those disorders.

LO 4 **Nonpharmacologic Therapy** Long-term treatment of patients with 2° or 3° AV block due to idiopathic AV node degeneration requires implantation of a permanent pacemaker.[8]

▶ *Outcome Evaluation*

- Monitor for termination of AV block and restoration of normal sinus rhythm, heart rate, and alleviation of symptoms.
- If atropine is administered, monitor for adverse effects, including dry mouth, mydriasis, urinary retention, and tachycardia.

Atrial Fibrillation

AF is the most common arrhythmia encountered in clinical practice. It is important for clinicians to understand AF because it is associated with substantial morbidity and mortality, and because many strategies for drug therapy are available. Some drugs used to treat AF have a narrow therapeutic index and a broad adverse effect profile.

▶ *Epidemiology and Etiology*

Approximately 2.7–6.1 million Americans have AF,[9] and as many as 4.5 million in the European Union. Prevalence and incidence of AF increases with advancing age; roughly 8% of patients between 80 and 89 years old have AF. AF occurs more commonly in men than women.

LO 3 Etiologies of AF are presented in Table 9–4.[10,13-17] The common feature of the majority of etiologies is the development of left atrial hypertrophy. Hypertension may be the most important risk factor for AF development. However, AF also occurs commonly in patients with CAD. HF is increasingly recognized as a cause; approximately 25% to 30% of patients with New York Heart Association (NYHA) class III HF and as many as 50% of patients with NYHA class IV HF have AF.[14] AF is responsible for more than 467,000 annual hospitalizations in the United States.[17]

Drug-induced AF is relatively uncommon but has been reported (see Table 9–4).[10,15,16] Acute ingestion of large amounts of alcohol may cause AF. Recent evidence suggests that chronic moderate alcohol intake also may be associated with an increased risk of AF. In addition, recent reports have associated use of some bisphosphonate drugs with new-onset AF, but this potential relationship requires further study.[16]

Table 9–4

Etiologies of Atrial Fibrillation (AF)[10,13-17]

Older age
Hypertension
Myocardial infarction
Heart failure
Diabetes mellitus
Hyperthyroidism
Rheumatic heart disease
Diseases of the heart valves:
Mitral stenosis or regurgitation
Mitral valve prolapse
Obesity
Smoking
Obstructive sleep apnea
Pericarditis
Amyloidosis
Myocarditis
Pulmonary embolism
Idiopathic
Family history
Genetic predisposition
Thoracic surgery:
Coronary artery bypass graft surgery
Pulmonary resection
Thoracoabdominal esophagectomy
Drugs:
Adenosine
Albuterol
Alcohol
Alendronate
Dobutamine
Doxorubicin
Enoximone
Fingolimod
Interleukin-2
Ivabradine
Methylprednisolone
Milrinone
Mitoxantrone
Morphine
Paclitaxel
Propafenone
Theophylline
Verapamil
Zoledronic acid

▶ *Pathophysiology*

AF may be caused by both abnormal impulse formation and abnormal impulse conduction. Traditionally, AF was believed to be initiated by premature impulses initiated in the atria. However, it is now understood that in most patients AF is triggered by electrical impulses generated within the pulmonary veins.[18] These impulses initiate the process of reentry within the atria, and AF is believed to be sustained by multiple reentrant wavelets operating simultaneously within the atria. Some believe that, at least in some patients, the increased automaticity in the pulmonary veins may be the sole mechanism of AF and that the multiple reentrant wavelet hypothesis may be incorrect. However, the concept of multiple simultaneous reentrant wavelets remains the predominant hypothesis regarding the mechanism of AF.[17]

AF leads to electrical remodeling of the atria. Episodes that are of longer duration and occur with increasing frequency result in progressive shortening of atrial refractory periods, further

Patient Encounter Part 1

A 77-year-old man presents to the emergency department (ED) complaining that he can feel his heart fluttering and pounding in his chest. He states that this started several hours ago, and he waited to see if it would stop, but it has not. He also complains of feeling light-headed and says that he "nearly passed out." His pulse is irregular, with a rate of 140 beats/min.

What information is suggestive of AF?

What additional information do you need to develop a treatment plan?

potentiating atrial reentry.[19] Therefore, it is often said that "atrial fibrillation begets atrial fibrillation"; that is, AF causes atrial electrophysiologic alterations that further promote AF.[17,19] AF is associated with chaotic, disorganized atrial electrical activity, resulting in no completed atrial depolarizations and therefore no atrial contraction.

LO 3 AF occurs when structural and/or electrophysiologic abnormalities occur that promote abnormal atrial and/or pulmonary vein automaticity and/or atrial reentry.[17] Structural abnormalities of the atria may include fibrosis, dilation, ischemia, infiltration, and hypertrophy.[17] Other contributing factors may include inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system, autonomic nervous system activation, and genetic variants in myocardial ion channels and those leading to cardiomyopathy.[17] A substantial amount of the atrial electrical activity occurring during AF is conducted through the AV node into the ventricles, resulting in ventricular rates ranging from 100 to 200 beats/min.

AF is categorized into classifications.[17] Paroxysmal AF is defined as that which terminates spontaneously or with interventions within 7 days of onset.[17] Episodes begin suddenly and spontaneously, last minutes to hours, or sometimes as long as several days, and terminate suddenly and spontaneously. The frequency of recurrence in patients with paroxysmal AF is variable. Persistent AF is defined as continued AF of duration longer than 7 days.[17] Long-standing persistent AF is defined as continuous AF lasting longer than 12 months.[17] The term permanent AF is used when patient and clinician jointly decide to terminate further attempts to restore and/or maintain sinus rhythm.[17] Acceptance of AF represents a specific therapeutic viewpoint from the patient and clinician rather than a pathophysiological characteristic of the AF, and may change as symptoms, efficacy of treatments, and patient and clinician preferences develop and evolve.[17]

AF is associated with substantial morbidity and mortality, including risk of ischemic stroke of approximately 5% per year.[17] The risk of stroke is increased two- to sevenfold in patients with AF compared to patients without this arrhythmia.[9] AF is the cause of roughly one of every six strokes. During AF, atrial contraction is absent. Because atrial contraction is responsible for approximately 30% of LV filling, blood that is not ejected from the left atrium to the LV pools in the atrium, particularly in the left atrial appendage. Blood pooling facilitates the formation of a thrombus, which subsequently may travel through the mitral valve into the LV and may be ejected during ventricular contraction. The thrombus then may travel through a carotid artery into the brain, resulting in an ischemic stroke. Patients with AF are also at increased risk for systemic thromboembolism.

AF is associated with a threefold increase in the risk of HF as a result of tachycardia-induced cardiomyopathy.[17] AF increases the risk of dementia and mortality approximately twofold compared to patients without AF;[17] causes of death are likely stroke or HF.

Clinical Presentation and Diagnosis of AF

LO 3

Symptoms

- Approximately 20% to 30% of patients with AF remain asymptomatic
- Symptoms include fatigue, palpitations, dizziness, lightheadedness, dyspnea, chest pain (if underlying CAD is present), near-syncope, and syncope. Patients commonly complain of palpitations; often the complaint is "I can feel my heart beating fast" or "I can feel my heart fluttering" or "It feels like my heart is going to beat out of my chest"
- Other symptoms depend on the degree to which cardiac output is diminished, which in turn depends on ventricular rate and the degree to which stroke volume is reduced by the rapidly beating heart
- In some patients, the first symptom of AF is stroke

Diagnosis

- Because symptoms of all tachyarrhythmias depend on heart rate and are therefore essentially the same, diagnosis depends on the presence of AF on the ECG
- Characterized on ECG by an absence of P waves, an undulating baseline that represents chaotic atrial electrical activity, and an irregularly irregular rhythm, meaning the intervals between the R waves are irregular and there is no pattern to the irregularity
- Sometimes first diagnosed in patients presenting with ischemic stroke

▶ *Treatment*

LO 3 **Desired Outcomes** KEY CONCEPT The goals of individualized therapy for AF are: (a) ventricular rate control; (b) termination of AF and restoration of sinus rhythm (commonly referred to as "cardioversion" or "conversion to sinus rhythm"); (c) maintenance of sinus rhythm, or reduction in the frequency of episodes of paroxysmal AF; and/or (d) prevention of stroke and systemic embolism. These goals of therapy do not necessarily apply to all patients; the specific goal(s) that apply depend on the patient's AF classification (Table 9–5).

Hemodynamically Unstable AF For patients who present with an episode of AF that is hemodynamically unstable, emergent conversion to sinus rhythm is necessary using direct current

Table 9–5

Treatment Goals According to Atrial Fibrillation (AF) Classification

Paroxysmal AF	Persistent AF	Long-Standing Persistent AF	Permanent AF
Ventricular rate control Prevention of stroke and systemic embolism Maintenance of sinus rhythm *if ventricular rate control is not sufficient to control symptoms*	Ventricular rate control Prevention of stroke and systemic embolism Conversion to sinus rhythm	Ventricular rate control Prevention of stroke and systemic embolism Conversion to sinus rhythm	Ventricular rate control Prevention of stroke and systemic embolism

cardioversion (DCC). Hemodynamic instability may be defined as the presence of any one of the following: (a) acutely altered mental status; (b) hypotension (systolic blood pressure < 90 mm Hg) or other signs of shock; (c) ischemic chest discomfort; and/or (d) acute HF.[11]

DCC is the process of administering a synchronized electrical shock to the chest. The purpose of DCC is to simultaneously depolarize all of the myocardial cells, resulting in interruption and termination of the multiple reentrant circuits and restoration of normal sinus rhythm. The recommended initial energy level for conversion of AF to sinus rhythm is 120 to 200 joules (J) for biphasic shocks or 200 J for monophasic shocks. If the DCC attempt is unsuccessful, DCC energy should be increased in a stepwise fashion.[11] Delivery of the shock is synchronized to the ECG by the cardioverter machine, such that the electrical charge is not delivered during the latter portion of the T wave (ie, the relative refractory period) to avoid delivering an electrical impulse that may be conducted abnormally, which may result in a life-threatening ventricular arrhythmia.

The remainder of this section is devoted to pharmacologic management of hemodynamically stable AF.

LO 5 LO 10

Ventricular Rate Control Ventricular rate control can be achieved by inhibiting the proportion of electrical impulses conducted from the atria to the ventricles through the AV node. Therefore, drugs that are effective for ventricular rate control are those that inhibit AV node impulse conduction: β-blockers, diltiazem, verapamil, digoxin, and amiodarone (Tables 9–6[17] and 9–7).

In patients who present to the emergency department (ED) with an episode of symptomatic persistent AF or paroxysmal AF for which intervention is desired, ventricular rate control is usually initially achieved using IV drugs. A decision algorithm for selecting a specific drug for ventricular rate control is presented in Figure 9–4.[17] In general, an IV CCB or β-blocker is preferred for ventricular rate control in patients with normal LV function because ventricular rate control can often be achieved within several minutes. In patients with acutely decompensated HF (ADHF) or HFrEF, IV diltiazem and verapamil should be avoided, as these drugs confer negative inotropic effects and may exacerbate HFrEF.[17] An IV β-blocker may be administered in these patients, but only following stabilization of ADHF, due to potential for exacerbation.

For patients with paroxysmal or permanent AF requiring long-term rate control with oral medications, the treatment algorithm is the same (Figure 9–4). Although digoxin is effective for ventricular rate control in patients at rest, it is less effective than CCBs or β-blockers for ventricular rate control in patients undergoing physical activity, including activities of daily living. This is likely because activation of the sympathetic nervous system during exercise and activity overwhelms the stimulating effect of digoxin on the parasympathetic nervous system. Some recent evidence suggests digoxin therapy may be independently associated with an increased risk of mortality in patients with AF.[20,21] Overall, in patients with normal LV function, CCBs or β-blockers are preferred for long-term ventricular rate control. Diltiazem may be preferable to verapamil in older patients due to a lower incidence of constipation. However, in patients with HFrEF, oral diltiazem and verapamil are contraindicated as a result of their negative inotropic activity and propensity to exacerbate HFrEF. Therefore, the options in this population are β-blockers or digoxin. Most patients with HFrEF should be receiving therapy with an oral β-blocker with the goal of achieving mortality risk reduction. In patients with HFrEF who develop rapid AF while receiving therapy with β-blockers, digoxin can be administered for purposes of ventricular rate control. Fortunately, studies have found the combination of digoxin and β-blockers to be effective for ventricular rate control, likely as a result of β-blocker–induced attenuation of the inhibitory effects of the sympathetic nervous system on the efficacy of digoxin.[22]

Conversion to Sinus Rhythm Termination of AF in hemodynamically stable patients may be performed using antiarrhythmic drug therapy or elective DCC. Drugs that may be used for conversion to sinus rhythm are presented in Table 9–8.[17] These agents slow atrial conduction velocity and/or prolong refractoriness, facilitating interruption of reentrant circuits and restoration of sinus rhythm. DCC is generally more effective than drug therapy for conversion of AF to sinus rhythm. However, patients who undergo elective DCC must be sedated and/or anesthetized to avoid the discomfort associated with delivery of 120 to greater than or equal to 200 J of electricity to the chest. Therefore, it is important that patients scheduled to undergo elective DCC do not eat within approximately 8 to 12 hours of the procedure to avoid aspiration of stomach contents and resulting aspiration pneumonitis during the period of sedation/anesthesia. This often factors into the decision as to whether to use elective DCC or drug therapy for conversion of AF to sinus rhythm. If a patient presents with AF requiring nonemergent conversion to sinus rhythm, and the patient has eaten a meal that day, then pharmacologic conversion methods must be used on that day, or DCC must be postponed to the following day to allow for a period of fasting prior to the procedure.

A decision strategy for conversion of AF to sinus rhythm is presented in Figure 9–5.[17] The cardioversion decision strategy depends greatly on the duration of AF. If the AF episode began within 48 hours, conversion to sinus rhythm is safe and may be attempted with elective DCC or specific drug therapy. However, if the duration of the AF episode is 48 hours or longer, or if there is uncertainty regarding duration, two strategies for

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension × 19 years; MI 4 years ago; HFrEF × 4 years (LVEF 35% [0.35])

Meds: Aspirin 81 mg once daily; lisinopril 20 mg orally once daily; metoprolol succinate 100 mg orally once daily; furosemide 40 mg orally once daily; spironolactone 25 mg orally once daily.

PE:

Ht 5′9″ (175 cm), Wt 88 kg (194 lb), BP 105/68 mm Hg, P 140 beats/min, RR 18 breaths/min; remainder of physical examination noncontributory

Labs: All within normal limits. Serum creatinine 1.1 mg/dL (97 μmol/L)

CXR: Mild pulmonary edema

ECG: Atrial fibrillation

What is your assessment of the patient's condition?

What are your treatment goals?

What pharmacologic or nonpharmacologic alternatives are available for each treatment goal?

Table 9–6

Drugs for Ventricular Rate Control in Atrial Fibrillation (AF)[17]

Drug	Mechanism of Action	Intravenous Administration	Usual Oral Maintenance Dose	Drug Interactions
Amiodarone	β-Blocker CCB	300 mg over 1 hour, then 10–50 mg/hour over 24 hours via continuous infusion	100–200 mg once daily	Inhibits clearance of digoxin, warfarin, some statins, and other drugs
β-Blockers[a]	Inhibit AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	Esmolol 500 mcg/kg over 1 minute, then 50–300 mcg/kg/min continuous infusion Propranolol 1 mg over 1 minute, up to 3 doses at 2 minute intervals Metoprolol tartrate 2.5–5 mg over 2 minutes; up to 3 doses	Atenolol 25–100 mg once daily Bisoprolol 2.5–10 mg once daily Carvedilol 3.125–25 mg twice daily Metoprolol tartrate 25–100 mg twice daily Metoprolol XL (succinate) 50–400 mg once daily Nadolol 10–240 mg once daily Propranolol 10–40 mg three or four times daily	
Diltiazem	Inhibits AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	0.25-mg/kg bolus over 2 minutes, then 5–15 mg/hour continuous infusion	120–360 mg once daily (extended release)	Increases carbamazepine, cyclosporine, midazolam, triazolam, theophylline, atorvastatin, cerivastatin, lovastatin, simvastatin concentrations Cimetidine, ranitidine, diazepam, grapefruit juice may increase serum diltiazem concentrations Dantrolene (combination may lead to ventricular arrhythmias)
Verapamil	Inhibits AV nodal conduction by slowing AV nodal conduction and prolonging AV nodal refractoriness	0.075–0.15-mg/kg bolus over 2 minutes. If no response after 30 minutes, may give an additional 10 mg, then 0.005 mg/kg/min continuous infusion	180–480 mg daily (extended release)	Increases digoxin, carbamazepine, cyclosporine, theophylline, atorvastatin, cerivastatin, lovastatin, simvastatin concentrations Dantrolene (combination may lead to ventricular arrhythmias)
Digoxin	Inhibits AV nodal conduction by (a) vagal stimulation (b) directly slowing AV nodal conduction, and (c) prolonging AV nodal refractoriness	0.25 mg every 2 hours, up to 1.5 mg over 24 hours	0.125–0.25 mg once daily	Amiodarone, verapamil inhibit digoxin elimination

[a]In patients with acute decompensated heart failure, therapy with intravenous β-blockers should be initiated only after the patient has been stabilized.

AV, atrioventricular; CCB, calcium channel blocker.

conversion may be considered. Data indicate that a thrombus may form in the left atrium during AF episodes of 48 hours or longer; if an atrial thrombus is present, the process of conversion to sinus rhythm, whether with DCC or drugs, can dislodge the atrial thrombus, leading to embolization and a stroke. Therefore, in patients experiencing an AF episode of 48 hours or longer, conversion to sinus rhythm should be deferred unless it is known that an atrial thrombus is not present. One option in patients with AF of duration 48 hours or longer, or of unknown duration, is to anticoagulate with warfarin (maintaining an **international normalized ratio** [INR] of 2–3), dabigatran, rivaroxaban, apixaban or edoxaban for 3 weeks, after which cardioversion may be performed. Patients should subsequently be anticoagulated for a minimum of 4 weeks following the restoration of sinus rhythm. An alternative approach is to perform a **transesophageal echocardiogram** (TEE) to determine whether an atrial thrombus is present; if such a thrombus is not present, DCC or pharmacologic cardioversion may be performed. If this strategy is selected, hospitalized patients should undergo anticoagulation with IV unfractionated heparin, with the dose targeted to an activated partial thromboplastin time (aPTT) of 60 seconds (range: 50–70 seconds), low molecular weight heparin, or oral anticoagulation therapy with warfarin (target INR: 2.5; range: 2–3), dabigatran, rivaroxaban, apixaban or

Table 9–7

Adverse Effects of Drugs Used to Treat Arrhythmias

Drug	Adverse Effects
Adenosine	Chest pain, flushing, dyspnea, transient sinus bradycardia/AV block
Amiodarone	IV: Hypotension, sinus bradycardia, phlebitis, QT interval prolongation, torsades de pointes Oral: Blue-gray skin discoloration, photosensitivity, corneal microdeposits, pulmonary fibrosis, hepatotoxicity, sinus bradycardia, hypo- or hyperthyroidism, peripheral neuropathy, weakness, AV block
Atenolol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Atropine	Tachycardia, urinary retention, blurred vision, dry mouth, mydriasis
Bisoprolol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Carvedilol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Digoxin	Nausea, vomiting, anorexia, visual changes such as green-yellow halos around objects, AV block, ventricular arrhythmias
Diltiazem	Hypotension, sinus bradycardia, HF exacerbation, AV block
Dofetilide	Torsades de pointes
Dronedarone	Diarrhea, asthenia, nausea and vomiting, abdominal pain, bradycardia, GI distress, hepatotoxicity
Esmolol	Hypotension, sinus bradycardia, AV block, bronchospasm, HF exacerbation
Flecainide	Dizziness, blurred vision, HF exacerbation, torsades de pointes, life-threatening ventricular tachycardia (in patients with underlying CAD)
Ibutilide	Torsades de pointes
Lidocaine	Slurred speech, diminished consciousness, seizures, bradycardia
Metoprolol	Hypotension, sinus bradycardia, AV block, fatigue, bronchospasm, HF exacerbation[a]
Mexiletine	Nausea, vomiting, GI distress, tremor, dizziness, fatigue, seizures (if dose too high)
Nadolol	Hypotension, bradycardia, AV block, HF exacerbation[a]
Procainamide	Hypotension, HF exacerbation, QT interval prolongation, torsades de pointes
Propafenone	Dizziness, blurred vision, life-threatening ventricular tachycardia (in patients with underlying CAD)
Propranolol	Hypotension, sinus bradycardia, AV block, bronchospasm, HF exacerbation[a]
Sotalol	Sinus bradycardia, AV block, fatigue, torsades de pointes
Verapamil	Hypotension, HF exacerbation, bradycardia, AV block, constipation (oral)

[a]Associated with intravenous administration (metoprolol, propranolol), inappropriately high oral doses at initiation of therapy, or overly aggressive and rapid dose titration.

AV, atrioventricular; CAD, coronary artery disease; GI, gastrointestinal; HF, heart failure; IV, intravenous.

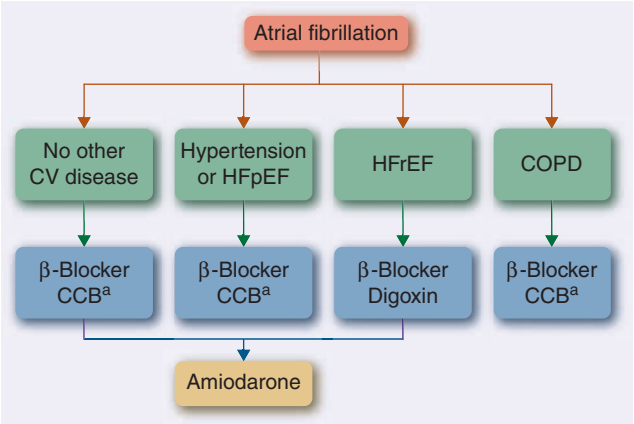

FIGURE 9–4. Decision algorithm for selecting drug therapy for ventricular rate control. In boxes where multiple medications are listed, drugs are listed alphabetically, not in order of preference. [a]When administered intravenously, diltiazem is generally preferred over verapamil because of a lower risk of severe hypotension. (CCB, calcium channel blocker [diltiazem or verapamil]; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.) (Adapted with permission from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;64:e1–e76).

edoxaban during the hospitalization period prior to the TEE and cardioversion procedure. If a thrombus is not present during TEE and cardioversion is successful, patients should remain on oral anticoagulation therapy for at least 4 weeks. If a thrombus is observed during TEE, then cardioversion should be postponed and anticoagulation should be continued indefinitely. Another TEE should be performed prior to a subsequent cardioversion attempt.[17]

Conversion of hemodynamically stable AF to sinus rhythm may be performed in patients with a symptomatic episode of persistent or paroxysmal AF. In patients who have been designated as being in permanent AF, a joint decision has been made by the patient and clinician to terminate further attempts to restore and/or maintain sinus rhythm.[17] Therefore, in patients with permanent AF, conversion to sinus rhythm is not attempted.

Maintenance of Sinus Rhythm/Reduction in the Frequency of Episodes of Paroxysmal AF In many patients, permanent maintenance of sinus rhythm after cardioversion is an unrealistic goal. Many patients experience recurrence of AF after cardioversion. Similarly, in patients with paroxysmal AF, complete maintenance of sinus rhythm without recurrent AF episodes is often not achievable. Therefore, a more realistic goal for many patients is not permanent maintenance of sinus rhythm, but rather reduction in the frequency of episodes of paroxysmal AF. Maintenance of sinus rhythm is more likely to be successful in patients with AF duration of less than 6 months.

LO 3

Table 9–8

Drugs for Conversion of Atrial Fibrillation (AF) to Normal Sinus Rhythm[17]

Treatment	IV Administration	Oral Administration	Drug Interactions
Amiodarone	Not recommended for conversion of AF to sinus rhythm	600–800 mg daily in divided doses up to a total load of 10 g, then maintenance dose of 200 mg daily	Inhibits elimination of digoxin, warfarin, some statins, and other drugs
Dofetilide	Not available IV	CrCl (mL/min)[a,b]: > 60 mL/min: 500 mcg twice daily 40–60 mL/min: 250 mcg twice daily 20–40 mL/min: 125 mcg twice daily < 20 mL/min: Not recommended	Cimetidine, hydrochlorothiazide, ketoconazole, medroxyprogesterone, promethazine, trimethoprim, verapamil (all inhibit dofetilide elimination, most by inhibition of renal cation transport)
Flecainide	Not available IV in the United States	200–300 mg × one dose[c]	Quinidine, fluoxetine, tricyclic antidepressants increase flecainide concentrations
Ibutilide	1 mg IV over 10 minutes, followed by a second 1 mg IV dose if necessary. If weight < 60 kg (132 lb), dose should be 0.01 mg/kg	Not available orally	—
Propafenone	Not available IV	450–600 mg × one dose[c]	Quinidine, fluoxetine, tricyclic antidepressants increase propafenone concentrations Increases serum digoxin concentrations Inhibits CYP2C9, inhibits warfarin metabolism

[a]Creatinine clearance of > 60, 40–60, 20–40, and < 20 mL/min corresponds to > 1.0, 0.67–1.0, 0.33–0.67, and < 0.33 mL/s, respectively.

[b]Dofetilide therapy must be initiated in the hospital, due to the risk of QT interval prolongation that may lead to torsades de pointes.

[c]It is recommended that a β-blocker or nondihydropyridine calcium channel blocker be administered ≥ 30 minutes prior to administering flecainide or propafenone to avoid accelerated AV node conduction and increased heart rate.

CrCl, creatinine clearance; CYP, cytochrome P450; IV, intravenous.

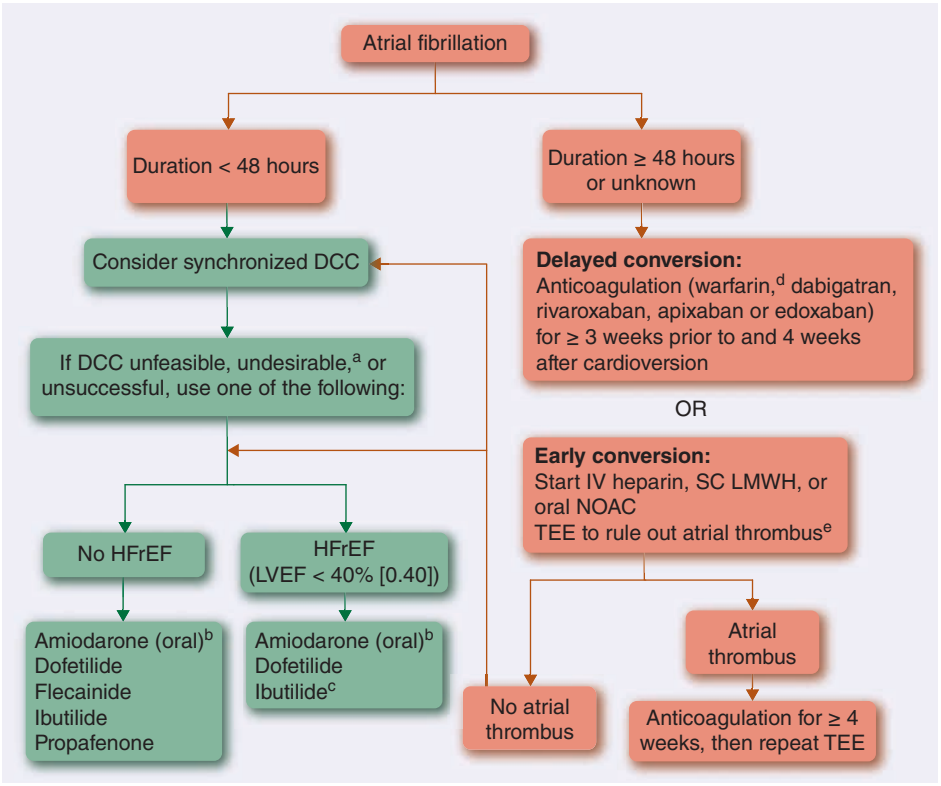

FIGURE 9–5. Decision algorithm for conversion of hemodynamically stable atrial fibrillation to normal sinus rhythm. [a]Patients should not be sedated for synchronized DCC if they have eaten a meal within 12 hours, due to risk of aspiration. [b]Drugs are listed in alphabetical order, not order of preference. [c]Ibutilide can be administered to patients with LVEF 30%–40% (0.30–0.40) but should be avoided in patients with LVEF < 30% (0.30) due to risk of ventricular proarrhythmia. [d]International normalized ratio (INR) of 2–3. [e]Anticoagulation must be achieved prior to TEE and maintained for more than or equal to 4 weeks after TEE. (DCC, direct current cardioversion; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist oral antiacoagulant; SC, subcutaneous; TEE, transesophageal echocardiogram.)

In recent years, numerous studies have been performed to determine whether drug therapy for maintenance of sinus rhythm is preferred to drug therapy for ventricular rate control.[23-27] In these studies, patients were assigned randomly to receive therapy either with drugs for rate control or drugs for rhythm control (Table 9–9). These studies found no significant differences in mortality between the two strategies.[23-27] However, patients assigned to the rhythm control strategy were more likely to be hospitalized[23,25-27] and to experience adverse effects associated with drug therapy.[23,24]

LO 5 LO 10

KEY CONCEPT Therefore, drug therapy for the purpose of maintaining sinus rhythm or reducing the frequency of episodes of AF should be initiated only in those patients with episodes of paroxysmal AF who continue to experience symptoms despite maximum tolerated doses of drugs for ventricular rate control. A decision strategy for maintenance therapy of sinus rhythm is presented in Figure 9–6.[17] Therapy with dofetilide or sotalol should be initiated in the hospital with patients undergoing continuous ECG monitoring, due to the risk of torsades de pointes (TdP). Drug therapy for maintenance of sinus rhythm and/or reduction in the frequency of episodes of paroxysmal AF should not be initiated in patients with underlying correctable causes of AF, such as hyperthyroidism; rather, the underlying cause should be corrected. Drug therapy for maintenance of sinus rhythm should be discontinued when AF becomes designated as permanent.

The nonpharmacologic treatment strategy of catheter ablation is also an option for rhythm control in patients with paroxysmal AF. During this procedure, a catheter is introduced transvenously and directed to the left atrium under fluoroscopic guidance. Energy is delivered through the catheter to ablate, or destroy, reentrant circuits responsible for propagating the AF. The most common energy source for catheter ablation is radiofrequency energy, though cryoablation is sometimes used as an alternative to radiofrequency energy. Catheter ablation is often reserved for

Table 9–9

Drugs for Maintenance of Sinus Rhythm/Reduction in the Frequency of Episodes of Atrial Fibrillation

Drug	Dose
Amiodarone	400–600 mg orally in 2–3 divided doses for 2–4 weeks; maintenance dose 100–200 mg orally once daily
Dofetilide[a]	As described in Table 9–8
Dronedarone	400 mg orally every 12 hours
Flecainide	50–200 mg orally every 12 hours
Propafenone	Immediate release: 150–300 mg orally every 8 hours Extended release: 225–425 mg orally every 12 hours
Sotalol[a]	Initial dose, CrCl[b] > 60 mL/min: 80 mg orally twice daily Initial dose, CrCl[b] 40–60 mL/min: 80 mg orally once daily CrCl[b] < 40 mL/min: Contraindicated Maintenance dose: If 80 mg doses are tolerated and QTc interval remains < 500 ms after 3 days, patients can be discharged. Alternatively, dose can be increased to 120 mg orally once or twice daily as appropriate during hospitalization and patient followed for 3 days on this dose

[a]Dofetilide and sotalol therapy must be initiated in the hospital due to the risk of QT interval prolongation that may lead to torsades de pointes.

[b]CrCl of > 60, 40–60, and < 40 mL/min corresponds to > 1.0, 0.67–1.0, and < 0.67 mL/s, respectively.

CrCl, creatinine clearance; ms, milliseconds.

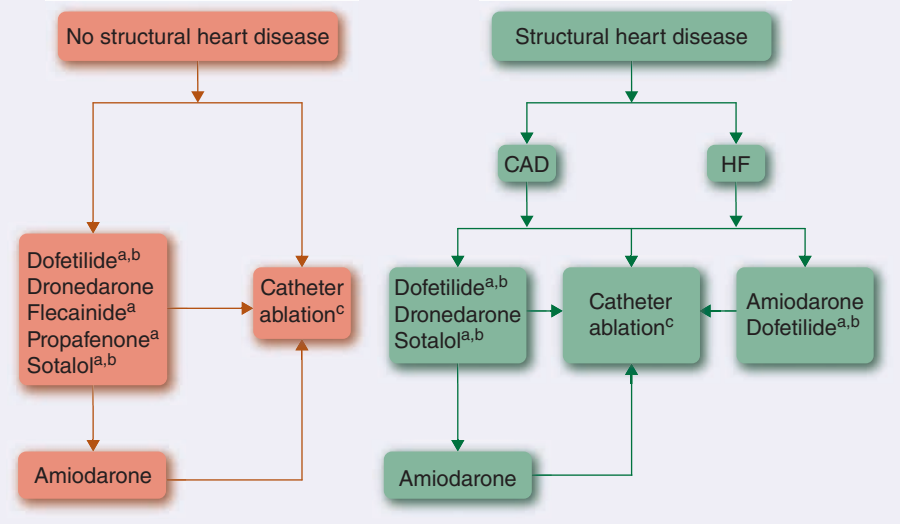

FIGURE 9–6. Decision algorithm for maintenance of sinus rhythm/reduction in the frequency of episodes of atrial fibrillation (AF) for patients with symptomatic paroxysmal or persistent AF despite rate control therapy. In boxes where multiple medications are listed, drugs are listed alphabetically, not in order of preference. [a]Not recommended in patients with severe left ventricular hypertrophy. [b]Should be used cautiously in patients at risk for torsades de pointes. [c]Catheter ablation is only recommended as first-line therapy in patients with paroxysmal AF and is recommended depending on patient preference when performed at experienced centers. (CAD, coronary artery disease; HF, heart failure.) (Adapted with permission from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;64:e1–e76.)

patients in whom symptomatic AF is refractory to, or the patient is intolerant of, at least one antiarrhythmic agent. However, some patients select catheter ablation as the preferred strategy, to avoid adverse effects of antiarrhythmic drugs.

LO 6 LO 10

Prevention of Stroke and Systemic Embolism Most patients with paroxysmal, persistent, or permanent AF should receive therapy for prevention of stroke and systemic embolism unless compelling contraindications exist. A decision strategy for assigning patients to receive anticoagulation for prevention of stroke or systemic embolism in AF is presented in Table 9–10.[17] In general, most patients require oral anticoagulation; however, in patients with nonvalvular AF and a CHA_2DS_2-VASc[17] score of 0, anticoagulation is not recommended.

Table 9–10

American Heart Association/American College of Cardiology/Heart Rhythm Society Recommendations for Prevention of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation (AF)[a,17]

CHA_2DS_2-VASc Score	Recommended Stroke Prevention Strategy
0	Antithrombotic therapy is not recommended
1	No antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered
≥ 2	Oral anticoagulation recommended. Options include: Warfarin (INR: 2.0–3.0) Dabigatran Rivaroxaban Apixaban Edoxaban[b]
CHA_2DS_2-VASc score calculated as follows:[17]	
Congestive heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	2 points
Diabetes mellitus	1 point
History of **s**troke, TIA or thromboembolism	2 points
Vascular disease (prior MI, PAD or aortic plaque)	1 point
Age 65–74 years	1 point
Female **s**ex	1 point
Maximum score	9 points

[a]Patients with AF who have mechanical heart valves should receive warfarin titrated to an INR of 2.0–3.0 or 2.5–3.5 depending on the type and location of the prosthetic heart valve.

[b]Edoxaban is not recommended in the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society recommendations for prevention of thromboembolism in patients with nonvalvular AF, as data comparing its efficacy for prevention of thromboembolism in patients with AF had not been published at the time the guidelines were published. However, since 2014, data from a large study have shown edoxaban to be noninferior to warfarin for prevention of stroke and systemic embolism in patients with AF, with a lower rate of major bleeding. Therefore, edoxaban is an acceptable anticoagulant for patients with AF.

INR, international normalized ratio; MI, myocardial infarction; PAD, peripheral arterial disease; TIA, transient ischemic attack.

The landscape of anticoagulation for stroke prevention in AF has changed with the availability of the non-vitamin K antagonist oral anticoagulants (NOACs) dabigatran, rivaroxaban, apixaban, and edoxaban. Dabigatran, approved by the Food and Drug Administration (FDA) in 2010, is a direct thrombin inhibitor for reducing the risk of stroke and systemic embolism in patients with nonvalvular AF. Dabigatran is associated with lower rates of stroke and systemic embolism than warfarin in patients with AF, with a similar incidence of major bleeding.[28] Dabigatran should not be used in patients with end-stage kidney disease (creatinine clearance [CrCl] under 15 mL/min [0.25 mL/s]) or advanced liver disease (impaired baseline clotting function). The recommended dabigatran dose is 150 mg twice daily, except for patients with severe kidney disease (CrCl: 15–30 mL/min [0.25–0.50 mL/s]) for whom the recommended dose is 75 mg twice daily.

Advantages of dabigatran include the fact that INR monitoring is not required and the drug's onset of action is rapid, eliminating the need for bridging with unfractionated or low molecular weight heparins. In addition, there is a lower likelihood of drug interactions with dabigatran than with warfarin. Dabigatran is a P-glycoprotein (P-gp) substrate, and therefore concomitant administration with P-gp inhibitors such as ketoconazole, amiodarone, and verapamil may result in increases in plasma dabigatran concentrations; however, there is no recommendation for a change in dabigatran dose when administered concomitantly with these drugs. Similarly, concomitant administration of dabigatran with P-gp inducers such as rifampin may reduce plasma dabigatran concentrations. A previous disadvantage was that there was no antidote with which to reverse major bleeding associated with dabigatran. However, such an antidote is now available: idarucizumab is a humanized monoclonal antibody fragment with a high affinity for dabigatran, which binds to dabigatran and rapidly reverses its anticoagulant effects.[29] Finally, while none of the NOACs are recommended for administration to patients with AF that has occurred as a result of valvular heart disease, dabigatran is specifically contraindicated in patients with mechanical heart valves, due to higher risk of stroke, MI and thrombus formation on the mechanical valve compared with warfarin.

Rivaroxaban, an oral factor Xa inhibitor, was approved by the FDA in 2011 for reducing the risk of stroke and systemic embolism in patients with nonvalvular AF. Rivaroxaban was shown to be noninferior to warfarin for prevention of stroke or systemic embolism in patients with AF, and compared with warfarin, rivaroxaban was associated with a lower risk of intracranial and fatal bleeding.[30] Rivaroxaban is contraindicated in patients with end-stage renal disease (CrCl < 15 mL/min [0.25 mL/s]). The recommended rivaroxaban dose is 20 mg once daily with the evening meal. For patients with moderate-to-severe kidney disease (CrCl 15–50 mL/min [0.25–0.83 mL/s]), the dose should be reduced to 15 mg once daily with the evening meal. Rivaroxaban dose may require adjustment when used in combination with dual P-gp and strong cytochrome P-450 (CYP) 3A4 inducers or inhibitors.

Apixaban, an oral factor Xa inhibitor, was approved by the FDA in 2012 for reducing the risk of stroke and systemic embolism in patients with nonvalvular AF. Apixaban is superior to warfarin for prevention of stroke or systemic embolism in patients with AF, with lower bleeding risk.[31] The recommended dose of apixaban is 5 mg orally twice daily. In patients with moderate kidney disease (CrCl 30–50 mL/min [0.50–0.83 mL/s]), the dose should be reduced to 2.5 mg orally twice daily. There are

no data or dosage recommendations for patients with CrCl less than 30 mL/min (0.50 mL/s). Apixaban dose should be reduced to 2.5 mg orally twice daily when any two of the following characteristics are present: serum creatinine greater than 1.5 mg/dL (133 μmol/L), 80 years of age or older, body weight less than or equal to 60 kg (132 lb). Apixaban should not be administered to patients with severe liver disease.

Edoxaban, another oral factor Xa inhibitor, was approved by the FDA in 2015 for reduction in risk of stroke and systemic embolism in patients with nonvalvular AF. Edoxaban is noninferior to warfarin for prevention of stroke or systemic embolism in patients with AF, with a lower bleeding risk.[32] The recommended dose of edoxaban is 60 mg orally once daily in patients with CrCl greater than 50 mL/min (0.83 mL/s) to less than or equal to 95 mL/min (1.59 mL/s). In patients with kidney disease (CrCl 15–50 mL/min [0.25–0.83 mL/s]), the dose should be reduced to 30 mg orally once daily. There are no data or dosage recommendations for patients with CrCl less than 15 mL/min (0.25 mL/s). Interestingly, edoxaban is not recommended for administration to patients with CrCl greater than 95 mL/min (1.59 mL/s), as these patients had an increased risk of ischemic stroke associated with edoxaban 60 mg once daily compared to warfarin-treated patients. The most likely reason for this finding is that a higher dose of edoxaban is required in patients with CrCl greater than 95 mL/min (1.59 mL/s), but until the efficacy and safety of alternative doses of edoxaban are studied in these patients, the drug should be avoided in this patient population. Concomitant use of edoxaban and rifampin should be avoided, and edoxaban should not be administered to patients with moderate or severe liver disease.

For patients for whom warfarin is preferred over other oral anticoagulants (such as in patients with mechanical prosthetic heart valves, those with valvular AF, and patients with end-stage kidney disease), specific genetic tests to guide the initiation of therapy have been approved by the FDA. These tests assess single nucleotide polymorphisms of the gene that encodes CYP 2C9, the primary hepatic enzyme responsible for warfarin metabolism, and the gene *VKORC1*, which encodes vitamin K epoxide reductase complex subunit 1, the enzyme that is inhibited by warfarin as its mechanism of anticoagulation. Patients with specific polymorphisms of one or both of these genes may require adjustment of the initial warfarin dose to achieve adequate anticoagulation or avoid over-anticoagulation and toxicity; guidelines for pharmacogenetics-guided warfarin dosing have been published.[33] Genetic testing to guide the initiation of warfarin therapy has not yet become standard practice, and many have questioned the efficacy and cost effectiveness of incorporation of routine genetic testing into warfarin therapy. The role of routine genetic testing in selecting initial warfarin doses is likely to continue to evolve. However, in patients for whom *VKORC1* and/or CYP2C9 genotype information is available, the pharmacogenetics-guided warfarin dosing guidelines are useful for guiding selection of initial warfarin dose.[33] For patients in whom *VKORC1* and/or CYP2C9 genotype information is not available, a standard empirical dosing approach can be used, such as initiating warfarin at 5 mg once daily and titrating based on daily INR measurements until a stable therapeutic INR is achieved. Alternatively, for patients in whom *VKORC1* and/or CYP2C9 genotype information is not available, a clinical dosing algorithm such as those available at warfarindosing.org can be used to determine the initial dose of warfarin;[33] dose titration based on daily INR measurements is still required if this approach is employed.

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for the patient's acute AF episode and for long-term management of his AF.

Your plan should include (a) a statement of the drug-related needs and/or problems, (b) the goals of therapy, (c) a patient-specific detailed therapeutic plan, and (d) a plan for follow-up to determine whether the goals have been achieved and adverse effects avoided.

▶ *Outcome Evaluation*

- Monitor the patient to determine whether the goal of ventricular rate control is met. A target heart rate less than 80 beats/min is recommended for symptomatic patients and those with HFrEF. A target heart rate of less than 110 beats/min may be reasonable for patients who remain asymptomatic and have preserved LV systolic function.[17]
- Monitor ECG to assess continued presence of AF and determine whether conversion to sinus rhythm has occurred.
- In patients receiving warfarin, monitor INR approximately monthly to make sure it is therapeutic (target: 2.5; range: 2.0–3.0).
- Monitor for adverse effects of specific drug therapy (see Table 9–7). Monitor patients receiving oral anticoagulation for signs and symptoms of bruising or bleeding.

Paroxysmal Supraventricular Tachycardia

LO 3

Paroxysmal supraventricular tachycardia (PSVT) is a term that refers to a number of arrhythmias that originate above the ventricles and require atrial or AV nodal tissue for initiation and maintenance.[34] The most common of these arrhythmias is known as AV nodal reentrant tachycardia, in which the arrhythmia is caused by a reentrant circuit that involves the AV node or tissue adjacent to the AV node. Other types of PSVT include the relatively uncommon Wolff-Parkinson-White syndrome, which is caused by reentry through an accessory extra-AV nodal pathway. For the purposes of this section, the term *PSVT* refers to AV nodal reentrant tachycardia.

▶ *Epidemiology and Etiology*

LO 3

Approximately 570,000 persons in the United States have PSVT, with an estimated prevalence of 2.29 per 1000 individuals.[9,34] The incidence of PSVT is 35 per 100,000 person-years,[9] and there are roughly 89,000 new cases annually.[34] The average age of onset of PSVT is 57 years. PSVT occurs more commonly in women than men, and individuals older than 65 years of age have five times the risk of developing PSVT compared to younger people.[9,34] Although PSVT can occur in patients experiencing myocardial ischemia or MI, it sometimes occurs in individuals with no history of cardiac disease.

▶ *Pathophysiology*

PSVT is caused by reentry that includes the AV node as a part of the reentrant circuit. Typically, electrical impulses travel forward (antegrade, from atria to ventricles) down the AV node and then travel back up the AV node (retrograde, from

Clinical Presentation and Diagnosis of PSVT

LO 3

Symptoms

- Symptoms include palpitations, "neck-pounding," dizziness, light-headedness, shortness of breath, polyuria, chest pain (if underlying CAD is present), near-syncope, and syncope. Patients commonly complain of palpitations; often the complaint is "I can feel my heart beating fast" or "I can feel my heart fluttering" or "It feels like my heart is going to beat out of my chest"
- Other symptoms depend on the degree to which cardiac output is diminished, which in turn depends on heart rate and degree to which stroke volume is reduced by the rapidly beating heart

Diagnosis

- Because the symptoms of all tachyarrhythmias depend primarily on heart rate and are therefore similar, diagnosis depends on the presence of PSVT on the ECG, characterized by narrow QRS complexes (< 0.12 seconds). P waves are usually visible, but may be difficult to discern if the heart rate is extremely rapid
- PSVT is a regular rhythm and occurs at rates ranging from 100 to 250 beats/min

ventricles to atria) in a repetitive circuit. In some patients, the retrograde conduction pathway of the reentrant circuit may exist in extra-AV nodal tissue adjacent to the AV node. One of these pathways usually conducts impulses rapidly while the other usually conducts impulses slowly. Most commonly, during PSVT the impulse conducts antegrade through the slow pathway and retrograde through the faster pathway; in approximately 5% to 10% of patients, the reentrant circuit is reversed.[34]

▶ *Treatment*

LO 3

Desired Outcomes The desired outcomes for treatment are to terminate the arrhythmia, restore sinus rhythm, and prevent recurrence. Drug therapy is used to terminate the arrhythmia and restore sinus rhythm; nonpharmacologic measures are generally preferred to prevent recurrence, though some patients prefer drug therapy.

LO 3 LO 7 LO 10

Termination of PSVT KEY CONCEPT The primary method of termination of PSVT is inhibition of impulse conduction and/or prolongation of the refractory period within the AV node. Because PSVT is propagated via a reentrant circuit involving the AV node, inhibition of conduction within the AV node interrupts and terminates the reentrant circuit.

KEY CONCEPT Prior to initiation of drug therapy for termination of PSVT, some simple nonpharmacologic methods known as vagal maneuvers may be attempted.[11,34] Vagal maneuvers stimulate the activity of the parasympathetic nervous system, which inhibits AV nodal conduction, facilitating termination of the arrhythmia. Vagal maneuvers alone may terminate PSVT in up to 28% of cases.[34] The simplest vagal maneuver to perform is cough, which stimulates the vagus nerve. Instructing the patient to cough two or three times may successfully terminate the PSVT. Another vagal maneuver that may be attempted is carotid sinus massage; one of the carotid sinuses, located in the neck in the vicinity of the carotid arteries, may be gently massaged for 5 to 10 seconds, stimulating vagal activity. Carotid sinus massage should not be performed in patients with a history of stroke or transient ischemic attack, or in those in whom carotid bruits may be heard on auscultation. The Valsalva maneuver, during which patients bear down against a closed glottis for 10 to 30 seconds, may also be attempted. The Valsalva maneuver is more effective than carotid sinus massage.[34] If one vagal maneuver is unsuccessful, switching to another vagal maneuver may successfully terminate PSVT.[34]

If vagal maneuvers are unsuccessful, IV drug therapy should be initiated.[11,34,35] Drugs used for termination of hemodynamically stable PSVT are presented in Table 9–11.[11]

Table 9–11

Drugs for Termination of Paroxysmal Supraventricular Tachycardia[11,34]

Drug	Mechanism of Action	Dose
Adenosine	Direct AV node inhibition	6-mg IV rapid push followed by rapid saline flush. If no response in 1–2 minutes, 12-mg IV rapid push followed by rapid saline flush. If no response in 1–2 minutes, administer second 12 mg IV rapid push, followed by rapid saline flush
Diltiazem	Direct AV node inhibition	0.25 mg/kg IV over 2 minutes, followed by continuous IV infusion of 5–10 mg/hour, up to 15 mg/hour
Verapamil	Direct AV node inhibition	5–10 mg (0.75–0.15 mg/kg) IV over 2 minutes If no response, administer an additional 10 mg (0.15 mg/kg) IV, then continuous infusion of 0.005 mg/kg/min
β-Blockers	Direct AV node inhibition	Esmolol 500 mcg/kg IV over 1 minute Then 50 mcg/kg/min continuous infusion. If inadequate response, give second loading dose of 500 mcg/kg and increase maintenance infusion to 100 mcg/kg/min. Increment 50 mcg/kg/min dose increases in this manner as necessary to maximum infusion rate of 300 mcg/kg/min Propranolol 1 mg IV over 1 minute; if necessary, repeat 1 mg IV doses at 2 minute intervals, up to 3 doses Metoprolol 2.5–5 mg IV over 2 minutes; if necessary, repeat 2.5–5 mg IV bolus in 10 minutes, up to 3 doses
Digoxin	Vagal stimulation, direct AV node inhibition	0.25–0.5 mg IV bolus; if necessary, repeat 0.25 mg IV bolus every 6–8 hours, to a maximum dose of 1 mg (8–12 mcg/kg) over 24 hours

AV, atrioventricular; CCB, calcium channel blocker; IV, intravenous.

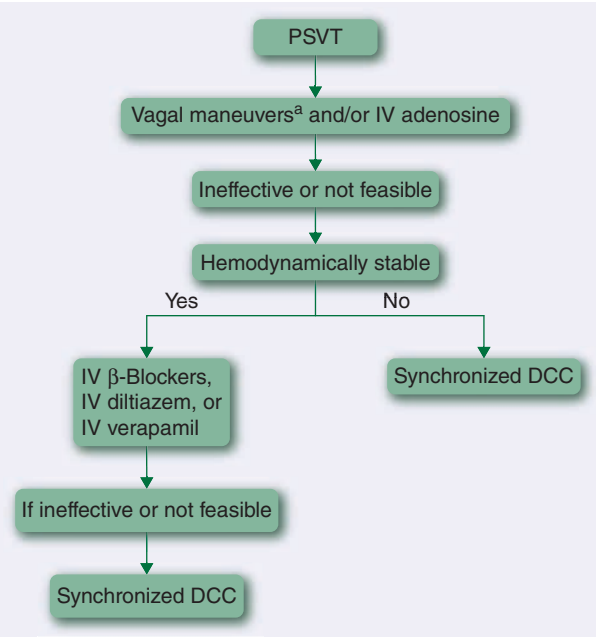

FIGURE 9–7. Decision algorithm for termination of PSVT. [a]Cough, carotid sinus massage (do not perform in patients with carotid bruits), Valsalva maneuver. (DCC, direct current cardioversion; IV, intravenous; PSVT, paroxysmal supraventricular tachycardia.) (Adapted with permission from Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27–e115.)

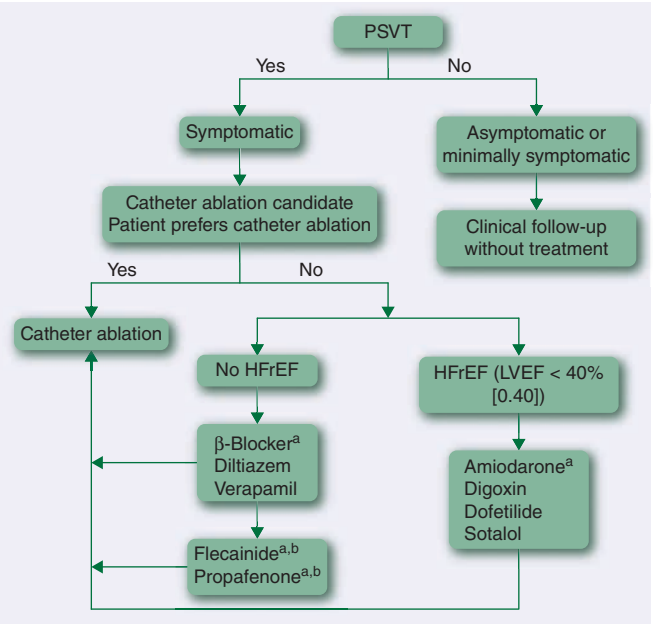

FIGURE 9–8. Decision algorithm for prevention of recurrence of PSVT. Drug doses as in Tables 9–6 and 9–9. [a]Drugs are listed alphabetically, not in order of preference. [b]Neither flecainide nor propafenone should be used in patients with known ischemic heart disease. (HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; PSVT, paroxysmal supraventricular tachycardia.) (Adapted with permission from Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27–e115.)

A decision strategy for pharmacologic termination of PSVT is presented in Figure 9–7.[34]

KEY CONCEPT Adenosine is the drug of choice for pharmacologic termination of PSVT and is successful in 95% of patients. Adenosine inhibits conduction transiently and is associated with adverse effects (see Table 9–7), including flushing, transient sinus bradycardia or AV block, and bronchospasm in susceptible patients. In addition, adenosine may cause chest pain that mimics the discomfort of myocardial ischemia but is not actually associated with ischemia. The half-life of adenosine is approximately 10 seconds, due to deamination in the blood; therefore, in the vast majority of patients, adverse effects are of short duration.

If adenosine therapy is unsuccessful for termination of PSVT, subsequent choices of therapy depend on whether the patient is hemodynamically stable or not. If the patient is hemodynamically unstable, synchronized DCC should be administered, using an initial energy level of 50 to 100 J; if the initial DCC attempt is unsuccessful, the shock energy should be increased in a stepwise fashion.[11] If the patient is hemodynamically stable, IV β-blockers, diltiazem or verapamil may be administered. β-Blockers are preferred if the patient has underlying HFrEF.

Prevention of Recurrence A decision strategy for prevention of recurrent PSVT is presented in Figure 9–8. If the patient's episodes of PSVT are asymptomatic or minimally symptomatic, long-term treatment may not be necessary. However, for patients with symptomatic episodes of PSVT, catheter ablation is a nonpharmacologic treatment option. During this procedure, a catheter is introduced transvenously and directed to the right atrium under fluoroscopic guidance. The catheter is advanced to the AV node, and energy is delivered through the catheter to ablate, or destroy, the extranodal pathway of the reentrant circuit. The most common energy source for catheter ablation is radiofrequency energy, though cryoablation is sometimes used as an alternative to radiofrequency energy to minimize damage to the AV node. This procedure usually achieves a complete cure of PSVT and therefore obviates the need for long-term antiarrhythmic drug therapy in this population. The complication rate associated with catheter ablation of PSVT is low (< 1%), and includes complete AV block (via inadvertent ablation of the AV node), perforation, pseudoaneurysm, bleeding at the site of catheter insertion in the groin, and pulmonary edema.

Despite the success rates achieved with catheter ablation and the relatively low risk of complications, some patients prefer not to undergo the procedure, while others are not considered suitable candidates. For these patients, drug therapy may be administered to prevent recurrence of PSVT or at least reduce the frequency of recurrent episodes. For patients with normal LV function, oral β-blockers, diltiazem, or verapamil are preferred agents. In patients for whom a trial of one or more of those drugs provides an unsatisfactory response, oral flecainide or propafenone may be administered; however, flecainide and propafenone are contraindicated in patients with a history of MI or any known underlying CAD, due to an increased risk of death associated with those drugs in that population. For patients with

HFrEF, diltiazem, verapamil, flecainide, and propafenone are contraindicated due to negative inotropic effects and the potential to exacerbate HF. In this patient population, oral amiodarone, digoxin, dofetilide, or sotalol may be used.

▶ *Outcome Evaluation*

- Monitor for termination of PSVT and restoration of normal sinus rhythm.
- Monitor for adverse effects of adenosine or any other antiarrhythmic agents administered (see Table 9–7).
- In patients taking drug therapy for long-term prevention of recurrence of PSVT, monitor for recurrence of symptoms and frequency of symptoms, as well as for adverse drug effects (Table 9–7).

VENTRICULAR ARRHYTHMIAS

Premature Ventricular Complexes

LO 3

PVCs are ectopic electrical impulses originating in ventricular tissue, resulting in wide, misshapen, abnormal QRS complexes. PVCs have also been known by other terms, ventricular premature beats (VPBs), ventricular premature contractions (VPCs), and ventricular premature depolarizations (VPDs).

▶ *Epidemiology, Etiology, and Pathophysiology*

PVCs occur with variable frequency, depending on underlying comorbid conditions. In a population of healthy individuals, the prevalence of PVCs was 0.8%.[9] In another study in which individuals without HF underwent ambulatory ECG monitoring (median duration 22 hours), 0.011% of all heartbeats were PVCs.[9] The prevalence of PVCs increases with age, and is approximately 0.5% in individuals less than 20 years of age and 2.2% in people older than 50 years of age. Roughly 60% of middle-aged men with or without heart disease had at least one PVC on a 6-hour continuous ECG recording. The prevalence of complex or frequent VPDs is approximately 33% and 12% in men with or without CAD, respectively;[35] in women, the prevalence of complex or frequent VPDs is 26% and 12% in those with or without CAD, respectively.[36]

PVCs occur as a result of abnormal ventricular automaticity due to enhanced activity of the sympathetic nervous system and altered electrophysiological characteristics of the heart during myocardial ischemia and following MI. In men without CAD, complex or frequent PVCs are associated with an increased risk of death and MI or death from CAD.[35] In patients with underlying CAD or a history of MI, the presence of complex or frequent PVCs is associated with an increased risk of mortality due to sudden cardiac death.[37] Therefore, in some patients, the occurrence of complex PVCs has negative prognostic implications.

▶ *Treatment*

Desired Outcomes Desired outcomes are to alleviate patient symptoms and reduce the risk of PVC-induced cardiomyopathy in patients with very frequent PVCs.

LO 8 LO 10

Pharmacologic Therapy KEY CONCEPT Asymptomatic PVCs should not be treated with antiarrhythmic drug therapy. Given that complex or frequent PVCs increase the risk of sudden cardiac death in patients with a history of MI, the Cardiac Arrhythmia Suppression Trials (CAST and CAST II) tested the hypothesis that suppression of asymptomatic PVCs with the drugs flecainide, encainide, or moricizine in patients with a relatively recent history of MI would lead to a reduction in the incidence of sudden cardiac death.[38,39] However, the results showed that not only did antiarrhythmic agents not reduce the risk of sudden cardiac death, there was a significant *increase* in the risk of death in patients who received therapy with encainide or flecainide compared with those who received placebo.[38] During the continuation of the study with moricizine (CAST II), there was a significantly higher incidence of death in the moricizine group compared to the placebo group during the first 2 weeks of therapy.[39] Additional evidence suggests that other Vaughan Williams class I agents, including quinidine, procainamide, and disopyramide, increase the risk of death in patients with complex PVCs following MI.[40]

KEY CONCEPT In patients with symptomatic PVCs who do not have structural heart disease, treatment with β-blockers or nondihydropyridine CCBs is recommended to reduce the frequency of recurrent PVCs and improve symptoms. Patients with symptomatic PVCs who do not have structural heart disease and in whom β-blockers or nondihydropyridine CCBs are ineffective or poorly tolerated can be treated with an antiarrhythmic drug. For patients with symptomatic PVCs and underlying structural heart disease, treatment with β-blockers is recommended. β-Blockers have been shown to reduce mortality in this population and to be effective for PVC suppression.[41] Patients with frequent symptomatic PVCs who do not respond adequately to β-blockers, nondihydropyridine CCBs or antiarrhythmic drugs, or who do not tolerate those medications, can undergo catheter ablation. Catheter ablation of infrequent PVCs is not recommended. For patients with PVC-induced cardiomyopathy, β-blockers or amiodarone are recommended to reduce the frequency of PVCs and improve symptoms and left ventricular function.

▶ *Outcome Evaluation*

- Monitor patients for PVC frequency and relief of symptoms.
- Monitor for adverse effects of β-blockers: bradycardia, hypotension, fatigue, masking symptoms of hypoglycemia, glucose intolerance (in diabetic patients), wheezing or shortness of breath (in patients with severe asthma or chronic obstructive pulmonary disease [COPD]).

Clinical Presentation and Diagnosis of PVCs

LO 3

- PVCs are usually categorized as simple or frequent/repetitive: simple PVCs are those that occur as infrequent, isolated single abnormal beats; frequent/repetitive PVCs are those that occur frequently (at least one PVC on a 12-lead ECG or ≥ 30 per hour) and/or in specific patterns. Very frequent PVCs are defined as greater than 10,000–20,000 per day
- Two consecutive PVCs are referred to as a couplet. The term *bigeminy* refers to a PVC occurring with every other beat; *trigeminy* means a PVC occurring with every third beat; *quadrigeminy* means a PVC occurring every fourth beat

Symptoms

- Most patients who experience simple or complex PVCs are asymptomatic. Occasionally, patients with complex or frequent PVCs may experience symptoms of palpitations, light-headedness, or dizziness

Table 9–12

Etiologies of Ventricular Tachycardia and Ventricular Fibrillation

Coronary artery disease
Myocardial infarction
Heart failure
Electrolyte abnormalities: hypokalemia, hypomagnesemia
Drugs:

Adenosine	Procainamide
Amiodarone	Propafenone
Chlorpromazine	Sotalol
Cocaine	Terbutaline
Digoxin	Thioridazine
Disopyramide	Trazodone
Flecainide	Venlafaxine
Ibutilide	

Ventricular Tachycardia

LO 3 VT is a series of three or more consecutive PVCs at a rate greater than 100 beats/min. VT is defined as nonsustained if it lasts greater than or equal to 3 beats and terminates spontaneously; sustained VT lasts greater than 30 seconds or requires termination because of hemodynamic instability in less than 30 seconds.[42] VT is usually monomorphic, meaning that each QRS complex displays the same shape, axis, and amplitude. VT may occasionally be polymorphic, with QRS complexes displaying various shapes, axes, and amplitudes.

▶ *Epidemiology, Etiology, and Pathophysiology*

The prevalence of monomorphic VT in the general population is unknown.[9] In populations at risk, the incidence of VT is variable, depending on underlying etiologies and comorbidities. Etiologies of VT are presented in Table 9–12. Up to 20% of patients who experience acute MI experience ventricular arrhythmias.[43] Approximately 7% to 8% of patients with MI develop VT during the period of hospitalization.[43] Nonsustained VT occurs in 20% to 80% of patients with HF.[44] Other etiologies of VT include electrolyte abnormalities such as hypokalemia, hypoxia, and drugs. VT that occurs in the absence of structural heart disease is referred to as "idiopathic" VT. Some patients with idiopathic VT have verapamil-sensitive VT, while others have outflow tract VT, indicating that the VT originates in the outflow tract of the right or left ventricle.[42] Verapamil-sensitive VT and outflow tract VT are generally differentiated based on the ECG morphology. VT is usually initiated by a precisely timed PVC, occurring during the relative refractory period, which provokes reentry within ventricular tissue. Sustained VT requires immediate intervention, because if untreated, the rhythm may cause sudden cardiac death via hemodynamic instability and the absence of a pulse (pulseless VT) or via degeneration of VT into VF.

▶ *Treatment*

Desired Outcomes

LO 3 Desired outcomes are to terminate the arrhythmia and restore sinus rhythm, and prevent sudden cardiac death.

Pharmacologic Therapy Hemodynamically unstable VT should be terminated immediately using synchronized DCC beginning with 100 J (for monophasic shocks) and increasing subsequent shocks to 200, 300, and 360 J.[11] In the event that VT is present but the patient does not have a palpable pulse (and therefore no blood pressure), asynchronous defibrillation should be performed, at 360 J for monophasic waveforms and starting at 120 to 200 J for biphasic waveforms.[11]

LO 9 LO 10 Drugs used for the termination of hemodynamically stable VT are presented in Table 9–13.[42] A decision algorithm for management of hemodynamically stable VT is presented in Figure 9–9. For patients with structural heart disease who develop VT, DCC is the preferred therapy as it is considered to be more effective than drug therapy. For patients in whom DCC is undesirable (ie, if patients have eaten a meal that day and cannot be safely sedated for DCC), IV procainamide is the drug of choice. IV amiodarone or sotalol are recommended for patients in whom VT is unresponsive to procainamide.[42]

For patients with idiopathic VT for which the arrhythmia is verapamil-sensitive, verapamil should be administered (Figure 9–9). For patients with outflow tract VT, IV β-blockers are preferred agents.[42]

Nonpharmacologic Therapy: Prevention of Sudden Cardiac Death KEY CONCEPT LO 9 LO 10 In patients who have experienced VT and are at risk for sudden cardiac death, an implantable cardioverter-defibrillator (ICD) is the treatment of choice.[42,45] An ICD is a device that provides internal electrical cardioversion of VT or defibrillation of VF. The ICD does not prevent the patient from developing the arrhythmia, but it reduces the risk that the patient will die of sudden cardiac death as a result of the arrhythmia. Whereas early versions of ICDs required a thoracotomy for implantation, these devices now may be implanted transvenously, similarly to pacemakers, markedly reducing the incidence of complications. ICDs are indicated for patients who are survivors of cardiac arrest due to hemodynamically unstable VT or VF.[42,45]

Clinical Presentation and Diagnosis of VT

Symptoms

LO 3
- Symptoms depend primarily on heart rate and include palpitations, dizziness, light-headedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope
- Patients with nonsustained VT may be asymptomatic if the duration of the arrhythmia is sufficiently short. However, if the rate is sufficiently rapid, patients with nonsustained VT may experience symptoms
- Patients with sustained VT are usually symptomatic, provided the rate is fast enough to provoke symptoms. Patients with rapid sustained VT may be hemodynamically unstable
- In some patients, sustained VT results in the absence of a pulse or may deteriorate to VF, resulting in sudden cardiac death

Diagnosis

- Diagnosis of VT requires ECG confirmation
- VT is characterized by wide, misshapen QRS complexes, with the rate varying from 140 to 250 beats/min
- In most patients with VT, the shape and appearance of the QRS complexes are consistent and similar, referred to as monomorphic VT. However, some patients experience polymorphic VT, in which the shape and appearance of the QRS complexes vary

Table 9–13

Drugs for Termination of Ventricular Tachycardia[42]

Drug	Loading Dose	Maintenance Dose
Procainamide	20–50 mg/min continuous IV infusion until maximum dose of 10–17 mg/kg is reached	Continuous IV infusion 1–4 mg/min
Amiodarone	150 mg IV over 10 minutes	1 mg/min continuous infusion for 6 hours, then 0.5 mg/min for 18 hours
Sotalol	75 mg IV every 12 hours	—
Verapamil	2.5–5 mg/kg IV bolus every 15–30 minutes	
β-Blockers	Esmolol – see Table 9–6	See Table 9–6
	Metoprolol – see Table 9–6	See Table 9–6
	Propranolol – see Table 9–6	See Table 9–6

IV, intravenous.

ICDs are significantly more effective than antiarrhythmic drugs such as amiodarone or sotalol for reducing the risk of sudden cardiac death, and therefore are preferred therapy.[46,47] However, many patients with ICDs receive concurrent antiarrhythmic drug therapy to reduce the frequency with which patients experience the discomfort of shocks and to prolong battery life of the devices. Combined pharmacotherapy with amiodarone and a β-blocker is more effective than monotherapy with sotalol or β-blockers for reduction in the frequency of ICD shocks.[48]

▶ *Outcome Evaluation*

- Monitor patients for termination of VT and restoration of normal sinus rhythm.
- Monitor patients for adverse effects of antiarrhythmic drugs (see Table 9–7).

Ventricular Fibrillation

LO 3

VF is irregular, disorganized, chaotic electrical activity in the ventricles resulting in the absence of ventricular depolarizations, and consequently, lack of pulse, cardiac output, and blood pressure.

▶ *Epidemiology and Etiology*

The annual incidence of out-of-hospital cardiac arrest in the United States is approximately 76 to 111 individuals per 100,000 population, or roughly 230,000 to 356,000 people.[9] Approximately 11% of individuals experiencing emergency medical services (EMS)-treated out-of-hospital cardiac arrest survive to hospital

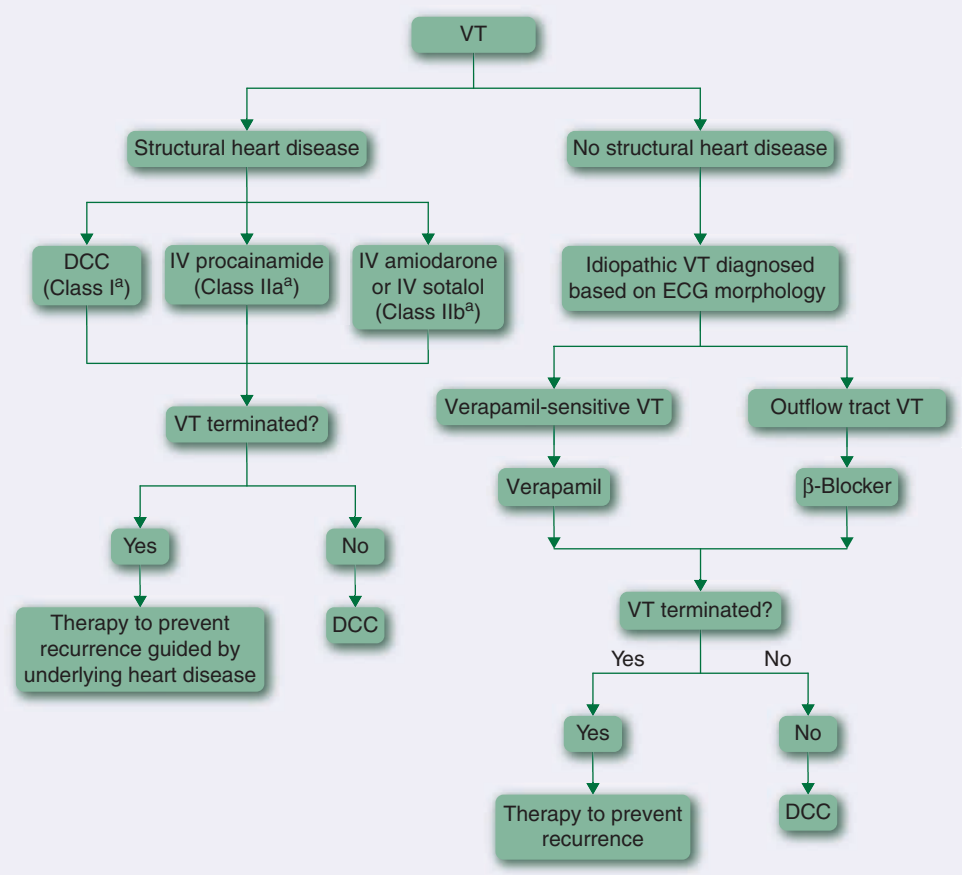

FIGURE 9–9. Decision algorithm for termination of hemodynamically stable ventricular tachycardia. [a]Class I recommendations represent strong level of evidence; Class IIa recommendations represent moderate level of evidence; and Class IIb recommendations represent weak level of evidence. (DCC, direct current cardioversion; ECG, electrocardiogram; IV, intravenous; VT, ventricular tachycardia.)

Clinical Presentation and Diagnosis of VF

Symptoms

LO 3

- VF results in immediate loss of pulse and blood pressure. Patients who are in the standing position at the onset of VF suddenly and immediately collapse to the ground.

Diagnosis

- The absence of a pulse does not guarantee VF because pulse may also be absent in patients with asystole, VT, or pulseless electrical activity.
- Confirmation of the diagnosis with an ECG is necessary to determine appropriate treatment. ECG reveals no organized, recognizable QRS complexes. If treatment is not initiated within a few minutes, death will occur, or at best, resuscitation of the patient with permanent anoxic brain injury.

discharge. Although some of these deaths occur as a result of asystole, the majority occur as a result of primary VF or VT that degenerates into VF. Etiologies of VF are presented in Table 9–12 and are similar to those of VT.

LO 3

▶ *Treatment*

Desired Outcomes Desired outcomes are to: (a) terminate VF, (b) achieve return of spontaneous circulation, and (c) achieve patient survival to hospital admission (in those with out-of-hospital cardiac arrest) and to hospital discharge.

LO 3

Pharmacologic and Nonpharmacologic Therapy VF is by definition hemodynamically unstable, due to the absence of a pulse and blood pressure. Initial management includes provision of basic life support, including calling for help and initiation of cardiopulmonary resuscitation (CPR).[11,49] Oxygen should be administered as soon as it is available. Most importantly, defibrillation should be performed as soon as possible. It is critically important to understand that the only means of successfully terminating VF and restoring sinus rhythm is electrical defibrillation. Defibrillation should be attempted using 360 J for monophasic defibrillators, and 120 to 200 J for biphasic shocks, after which CPR should be resumed immediately while the defibrillator charges. If the first shock was unsuccessful, subsequent defibrillation attempts should be performed at equivalent or higher energy doses.[11,49]

LO 9

If VF persists following two defibrillation shocks, drug therapy may be administered. KEY CONCEPT The purpose of drug administration for treatment of VF is to facilitate successful defibrillation. Drug therapy alone will not result in termination of VF. Drugs used for facilitation of defibrillation in patients with VF are listed in Table 9–14.[11,49] Drug administration should occur during CPR, before or after delivery of a defibrillation shock. The vasopressor agent epinephrine is administered initially because it has been shown that a critical factor in successful defibrillation is maintenance of coronary perfusion pressure, which is achieved via the vasoconstricting effects of this agent. A decision algorithm for the treatment of VF is presented in Figure 9–10. Vasopressin is no longer recommended as a vasopressor agent for cardiac arrest,

LO 9 LO 10

Table 9–14

Drugs for Facilitation of Defibrillation in Patients with Ventricular Fibrillation[11]

Drug	Dose
Epinephrine	1 mg IV/IO every 3–5 minutes
Amiodarone	300 mg IV/IO. One subsequent dose of 150 mg IV/IO may be administered

IO, Intraosseous; IV, intravenous.

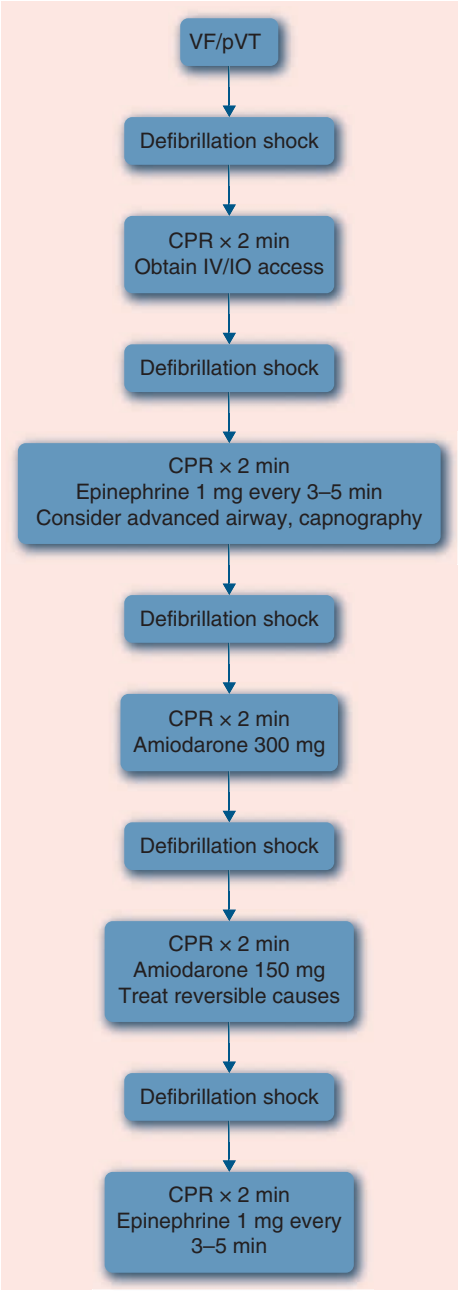

FIGURE 9–10. Decision algorithm for resuscitation of VF or pulseless VT. (CPR, cardiopulmonary resuscitation; IO, intraosseous; IV, intravenous; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia.) (Data from Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(suppl 2):S444–S464.)

including that caused by VF; epinephrine is the sole vasopressor drug recommended for this indication.[49] Amiodarone is effective for facilitation of defibrillation leading to survival to hospital admission in patients with VF.[11,49] Note that amiodarone doses recommended for administration during a resuscitation attempt for VF (see Table 9–14) are different than those recommended for administration for termination of VT (see Table 9–13).

▶ *Outcome Evaluation*

- Monitor the patient for return of pulse and blood pressure, and for termination of VF and restoration of normal sinus rhythm.
- After successful resuscitation, monitor the patient for adverse effects of drugs administered (see Table 9–7).

Torsades de Pointes

LO 3 TdP is a specific polymorphic VT associated with prolongation of the QTc interval in the sinus beats that precede the arrhythmia.[1,50]

▶ *Epidemiology and Etiology*

Incidence of TdP in the population at large is unknown. Attempts to estimate incidence suggests there may be 1000 to 13,000 cases annually in the United States. Incidence of TdP associated with specific drugs ranges from less than 1% to as high as 8% to 10%, depending on dose and plasma concentration of the drug and presence of other risk factors for the arrhythmia.

LO 3 TdP may be inherited or acquired. Patients with specific genetic mutations may have an inherited long QT syndrome, in which the QTc interval is prolonged, and these patients are at risk for TdP. Acquired TdP may be caused by numerous drugs (Table 9–15);[1,50] the list of drugs known to cause TdP continues to expand.

Table 9–15

Some Drugs[a] Known to Cause Torsades de Pointes[1,50]

Amiodarone	Haloperidol
Arsenic trioxide	Ibutilide
Azithromycin	Levofloxacin
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Ciprofloxacin	Ondansetron
Citalopram	Oxaliplatin
Clarithromycin	Pentamidine
Cocaine	Pimozide
Disopyramide	Procainamide
Dofetilide	Propofol
Donepezil	Quinidine
Dronedarone	Roxithromycin
Droperidol	Sevoflurane
Erythromycin	Sotalol
Escitalopram	Terlipressin
Flecainide	Thioridazine
Fluconazole	Vandetanib
Halofantrine	

[a]This table does not provide an exhaustive list of drugs that may cause torsades de pointes. For an exhaustive list, please consult reference 50.

Table 9–16

Risk Factors for Drug-Induced Torsades de Pointes (TdP)[1]

QTc interval > 500 ms
Increase in QTc interval by > 60 ms compared with the pretreatment value
Female sex
Age > 65 years
Heart failure
Electrolyte abnormalities: hypokalemia, hypomagnesemia, hypocalcemia
Bradycardia
Elevated plasma concentrations of QTc interval-prolonging drugs due to drug interactions or absence of dose adjustment for organ dysfunction
Rapid IV infusion of TdP-inducing drugs
Concomitant administration of more than one agent known to cause QTc interval prolongation/TdP
Concomitant administration of loop diuretics
Genetic predisposition
Sepsis
Previous history of drug-induced TdP

IV, intravenous; ms, milliseconds; QTc, corrected QT interval.

▶ *Pathophysiology*

TdP is caused by circumstances, often drugs, that lead to prolongation in the repolarization phase of the ventricular action potential (see Figure 9–2) manifested on the ECG by prolongation of the QTc interval. Prolongation of ventricular repolarization occurs via inhibition of efflux of potassium through potassium channels; therefore, drugs that inhibit conductance through specific potassium channels known as I_{Kr} (the rapid component of the delayed rectifier potassium current) may cause QTc interval prolongation and TdP. Prolongation of ventricular repolarization promotes the development of early ventricular afterdepolarizations during the relative refractory period, which may provoke reentry leading to TdP.

KEY CONCEPT Drug-induced TdP rarely occurs in patients without specific risk factors for the arrhythmia (Table 9–16).[1,50] In most cases, administration of a drug known to cause TdP is unlikely to cause the arrhythmia; however, the likelihood of the arrhythmia increases in patients with concomitant risk factors.

Onset of TdP associated with oral drug therapy is somewhat variable and in some cases may be delayed; often, a patient can be taking a drug known to cause TdP for months or longer without problem until another risk factor for the arrhythmia becomes present, which then may trigger the arrhythmia.

In some patients, TdP may be of short duration and may terminate spontaneously. However, TdP may not terminate on its own, and if left untreated, may degenerate into VF and result in sudden cardiac death.[1] Several drugs, including terfenadine, astemizole, cisapride, and grepafloxacin, have been withdrawn from the US market as a result of causing deaths due to TdP.

▶ *Treatment*

LO 3 **Desired Outcomes** Desired outcomes include (a) prevention of TdP, (b) termination of TdP, (c) prevention of recurrence, and (d) prevention of sudden cardiac death.

LO 10 **Pharmacologic and Nonpharmacologic Therapy** KEY CONCEPT In patients with risk factors for TdP, drugs with the potential to

Clinical Presentation and Diagnosis of TdP

LO 3

Symptoms

- Symptoms associated with TdP depend primarily on heart rate and arrhythmia duration, and include palpitations, dizziness, light-headedness, shortness of breath, chest pain (if underlying CAD is present), near-syncope, and syncope.
- TdP may be hemodynamically unstable if the rate is sufficiently rapid.
- Like sustained monomorphic VT, TdP may result in the absence of a pulse or may rapidly degenerate into VF, resulting in the syndrome of sudden cardiac death.

Diagnosis

- Diagnosis of TdP requires examination of the arrhythmia on ECG.
- TdP, or "twisting of the points," appears on ECG as apparent twisting of the wide QRS complexes around the isoelectric baseline.
- Associated with heart rates from 140 to 280 beats/min.
- Characteristic feature: a "long-short" initiating sequence that occurs as a result of a PVC followed by a compensatory pause followed by the first beat of the TdP.
- Episodes of TdP may self-terminate, with frequent recurrence.

cause QTc interval prolongation and TdP should be avoided or used with extreme caution, and diligent QTc interval monitoring should be performed.

A decision algorithm for management of TdP is presented in Figure 9–11. Management of drug-induced TdP includes discontinuation of the potential causative agent. Patients with hemodynamically unstable TdP should undergo immediate defibrillation, rather than synchronized DCC, because polymorphic arrhythmias are usually not responsive to DCC. In patients with hemodynamically stable TdP, electrolyte abnormalities such as hypokalemia, hypomagnesemia, or hypocalcemia should be corrected. Hemodynamically stable TdP should be treated with IV magnesium sulfate, irrespective of whether the patient is hypomagnesemic; magnesium has been shown to terminate TdP in normomagnesemic patients.[11,42] Magnesium sulfate should be administered IV in doses of 1 to 2 g,[42] diluted in 50 to 100 mL 5% dextrose in water (D_5W), administered over 15 minutes; doses may be repeated to a total of 6 g. Alternatively, a continuous magnesium infusion (0.5 to 1 g/hour) may be initiated after the first bolus. In addition, electrolyte repletion with potassium to greater than or equal to 4.0 mEq/L (4.0 mmol/L) and magnesium to greater than or equal to 2.0 mEq/L (1.0 mmol/L) is recommended.[42]

For hemodynamically stable TdP that is unresponsive to IV magnesium sulfate and is accompanied by bradycardia or triggered by pauses in rhythm, isoproterenol administered via continuous IV infusion 2 to 10 mcg/min may be administered or temporary transvenous atrial or ventricular pacing may be employed to increase the heart rate.[42]

▶ *Outcome Evaluation*

- Monitor vital signs (heart rate and blood pressure).
- Monitor the ECG to determine the QTc interval (maintain < 470 milliseconds [ms] in males and 480 ms in females)[1] and for the presence of TdP.
- Monitor serum potassium, magnesium, and calcium concentrations.
- Monitor for symptoms of tachycardia.

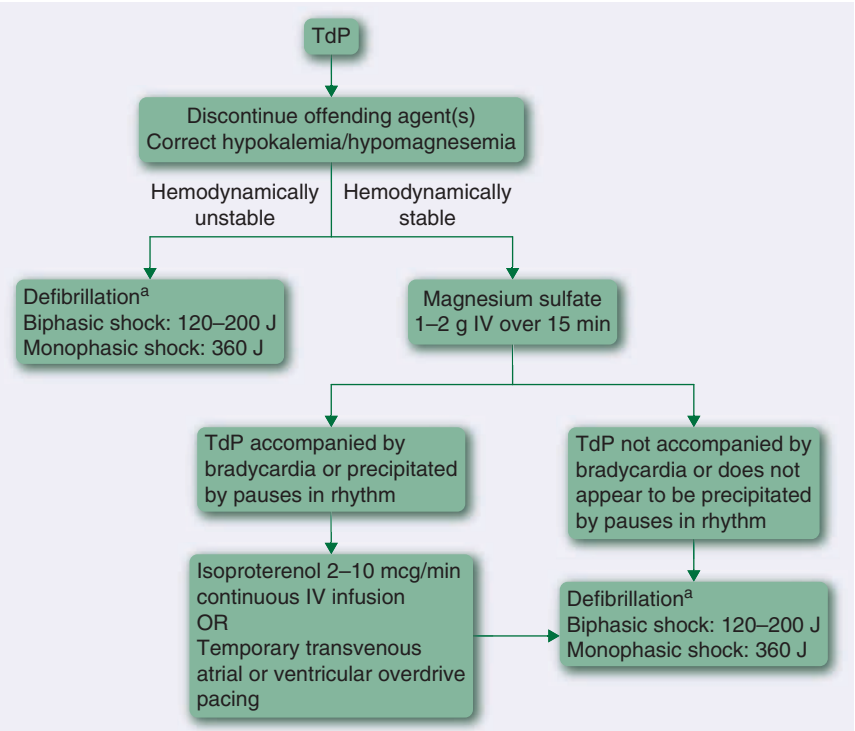

FIGURE 9–11. Decision algorithm for management of torsades de pointes. [a]As polymorphic arrhythmias do not permit synchronization, defibrillation is recommended, rather than synchronized direct current cardioversion. Administer sedation when possible. (IV, intravenous; J, Joules; TdP, torsades de pointes.) (Reprinted with permission from Erstad B, ed. Critical Care Pharmacotherapy. Lenexa, KS; American College of Clinical Pharmacy: 2016;730.)

Patient Care Process

Collect Information:

- Perform a thorough medication history to determine whether the patient is receiving prescription or nonprescription drugs that may cause or contribute to the development of an arrhythmia. See Tables 9–2, 9–3, 9–4, 9–12, and 9–15.
- Determine the patient's serum electrolyte concentrations to determine the presence of hypokalemia, hyperkalemia, hypomagnesemia, hypermagnesemia, or hypocalcemia.
- Consider the patient's heart rate, blood pressure, and symptoms to determine whether he or she is hemodynamically stable or unstable, and the degree to which symptoms are limiting function and quality of life.
- Review the patients' ECG(s) and/or ECG rhythm strips.

Assess the Information:

- Evaluate the patient for the presence of drug-induced diseases, drug allergies, and drug interactions.
- For patients with preexisting arrhythmias, assess the current drug therapy regimen for efficacy, side effects, and adherence.
- In patients currently receiving warfarin for AF, determine the INR and evaluate for appropriateness, adverse effects, and drug–drug and drug–food interactions.
- Assess adherence to current drug therapy regimens.
- Assess the patient's 12-lead ECG or single rhythm strips to determine if an arrhythmia is present, and identify the specific arrhythmia, and evaluate and monitor symptoms.
- Assess information from the chest X-ray, transthoracic echocardiograms or TEEs, and other physical examination and diagnostic information pertinent to arrhythmias.

Develop a Care Plan:

- Develop drug therapy treatment plans for management of the pertinent arrhythmia: sinus bradycardia, AV block, AF, PSVT, PVCs, VT (including TdP), or VF. See Figures 9–4 through 9–11 and Tables 9–6, 9–7, 9–8, 9–9, 9–10, 9–11, 9–13, and 9–14.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage adverse effects.
- Address patient concerns about arrhythmias and their management.
- Discuss importance of medication adherence and risk factor modification for management of arrhythmias.
- Determine whether the patient has prescription coverage and/or whether recommended agents are included on the institution's formulary.

Follow-up: Monitor and Evaluate:

- Develop specific drug therapy monitoring plans, including assessment of symptoms, ECG, adverse effects of drugs, and potential drug interactions.
- Monitor QTc interval in patients receiving QTc interval-prolonging drugs.
- Provide information regarding safe and effective oral anticoagulation:
  - Notify clinicians in the event of severe bruising, blood in urine or stool, melena, hemoptysis, hematemesis, or frequent epistaxis.
  - Patients taking warfarin should avoid radical changes in diet.
  - Avoid alcohol.
  - Do not take nonprescription medications or herbal/alternative/complementary medicines without notifying physician, pharmacist, and/or health care team members.
- Provide patient education regarding disease state and drug therapy.

Abbreviations Introduced in This Chapter

1°	First-degree
2°	Second-degree
3°	Third-degree
AF	Atrial fibrillation
ADHF	Acute decompensated heart failure
aPTT	Activated partial thromboplastin time
ATPase	Adenosine triphosphatase
AV	Atrioventricular
CAD	Coronary artery disease
CAST	Cardiac Arrhythmia Suppression Trial
CCB	Calcium channel blocker
COPD	Chronic obstructive pulmonary disease
CPR	Cardiopulmonary resuscitation
CrCl	Creatinine clearance
CYP	Cytochrome P450
DCC	Direct current cardioversion
D_5W	5% Dextrose in water
ECG	Electrocardiogram
ED	Emergency department
EMS	Emergency Medical Services
FDA	Food and Drug Administration
GI	Gastrointestinal
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
ICD	Implantable cardioverter-defibrillator
INR	International normalized ratio
IO	Intraosseous
IV	Intravenous
J	Joule
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
ms	Milliseconds
NOAC	Non-vitamin K antagonist oral anticoagulant
NYHA	New York Heart Association
P-gp	P-glycoprotein
PAD	Peripheral arterial disease
PSVT	Paroxysmal supraventricular tachycardia

PVC	Premature ventricular complex
QTc	Corrected QT interval
SA	Sinoatrial
TdP	Torsades de pointes
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
VF	Ventricular fibrillation
VPB	Ventricular premature beat
VPC	Ventricular premature contraction
VPD	Ventricular premature depolarization
VT	Ventricular tachycardia

REFERENCES

1. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsades de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2010;121:1047–1060.
2. Fogoros RN. Electrophysiologic Testing, 4th ed. Malden, MA: Blackwell, 2006:17.
3. Vaughan Williams EM. Classification of anti-arrhythmic drugs. In: Sandoe E, Flensted-Jansen E, Olesen KH, eds. Symposium on Cardiac Arrhythmias. Sodertalje, Sweden: AB Astra, 1970:449–472.
4. Singh BN, Vaughan Williams EM. A third class of anti-arrhythmic action. Effects on atrial and ventricular intracellular potentials, and other pharmacological actions on cardiac muscle, of MJ 1999 and AH 3474. Br J Pharmacol. 1970;39:675–687.
5. Singh BN, Vaughan Williams EM. A fourth class of anti-arrhythmic action? Effect of verapamil on ouabain toxicity, on atrial and ventricular intracellular potentials, and on other features of cardiac function. Cardiovasc Res. 1972;6:109–119.
6. Snyders J, Knoth KM, Roberds SL, Tamkun MM. Time-, voltage-, and state-dependent block by quinidine of a cloned human cardiac potassium channel. Mol Pharmacol. 1992;41:322–330.
7. Komeichi K, Tohse N, Nakaya H, et al. Effects of N-acetylprocainamide and sotalol on ion currents in isolated guinea-pig ventricular myocytes. Eur J Pharmacol. 1990;187:313–322.
8. Mangrum JM, DiMarco JP. The evaluation and management of bradycardia. N Engl J Med. 2000;342:703–709.
9. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics – 2017 update: a report from the American Heart Association. Circulation. 2017;135:e146–e603.
10. Tisdale JE. Supraventricular arrhythmias. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases: Prevention, Detection and Management, 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists, 2010:445–484.
11. Neumar RW, Otto CW, Link MS, et al. Part 8: Adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2010;122(Suppl 3):S729–S767.
12. Byrnes TJ, Costantini O. Tachyarrhythmias and bradyarrhythmias: differential diagnosis and initial management in the primary care office. Med Clin North Am. 2017;101:495–506.
13. Mayo Clinic. Atrial fibrillation. Available at: https://www.mayoclinic.org/diseases-conditions/atrial-fibrillation/symptoms-causes/syc-20350624. Accessed November 7, 2017.
14. Verma A, Kalman JM, Callans DJ. Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. Circulation. 2017;135:1547–1563.
15. McManus DD, Yin X, Gladstone R, et al. Alcohol consumption, left atrial diameter, and atrial fibrillation. J Am Heart Assoc. 2016;Sep 14;5(9): pii: e004060. doi: 10.1161/JAHA.116.004060.
16. Sharma A, Einstein AJ, Vallakati A, et al. Risk of atrial fibrillation with use of oral and intravenous bisphosphonates. Am J Cardiol. 2014;113:1815–1821.
17. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;64:e1–e76.
18. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–666.
19. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92:1954–1968.
20. Turakhia MP, Santangeli P, Winkelmayer WC, et al. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. J Am Coll Cardiol. 2014;64:660–668.
21. Qureshi W, O'Neal WT, Soliman EZ, et al. Systematic review and meta-analysis of mortaity and digoxin use in atrial fibrillation. Cardiol J. 2016;23:333–343.
22. Farshi R, Kistner D, Sarma JS, et al. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. J Am Coll Cardiol. 1999;33:304–310.
23. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347:1825–1833.
24. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med. 2002;347:1834–1840.
25. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol. 2003;41:1690–1696.
26. Opolski G, Torbicki A, Kosior D, et al. Rhythm control versus rate control in patients with persistent atrial fibrillation. Results of the HOT CAFE Polish Study. Kardiol Pol. 2003;59:1–16.
27. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med. 2008;358:2667–2677.
28. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–1151.
29. Pollack Jr CV, Reilly PA, van Ryn J, et al. Idaracizumab for dabigatran reversal – full cohort analysis. N Engl J Med. 2017;377:431–441.
30. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–891.
31. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365;981–992.
32. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–2104.
33. Johnson JA, Caudle KE, Gong L, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. Clin Pharmacol Ther. 2017;102:397–404.
34. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia. A report of the American College of Cardiology/American Heart Association Task Force on Clinical

Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2016;67:e27–e115.
35. Bikkina M, Larson MG, Levy D. Prognostic implications of asymptomatic ventricular arrhythmias: The Framingham Heart Study. Am J Cardiol. 1994;74:232–235.
36. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation. 1971;44:130–144.
37. Ruberman W, Weinblatt E, Goldberg JD, et al. Ventricular premature beats and mortality after myocardial infarction. N Engl J Med. 1977;297:750–757.
38. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Engl J Med. 1991;324:781–788.
39. The Cardiac Arrhythmia Suppression Trial II Investigators. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. N Engl J Med. 1992;327:227–233.
40. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction. An overview of results from randomized controlled trials. JAMA. 1993;270:1589–1595.
41. Chandraratna PA. Comparison of acebutolol with propranolol, quinidine, and placebo: results of three multicenter arrhythmia trials. Am Heart J. 1985;109:1198–1204.
42. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. ACC/AHA/ESC guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2017 Oct 30. [Epub ahead of print.]
43. Al-Khatib SM, Stebbins AL, Califf RM, et al. Sustained ventricular arrhythmias and mortality among patients with acute myocardial infarction: results from the GUSTO-III trial. Am Heart J. 2003;145:515–521.
44. Saltzman HE. Arrhythmias and heart failure. Cardiol Clin. 2014;32:125–133.
45. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRA focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Heart Rhythm Society. Circulation. 2013;127:e283–e352.
46. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med. 1997;337:1576–1583.
47. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation. 2000;101:1297–1302.
48. Connolly SJ, Dorian P, Roberts RS, et al. Comparison of β-blockers, amiodarone plus β-blockers, or sotalol for prevention of shocks from implantable cardioverter-defibrillators. The OPTIC study: a randomized trial. JAMA. 2006;295:165–171.
49. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2015;132(suppl 2):S444–S464.
50. Woosley RL, Romero KA, www.Crediblemeds.org, QTdrugs List, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755. Accessed August 31, 2017.

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10 Venous Thromboembolism

Edith A. Nutescu, James C. Lee, and Stuart T. Haines

LEARNING OBJECTIVES

LO

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

1. Identify risk factors and signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE).
2. Describe the processes of hemostasis and thrombosis.
3. Determine a patient's relative risk of developing venous thrombosis.
4. Formulate an appropriate prevention strategy for a patient at risk for DVT.
5. Select and interpret laboratory test(s) to monitor antithrombotic drugs.
6. Identify factors that place a patient at high risk of bleeding while receiving antithrombotic drugs.
7. State at least two potential advantages of newer anticoagulants (ie, low molecular weight heparins [LMWHs], fondaparinux, oral direct thrombin inhibitors [DTIs], and oral direct factor Xa inhibitors) over traditional anticoagulants (ie, unfractionated heparin and warfarin).
8. Manage a patient with toxicity secondary to warfarin (elevated international normalized ratio [INR] with or without bleeding).
9. Identify anticoagulant drug–drug and drug–food interactions.
10. Formulate an appropriate treatment plan for a patient who develops a DVT or PE.

INTRODUCTION

Venous thromboembolism (VTE) is one of the most common cardiovascular disorders in the United States. VTE is manifested as deep vein thrombosis (DVT; ie, thrombus causing obstruction of a deep vein in the leg, pelvis, or abdomen) and pulmonary embolism (PE; ie, thrombus causing obstruction of a pulmonary artery or one of its branches and resulting in pulmonary infarction) (Figure 10–1).[1,2] A thrombus is a blood clot attached to the vessel wall composed of platelets, fibrin, and clotting factors that may partially or completely occlude the lumen of a blood vessel and compromise blood flow and oxygen delivery to distal tissue. It is often provoked by prolonged immobility and vascular injury and most frequently seen in patients hospitalized for a serious medical illness, trauma, or major surgery. VTE can also occur with little or no provocation in patients who have an underlying hypercoagulable disorder.

Although VTE may initially cause few or no symptoms, the first overt manifestation of the disease may be sudden death from PE, which can occur within minutes, before effective treatment can be given.[2,3] A history of VTE is a significant risk factor for recurrent thromboembolic events.[4-7] Postthrombotic syndrome (PTS) is a complication of VTE that occurs due to damage to the vein caused by a blood clot and leads to development of symptomatic venous insufficiency such as chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration.

The treatment of VTE is fraught with substantial risks.[8] KEY CONCEPT Antithrombotic therapies (thrombolytics and anticoagulants) require precise dosing and meticulous monitoring, as well as ongoing patient assessment and education.[4,9,10] Well-organized anticoagulation management services improve quality of care and reduce overall cost. A systematic approach to drug therapy management reduces risks, but bleeding remains a common and serious complication.[10,11] Therefore, preventing VTE is paramount to improving outcomes. When VTE is suspected, a rapid and accurate diagnosis is critical to making appropriate treatment decisions. The optimal use of antithrombotic drugs requires not only an in-depth knowledge of their pharmacology and pharmacokinetic properties but also a comprehensive approach to patient management.[3,12]

EPIDEMIOLOGY AND ETIOLOGY

The true incidence of VTE in the general population is unknown because many patients, perhaps more than 50%, have no overt symptoms or go undiagnosed.[1,12,13] An estimated 2 million people in the United States develop VTE each year, of whom 600,000 are hospitalized and 60,000 die. The estimated annual direct medical costs of managing the disease are well over $1 billion. The incidence of VTE nearly doubles in each decade of life older than 50 years of age and is slightly higher in men. As the population ages, the total number of DVT and PE cases continues to rise.[1,2,13,14]

KEY CONCEPT The risk of VTE is related to several factors including age, history of VTE, major surgery (particularly orthopedic procedures of the lower extremities), trauma, malignancy, pregnancy, estrogen use, and hypercoagulable states (Table 10–1).[5-7] VTE risk factors can be categorized into one of the three elements of Virchow triad: stasis in blood flow, vascular endothelial injury, and inherited or acquired changes in blood constituents resulting in hypercoagulation states.[15-17]

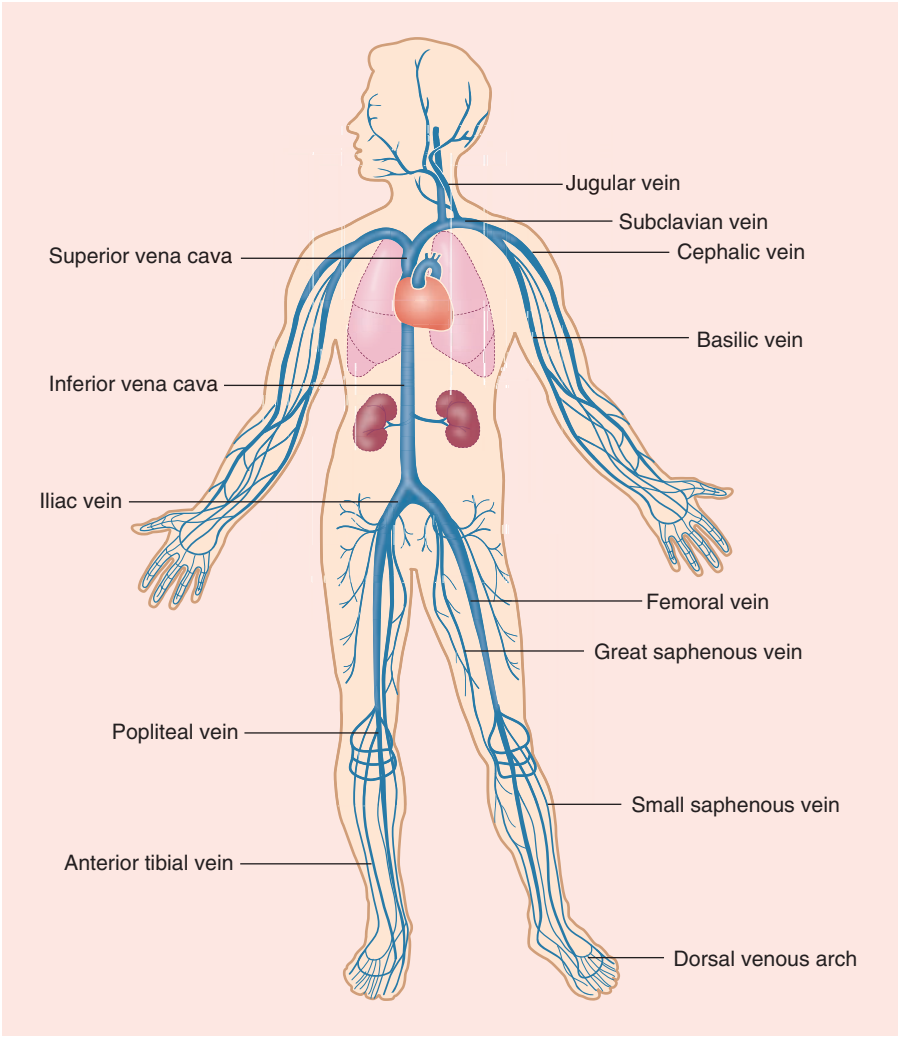

FIGURE 10–1. Venous circulation. (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:232.)

LO 1

These risk factors are additive, and some can be easily identified in clinical practice.[1,3] A prior history of venous thrombosis (in which blood changes from a liquid to a solid state and produces a blood clot) is perhaps the strongest risk factor for recurrent VTE, presumably because of damage to venous valves and obstruction of blood flow caused by the initial event.[5-7] Rapid blood flow (as in arteries) has an inhibitory effect on thrombus formation, but a slow rate of blood flow (as in veins) reduces the clearance of activated clotting factors in the zone of injury and slows the influx of regulatory substances. Stasis tips the delicate balance of procoagulation and anticoagulation in favor of **thrombogenesis**. The rate of blood flow in the venous circulation, particularly in the deep veins of the lower extremities, is relatively slow. Valves in the deep veins of the legs, as well as contraction of the calf and thigh muscles, facilitate the flow of blood back to the heart and lungs. Damage to the venous valves and periods of prolonged immobility result in venous stasis. Vessel obstruction, either from a thrombus or external compression, promotes clot propagation. Numerous medical conditions and surgical procedures are associated with reduced venous blood flow and increase the risk of VTE. Greater than normal blood viscosity, seen in myeloproliferative disorders like **polycythemia vera**, may also contribute to slowed blood flow and thrombus formation.[5-7,16,17]

While a normal endothelium is antithrombotic, damage to the endothelium creates a substrate for platelet binding and activation that ultimately leads to clot formation. Major surgery, trauma, and indwelling central catheters can cause endothelial damage. Smoking and hypertension can also lead to endothelial dysfunction by shifting the balance between clot formation and clot breakdown toward thrombosis.[5-7,16,17]

A growing list of hereditary deficiencies, gene mutations, and acquired diseases has been linked to hypercoagulability (Table 10–1).[18,19] Some patients may have multiple genetic defects. Hereditary deficiencies include activated protein C resistance also known as factor V Leiden, the prothrombin gene 20210A mutation, deficiencies of the natural anticoagulants protein C, protein S, and antithrombin (AT), and high concentrations of factors VIII, IX, and XI. Acquired disorders of hypercoagulability include malignancy, antiphospholipid antibodies, estrogen use, and pregnancy.[20,21] Estrogen-containing contraceptives, estrogen replacement therapy, and many of the selective estrogen receptor modulators (SERMs) increase the risk of venous thrombosis.[20,22] Although the mechanisms are not clearly understood, estrogens increase serum **clotting factor** concentrations and induce activated protein C resistance. Increased serum estrogen concentrations may explain, in part, the increased risk of VTE during pregnancy and the postpartum period.[22]

Table 10–1

Risk Factors for Venous Thromboembolism (VTE)

Risk Factor	Considerations and Examples
Age	Risk doubles with each decade after age 50
History of VTE	Strongest known risk factor
Venous stasis	Major medical illness (eg, heart failure, acute myocardial infarction, ischemic stroke, acute infection)
	Major surgery (eg, general anesthesia for > 30 minutes)
	Paralysis (eg, due to stroke or spinal cord injury)
	Polycythemia vera
	Obesity
	Varicose veins
	Immobility (eg, bedrest for ≥ 3 days during hospital admission)
Vascular injury	Major orthopedic surgery (eg, knee and hip replacement)
	Trauma (especially fractures of the pelvis, hip, or leg)
	Indwelling venous catheters
Hypercoagulable states	Malignancy, diagnosed or occult
	Activated protein C resistance/ factor V Leiden
	Prothrombin (20210A) gene mutation
	Protein C deficiency
	Protein S deficiency
	Antithrombin deficiency
	Factor VIII excess (> 90th percentile)
	Factor XI excess (> 90th percentile)
	Antiphospholipid antibodies
	Dysfibrinogenemia
	Plasminogen activator inhibitor-1 (PAI-1) excess
	Pregnancy/postpartum
Drug therapy	Estrogen-containing oral contraceptive pills
	Estrogen replacement therapy
	Selective estrogen receptor modulators (SERMs)
	Heparin
	Chemotherapy

PATHOPHYSIOLOGY

Hemostasis, the arrest of bleeding following vascular injury, is essential to life.[23] Within the vascular system, blood remains in a fluid state, transporting oxygen, nutrients, plasma proteins, and waste. When a vessel is injured, a dynamic interplay between thrombogenic (activating) and antithrombotic (inhibiting) forces results in the local formation of a hemostatic plug that seals the vessel wall and prevents further blood loss (Figures 10–2 and 10–3). A disruption of this delicate system of checks and balances may lead to inappropriate clot formation within the blood vessel that can obstruct blood flow or embolize to a distant vascular bed.

LO 2 Under normal circumstances, the endothelial cells that line the inside of blood vessels maintain blood flow by producing a number of substances that inhibit platelet adherence, prevent the activation of the coagulation cascade, and facilitate fibrinolysis.[16,17,23] Vascular injury exposes the subendothelium. Platelets adhere to the subendothelium with their glycoprotein (GP) Ib surface receptors and facilitated by von Willebrand factor (vWF). This causes platelets to become activated, releasing a number of procoagulant substances that stimulate circulating platelets to expose GP IIb and IIIa surface receptors and subsequently allowing platelets to adhere to one another, resulting in platelet aggregation (Figure 10–2). The damaged vascular tissue releases tissue factor that activates the extrinsic pathway of the coagulation cascade (Figure 10–3).

The clotting cascade is a stepwise series of enzymatic reactions that results in the formation of a fibrin mesh.[12] Clotting factors circulate in the blood in inactive forms. Once a precursor is activated by specific stimuli, it activates the next clotting factor in the sequence. The final steps in the cascade are the conversion of prothrombin (factor II) to thrombin (factor IIa) and fibrinogen to fibrin. Thrombin plays a key role in the coagulation cascade; it is responsible not only for the activation of fibrin but also for the activation of factors V and VIII, creating a positive feedback loop that greatly accelerates the entire cascade. Thrombin also enhances platelet aggregation.

Traditionally, the coagulation cascade has been divided into three distinct parts: the intrinsic, the extrinsic, and the common pathways. This artificial division is misleading because there are numerous interactions between the three pathways.[16,17,23] A number of tempering mechanisms modulate coagulation (Figure 10–2).[23,24] Without effective self-regulation, the coagulation cascade would proceed unabated until all the clotting factors and platelets are consumed.

CLINICAL PRESENTATION AND DIAGNOSIS

Although a thrombus can form in any part of the venous circulation, most begin in the lower extremities. Once formed, a venous thrombus may (a) remain asymptomatic, (b) spontaneously lyse, (c) obstruct the venous circulation, (d) propagate into more proximal veins, (e) embolize, and/or (f) slowly incorporate into the endothelial layer of the vessel.[1,3,16] Most patients with VTE never develop symptoms.[3,25] However, even those who initially experience no symptoms may suffer long-term consequences, such as PTS and recurrent VTE.

Given that VTE can be debilitating or fatal, it is important to treat it quickly and aggressively.[1,2,12] However, because major bleeding induced by antithrombotic drugs can be equally harmful, it is also important to avoid treatment when the diagnosis is not reasonably certain. Assessment should focus on patient-specific LO 1 risk factors during the medical history (Table 10–1).[1,2,12] Venous thrombosis is uncommon in the absence of risk factors, and the effects of these risk factors are additive. If a patient has multiple risk factors, VTE should be strongly suspected even when the symptoms are very subtle.

KEY CONCEPT The symptoms of DVT or PE are nonspecific, and it is extremely difficult to distinguish VTE from other disorders on clinical symptoms alone.[1-3,25] Therefore, objective tests are required to confirm or rule out the diagnosis. Patients with DVT frequently present with unilateral leg pain on the affected leg, swelling that can persist after a night's sleep, and cyanosis of the skin in the affected leg (Table 10–2). Similarly, PTS, a long-term complication of DVT caused by damage to the venous valves, produces chronic lower extremity swelling, pain, and tenderness that lead to skin discoloration and ulceration. To distinguish LO 3 acute DVT from PTS and other possible diagnoses, a clinical prediction rule that incorporates signs, symptoms, and risk factors can be used to categorize the patient as at low, intermediate, or high probability of having acute DVT. This model, known as the Wells criteria, is summarized in Table 10–2.[2,3,12] If the clinical probability of DVT is low, the D-dimer test can be used to

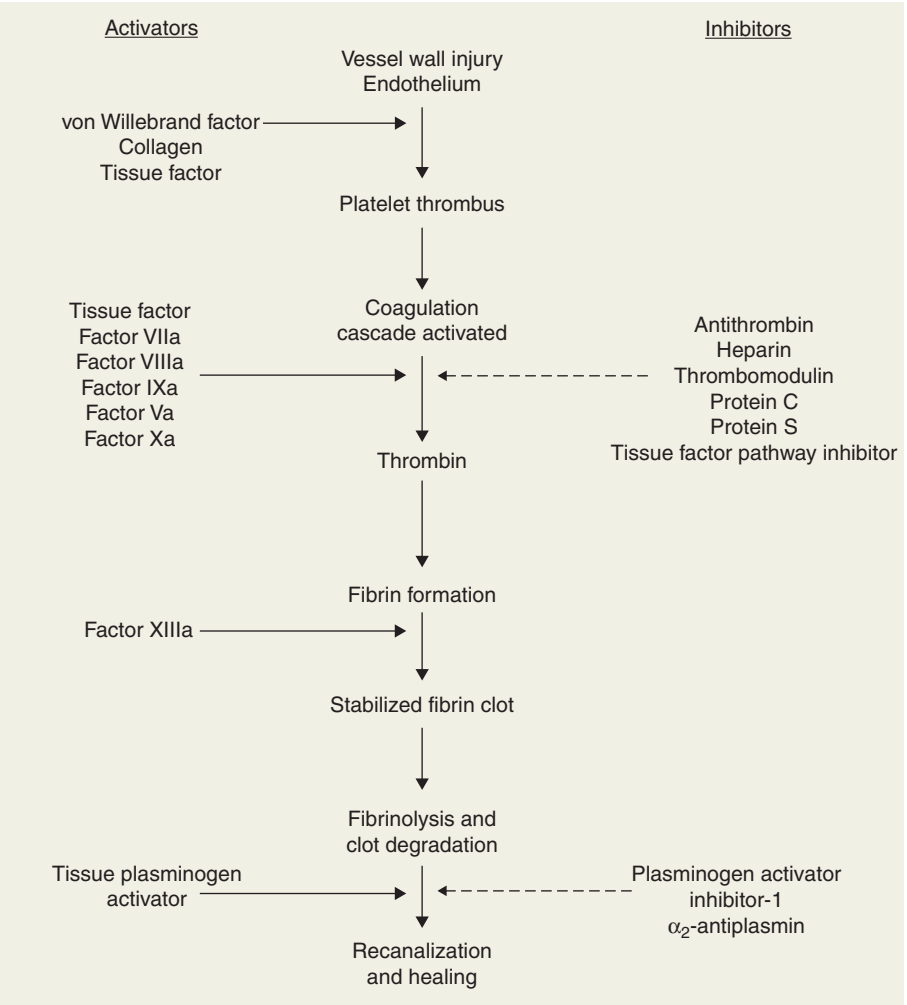

FIGURE 10–2. Hemostasis and thrombosis. (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:234.)

confirm the patient does not have DVT. The D-dimer test is a quantitative measure of fibrin breakdown in the serum, and it is a marker of acute thrombotic activity. D-dimer assays are sensitive but not specific markers for VTE, so a negative D-dimer test can be used to rule out the diagnosis of DVT.

If the D-dimer test is positive in a low-probability patient, or if the patient has a moderate or high probability of DVT, then an objective radiographic test is used to confirm the diagnosis of DVT. Contrast venography allows visualization of the entire venous system in the lower extremities. This radiographic contrast study is the most accurate and reliable method for diagnosis of DVT and considered the gold standard in clinical trials.[3,25,26] However, venography is an expensive, invasive procedure that is technically difficult to perform and evaluate. Severely ill patients may be unable to tolerate the procedure, and many develop hypotension and cardiac arrhythmias. Furthermore, the contrast material is irritating to vessel walls and toxic to the kidneys. For these reasons, noninvasive testing using duplex ultrasonography is preferred. See the Clinical Presentation and Diagnosis of DVT textbox for further information.

LO 1

Like DVT, the nonspecific nature of the signs and symptoms of PE requires further evaluation. Table 10–3 describes the Wells criteria, a validated prediction model that can be used to stratify patients into high, moderate, and low probability of PE.[3,25-27] In patients with a low clinical probability of PE, diagnosis of PE can be ruled out if D-dimer testing is negative. If D-dimer testing is positive, or if the patient has a moderate or high clinical probability of PE, diagnostic imaging studies should be performed. Pulmonary angiography allows visualization of the pulmonary arteries and is the gold standard for diagnosing PE but is an extremely invasive procedure. Diagnosis of VTE can be made if there is a persistent intraluminal filling defect observed on multiple x-ray films. However, as with DVT, a noninvasive test is preferred, such as computed tomographic pulmonary angiography, magnetic resonance imaging (MRI), and ventilation/perfusion (V/Q) scans. See the Clinical Presentation and Diagnosis of PE textbox for further information.

LO 3

LO 1

PREVENTION

Given that VTE is often clinically silent and potentially fatal, prevention strategies have the greatest potential to improve patient outcomes.[5-7] The goal of an effective VTE prophylaxis program is to identify all patients at risk, determine each patient's level of risk, and select and implement regimens that provide sufficient protection for the level of risk.[5-7] KEY CONCEPT At the time of hospital admission, transition of care, and prior to discharge, all patients should be evaluated for risk of VTE, and appropriate prophylaxis strategies should be routinely used. Prophylaxis should be continued throughout the period of risk.

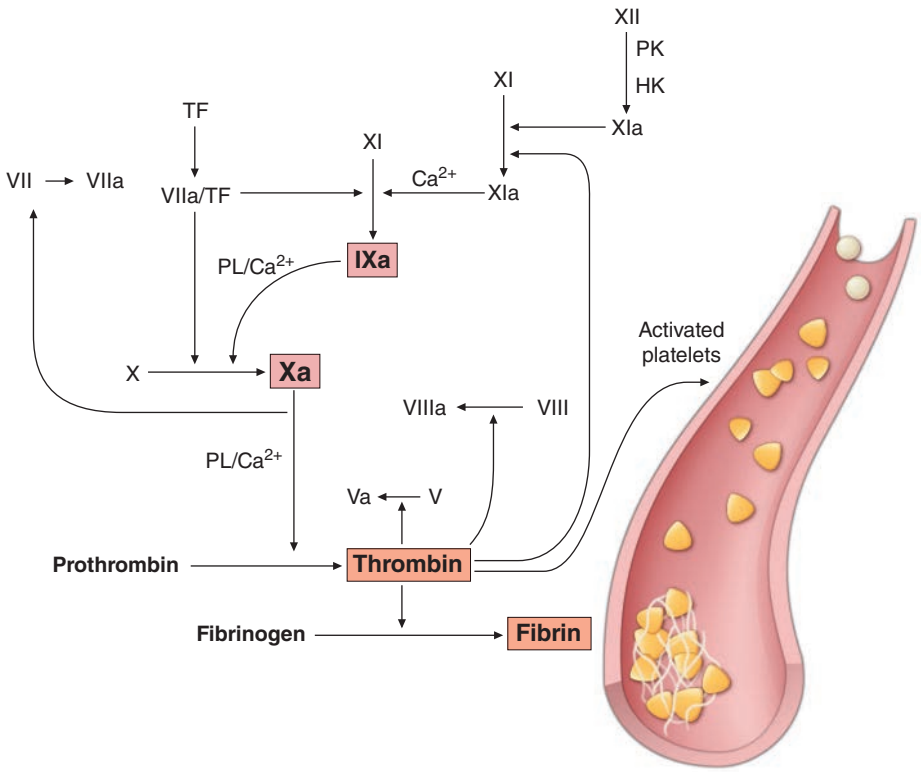

FIGURE 10–3. Summary of coagulation pathways. Specific coagulation factors ("a" indicates activated form) are responsible for the conversion of soluble plasma fibrinogen into insoluble fibrin. This process occurs via a series of linked reactions in which the enzymatically active product subsequently converts the downstream inactive protein into an active serine protease. The activation of thrombin leads to additional stimulation of platelets. (Ca^{2+}, Calcium; HK, high molecular weight kininogen; PK, prekallikrein; PL, phospholipid surface; TF, tissue factor.) (From Freedman JE, Loscalzo J. Arterial and venous thrombosis. In: Longo DL, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine, 18th ed. New York, NY: McGraw-Hill; 2012:985.)

Table 10–2

Clinical Model/Modified Wells Criteria for Evaluating the Pretest Probability of Deep Vein Thrombosis (DVT)

Clinical Characteristic	Score
Active cancer (cancer treatment within previous 6 months or currently on palliative treatment)	+1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	+1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swollen	+1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	+1
Pitting edema confined to the symptomatic leg	+1
Collateral superficial veins (nonvaricose)	+1
Previously documented DVT	+1
Alternative diagnosis at least as likely as DVT	–2

Assess the patient for the presence of any of the 9 clinical characteristics listed above
Assign a score of "+1" for each characteristic that is present.
Tally the total score.
If an alternative diagnosis is at least as likely as DVT, then substract 2 points from the total points tallied above.
In patients with symptoms in both legs, the more symptomatic leg is used.

Risk Score Interpretation

Total Risk Score	Clinical Probability of DVT
0	Low
1	Moderate
2	Moderate
3 or higher	High

Clinical Presentation and Diagnosis of DVT

General

Most commonly develops in patients with identifiable risk factors (Table 10–1) during or following a hospitalization. Many patients have asymptomatic disease.

Symptoms

Patient may complain of persistent unilateral leg swelling, pain, warmth, and/or skin discoloration. Symptoms are nonspecific, and objective testing must be performed to establish the diagnosis.

Signs

- Superficial veins may be dilated and a "palpable cord" may be felt in the affected leg.
- May experience unilateral leg edema with measurable difference in leg circumference compared to the unaffected leg, erythema, increase in warmth, and tenderness with palpation of calf muscles.
- May experience pain in the popliteal or calf region in the affected leg when the examiner dorsiflexes the foot while the knee is flexed/slightly bent (Homans sign).
- Note: The physical examination signs can be unreliable. Homans sign can also be unreliable.

Clinical Probability

Apply the Wells criteria to determine the probability that the patient's signs, symptoms, and risk factors are the result of DVT (Table 10–2).

Laboratory Tests

- The initial laboratory evaluation should include complete blood count (CBC) with differential, coagulation studies (such as prothrombin time [PT]/international normalized ratio [INR], activated partial thromboplastin time [aPTT]), serum chemistries with renal and liver function, and urinalysis.
- Serum concentrations of D-dimer, a by-product of thrombin generation, will be elevated in an acute event. A negative D-dimer in a patient with low clinical probability of DVT can be used to rule out DVT.
- Patient may have an elevated erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count.

Diagnostic Tests

- Duplex ultrasonography is the most commonly used test to diagnose DVT. It is a noninvasive test that can measure the rate and direction of blood flow and visualize clot formation in proximal veins of the legs. It cannot reliably detect small blood clots in distal veins. Coupled with a careful clinical assessment, it can confirm or rule out (exclude) the diagnosis in most cases. Repeat testing may be necessary if the first test is negative and the patient is still symptomatic.
- Venography (also known as phlebography) is the gold standard for the diagnosis of DVT. However, it is an invasive test that involves injection of radiopaque contrast dye into a foot vein. It is expensive and can cause anaphylaxis and nephrotoxicity.

LO 3

There are several risk assessment models available for estimating VTE risk specific to hospitalized medical and surgical patients.[5-7,12] While none of these models have been extensively validated, the Padua Prediction score is recommended for assessment of medical patients (Table 10–4) and the Caprini score is recommended for assessment of general surgical patients (Table 10–5). Bleeding risk should also be assessed to help identify patients in whom the risk of bleeding may outweigh benefits of pharmacologic prophylaxis.[5-7] Table 10–6 lists general and procedure-specific risk

Table 10–3

Clinical Model/Wells Criteria for Evaluating the Pretest Probability of Pulmonary Embolism (PE)

Clinical Characteristic	Score
Cancer	+1
Hemoptysis	+1
Previous PE or DVT	+1.5
Heart rate greater than 100 beats/min	+1.5
Recent surgery or immobilization	+1.5
Clinical signs of DVT	+3
Alternative diagnosis less likely than PE	+3

Risk Score Interpretation

Total Risk Score	Clinical Probability of PE
0–1	Low
2–6	Moderate
7 or higher	High

DVT, deep vein thrombosis.

Table 10–4

Risk Factors for Predicting Venous Thromboembolism (VTE) in Hospitalized Medical Patients (Padua Prediction Score)

Risk Factor	Points
Active cancer[a]	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility[b]	3
Already known thrombophilic condition[c]	3
Recent (≤ 1 month) trauma and/or surgery	2
Elderly age (≥ 70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatologic disorder	1
Obesity (body mass index ≥ 30)	1
Ongoing hormonal treatment	1
Cumulative score of ≥ 4 points indicates high risk of VTE	

[a]Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months.

[b]Anticipated bed rest with bathroom privileges (either because of patient's limitations or on physician's order) for at least 3 days.

[c]Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.

Adapted with permission from Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e195S–e226S.

Clinical Presentation and Diagnosis of PE

General

Most commonly develops in patients with risk factors for VTE (Table 10–1) during or following a hospitalization. Although many patients will have symptoms of DVT prior to developing a PE, many will not and some patients can be asymptomatic. Patients may die suddenly before effective treatment can be initiated.

Symptoms

- May complain of cough, pleuritic chest pain, chest tightness, shortness of breath with or without exertion, wheezing, orthopnea, or palpitations.
- May present with hemoptysis (spit or cough up blood).
- May complain of dizziness or experience syncope.
- May be misdiagnosed as a myocardial infarction (MI) or pneumonia, and objective testing must be performed to establish the diagnosis.

Signs

- May have tachypnea (increased respiratory rate) and tachycardia (increased heart rate).
- May appear diaphoretic (sweaty) and may have fever.
- Neck veins (external jugular veins) may be distended reflecting increased jugular venous pressure and increased heart pressure.
- The examiner may see use of accessory respiratory muscles and may hear diminished breath sounds, crackles, wheezes, or pleural friction rub during auscultation of the lungs. A parasternal lift or right ventricular S3, S4 may be found on the heart examination.
- In massive PE, the patient may appear cyanotic and hypotensive and may appear to have signs of right-sided heart failure. In such cases, oxygen saturation by pulse oximetry or arterial blood gas will likely indicate the patient is hypoxic.
- In the worst cases, the patient may go into circulatory shock and die within minutes.

Clinical Probability

Apply the Wells criteria to determine the probability that the patient's signs, symptoms, and risk factors are the result of PE (Table 10–3).

Laboratory Tests

- Serum concentrations of D-dimer, a by-product of thrombin generation, will be elevated. A negative D-dimer in a patient with low clinical probability of PE can be used to rule out PE.
- In patients with a low probability for PE, the PE rule-out criteria ("PERC rule") is an alternative to D-dimer testing. In patients who fulfill the following eight criteria the likelihood of PE is low and no further testing is required: age less than 50 years; heart rate less than 100 beats/min; oxyhemoglobin saturation at or above 95% (0.95); no hemoptysis; no estrogen use; no prior DVT or PE; no unilateral leg swelling; and no surgery/trauma requiring hospitalization within the prior 4 weeks.
- May have an elevated ESR and WBC count.
- May have elevated serum lactate dehydrogenase (LDH) or aspartate aminotransferase (AST; serum glutamic-oxaloacetic transaminase [SGOT]) with normal bilirubin.
- Serum troponin I and troponin T can be elevated in a large PE. These typically resolve within 40 hours if due to PE but persist longer after acute MI.
- Electrocardiogram may show nonspecific ST-segment and T-wave changes and tachycardia. Arterial blood gases may show acute respiratory alkalosis from hyperventilation.

Diagnostic Imaging Tests

- A computed tomography (CT) scan is the most commonly used test to diagnose PE, but some institutions still use a V/Q scan. Spiral CT scans can detect emboli in the pulmonary arteries. A V/Q scan measures the distribution of blood and air flow in the lungs. When there is a large mismatch between blood and air flow in one area of the lung, there is a high probability the patient has a PE.
- Pulmonary angiography is the gold standard for diagnosis of PE. However, it is an invasive test that involves injection of radiopaque contrast dye into the pulmonary artery. The test is expensive and associated with significant risk of mortality.

LO 4 factors for major bleeding complications. Patients with moderate to high risk of VTE should receive pharmacologic prophylaxis. If pharmacologic prophylaxis is contraindicated, such as in patients actively bleeding or at high risk of bleeding, nonpharmacologic prophylaxis should be used (Table 10–7).

Several pharmacologic and nonpharmacologic methods are effective for preventing VTE, and these can be used alone or in combination (Table 10–7).[5-7] Nonpharmacologic methods improve venous blood flow by mechanical means; drug therapy prevents thrombus formation by inhibiting the coagulation cascade.

Nonpharmacologic Therapy

LO 4 Ambulation as soon as possible following surgery lowers the incidence of VTE in low-risk patients.[5-7] Walking increases venous blood flow and promotes the flow of natural antithrombotic factors into the lower extremities. All hospitalized patients should be encouraged to ambulate as early as possible, and as frequently as possible.

Graduated compression stockings (GCS) are specialized hosiery that provide graduated pressure on the lower legs and feet to help prevent thrombosis. Compared with anticoagulant drugs, GCS are relatively inexpensive and safe; however, they are less effective and not recommended in moderate to higher risk patients.[2] They offer an alternate in low- to moderate-risk patients when pharmacologic interventions are contraindicated. When combined with pharmacologic interventions, GCS have an additive effect. However, some patients are unable to wear compression stockings because of the size or shape of their legs, and some patients may find them hot, confining, and very difficult to put on and remove.

LO 4 Similar to GCS, intermittent pneumatic compression (IPC) devices increase the velocity of blood flow in the lower extremities.[5-7] These devices sequentially inflate a series of

Table 10–5

Risk Factors for Predicting Venous Thromboembolism (VTE) in General Surgical Patients (Modified Caprini Risk Assessment Model for VTE in General Surgical Patients)

Risk Score			
1 Point	**2 Points**	**3 Points**	**5 Points**
Age 41–60 years	Age 61–74 years	Age ≥ 75 years	Stroke (< 1 month)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI > 25 kg/m^2	Major open surgery (> 45 minutes)	Family history of VTE	Acute spinal cord injury (< 1 month)
Swollen legs	Laparoscopic surgery (> 45 minutes)	Factor V Leiden	
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (> 72 hours)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (< 1 month)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (< 1 month)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Heart failure (< 1 month)			
History of inflammatory bowel disease			
Medical patient at bed rest			

Risk Score Interpretation	
Total Risk Score	**Risk of VTE**
0	Very low (< 0.5%)
1–2	Low (1.5%)
3–4	Moderate (3%)
≥ 5	High (6%)

BMI, body mass index.

Adapted with permission from Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e227S–e277S.

Table 10–6

Risk Factors for Major Bleeding Complications

General Risk Factors	Procedure-Specific Risk Factors	Procedures in Which Bleeding Complications May Have Especially Severe Consequences
Active bleeding	**Abdominal Surgery**	Craniotomy
Previous major bleeding	Male sex, preoperative hemoglobin level < 13 g/dL (130 g/L; 8.07 mmol/L), malignancy, and complex surgery defined as two or more procedures, difficult dissection, or more than one anastomosis	Spinal surgery
Known, untreated bleeding disorder	**Pancreaticoduodenectomy**	Spinal trauma
Severe renal or hepatic failure	Sepsis, pancreatic leak, sentinel bleed	Reconstructive procedures involving free flap
Thrombocytopenia	**Hepatic Resection**	
Acute stroke	Number of segments, concomitant extrahepatic organ resection, primary liver malignancy, lower preoperative hemoglobin level, and platelet counts	
Uncontrolled systemic hypertension	**Cardiac Surgery**	
Lumbar puncture, epidural, or spinal anesthesia within previous 4 hours or next 12 hours	Use of aspirin, use of clopidogrel within 3 days before surgery	
Concomitant use of anticoagulants, antiplatelet therapy, or thrombolytic drugs	BMI > 25 kg/m^2, nonelective surgery, placement of five or more grafts, older age, renal insufficiency, operation other than CABG, longer bypass time	
	Thoracic Surgery	
	Pneumonectomy or extended resection	

BMI, body mass index; CABG, coronary artery bypass graft.

Adapted with permission from Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e227S–e277S.

Table 10–7

Thrombosis Risk Classification and Recommended Venous Thromboembolism Prevention Strategies[5-7]

Indication and Level of Risk	Prevention Strategies
Hospitalized Medical Patients	
Low thrombosis risk	Early ambulation
High thrombosis risk[a] (Padua Score > 4)	LMWH, LDUH, fondaparinux, betrixaban
Critically Ill Patients	
High thrombosis risk[a]	LMWH, LDUH
General Surgical Patients	
Very low thrombosis risk (Caprini Score 0)	Early ambulation
Low thrombosis risk (Caprini Score 1–2)	IPC
Moderate thrombosis risk[b] (Caprini Score 3–4)	LMWH, LDUH, IPC
High thrombosis risk[b] (Caprini Score ≥ 5)	LMWH, LDUH, plus GCS or IPC
Cancer Surgery	LMWH
Major Orthopedic Surgery	
Hip fracture surgery[b]	LMWH, fondaparinux, LDUH, adjusted dose warfarin, aspirin
Hip and knee arthroplasty[b]	LMWH, fondaparinux, LDUH, warfarin, aspirin, apixaban, dabigatran, rivaroxaban

[a]Mechanical methods of prophylaxis with IPC or GCS should be used in patients actively bleeding or those at high risk of bleeding complications (see Table 10–6 for risk factors for major bleeding).

[b]Mechanical methods of prophylaxis with IPC should be used in patients actively bleeding or those at high risk of bleeding complications (see Table 10–6 for risk factors for major bleeding).

GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin.

cuffs wrapped around the patient's legs from the ankles to the thighs and then deflate in 1- to 2-minute cycles. Although IPC has been shown to reduce the risk of VTE in surgical patients, most studies failed to define the type of device used. IPC was frequently used in combination with other prophylaxis methods, making it difficult to quantify their efficacy. Although IPC is safe to use in patients who have contraindications to pharmacologic therapies, it does have a few drawbacks: it is more expensive than GCS, it is a relatively cumbersome technique, some patients may have difficulty sleeping while using it, and some patients find the devices hot and uncomfortable. To be effective, IPC needs to be used throughout the day. In practice, this is difficult to achieve, and special efforts should be made to ensure the devices are worn and operational for most of the day.

Inferior vena cava (IVC) filters, also known as Greenfield filters, provide short-term protection against PE in very high-risk patients by preventing the **embolization** of a thrombus formed in the lower extremities into the pulmonary circulation.[5-7] Insertion of a filter into the IVC is a minimally invasive procedure. Despite the widespread use of IVC filters, there are very limited data regarding their effectiveness and long-term safety. The evidence suggests that IVC filters, particularly in the absence of effective antithrombotic therapy, are thrombogenic themselves and increase the long-term risk of recurrent DVT and of filter thrombosis. Although IVC filters can reduce the short-term risk of PE in patients at highest risk, they should be reserved for patients in whom other prophylactic strategies cannot be used. To further reduce the long-term risk of VTE in association with IVC filters, pharmacologic prophylaxis is necessary in patients with IVC filters in place, and warfarin therapy should begin as soon as the patient is able to tolerate it.[2] If used, retrievable filters are preferred, which can be removed once pharmacologic prophylaxis can be safely administered or once the patient is no longer at risk for VTE.

Pharmacologic Therapy

Appropriately selected drug therapies can dramatically reduce the incidence of VTE in medical and surgical patients (Table 10–7). The choice of medication and dose to use for VTE prevention must be based on the patient's level of risk for thrombosis and bleeding risk, as well as the cost and availability of an adequate drug therapy monitoring system.[5-7]

LO 4 The most extensively studied drugs for the prevention of VTE are unfractionated heparin (UFH), the low molecular weight heparins (LMWHs; dalteparin and enoxaparin), fondaparinux, and warfarin.[5-7] Generally the LMWHs provide improved protection against VTE when compared with low-dose UFH in most medical and surgical patients and when compared to low-dose UFH and warfarin in major orthopedic surgery patients. Fondaparinux is more effective than LMWH in patients undergoing high-risk orthopedic surgery, but it has a heightened risk of bleeding.

For hospitalized general surgical and medical patients, the available evidence supports the use of UFH 5000 Units subcutaneously (SC) every 8–12 hours, enoxaparin 40 mg SC daily, dalteparin 2500–5000 Units SC daily, or fondaparinux 2.5 mg SC daily. Betrixaban is also approved for extended VTE prophylaxis in hospitalized adult patients with acute medical illnesses and was found noninferior to prophylactic-dose enoxaparin with no differences in major bleeding. Betrixaban is given as an initial 160 mg dose followed by 80 mg daily, with the dose halved in the setting of severe renal impairment (creatinine clearance [CrCl] 15–30 mL/min [0.25–0.5 mL/s]) or concomitant use of P-glycoprotein (P-gp) inhibitors.[28]

LO 4 For the prevention of VTE following major orthopedic surgery, current evidence supports the use of UFH, LMWH, fondaparinux, adjusted dose warfarin, aspirin, and the direct oral anticoagulants (DOACs; apixaban, dabigatran, and rivaroxaban). The role of aspirin for VTE prevention is controversial as it produces a very modest reduction in VTE following orthopedic surgeries of the lower extremities.[5]

The effectiveness of UFH, aspirin, and warfarin is lower than LMWH and long-term safety data are lacking for apixaban, dabigatran, and rivaroxaban; thus the American College of Chest Physicians (ACCP) guidelines recommend the use of LMWH or fondaparinux preferentially over other pharmacologic options in major orthopedic surgery patients.[5] The appropriate prophylactic dose for each LMWH product in orthopedic surgery is indication specific; however, enoxaparin 30 mg SC twice daily or 40 mg SC daily, and dalteparin 5000 Units SC daily are the most commonly used regimens. The dose of fondaparinux is 2.5 mg SC daily.

The dose of warfarin, another commonly used option for prevention of VTE following orthopedic surgery, must be adjusted to maintain an INR between 2 and 3.[5] Oral administration and low drug acquisition cost give warfarin some advantages over the LMWHs and fondaparinux. However, warfarin does not achieve its full antithrombotic effect for several days and requires

Patient Encounter 1

An 80-year-old obese woman (BMI 42 kg/m^2) with a history of PE and ulcerative colitis is admitted to the hospital with severe abdominal pain, fever, fatigue, and diarrhea. She is diagnosed with peritonitis and started on antibiotic therapy.

PMH: PE 10 years ago; ulcerative colitis × 10 years; depression × 5 years; chronic hip pain × 3 years; hypertension × 3 years.

FH: Father died at 55 years due to MI; mother died at 74 years due to breast cancer.

SH: Occasional alcohol use. Employed in county government. Lives at home with spouse and pets.

Home Meds: Aspirin 81 mg by mouth once daily; atenolol 100 mg by mouth once daily; paroxetine 20 mg by mouth once daily.

Allergies: NKDA

VS: BP 135/70 mm Hg, HR 72 beats/min, RR 16 breaths/min, T 38.7°C (101.7°F), Wt 90 kg (198 lb).

Labs: WBC 22.4 × 10^3/mm^3 (22.4 × 10^9/L); estimated glomerular filtration rate (eGFR) 80 mL/min/1.73 m^2; CrCl 78 mL/min (1.30 mL/s).

Hospital Treatment: Nothing by mouth; metronidazole 500 mg IV every 8 hours; ceftriaxone 1 gm IV every 24 hours.

Which risk factor(s) predispose this patient to VTE?

What is her estimated risk for developing VTE?

Given her presentation and history, create an appropriate VTE prophylaxis plan including the pharmacologic agent, dose, route and frequency of administration, duration of therapy, and monitoring parameters.

frequent monitoring and periodic dosage adjustments, making therapy cumbersome. Warfarin should only be used when a systematic patient monitoring system is available.

LO 4

The oral factor Xa inhibitors rivaroxaban and apixaban are also options for VTE prevention following hip and knee replacement surgery and offer a convenient alternative to traditional anticoagulants.[5,29,30] Both agents have shown superior efficacy compared to LMWH with a similar rate of bleeding complications. Rivaroxaban is given at a fixed dose of 10 mg once daily, and apixaban is given at a fixed dose of 2.5 mg twice daily. Both are given without the need for routine laboratory monitoring and dosing adjustments (as with warfarin) and without the inconvenience of administration by injection (as with LMWH and fondaparinux).

The oral direct thrombin inhibitor (DTI) dabigatran is another option for VTE prevention following orthopedic surgery, but is only approved for use following hip replacement surgery. Dabigatran is given as an initial 110 mg dose, followed by 220 mg once daily. Dabigatran should not be used in those with CrCl less than 30 mL/min (0.50 mL/s) or concomitantly with P-gp inhibitors.

The optimal duration for VTE prophylaxis is not well established but should be given throughout the period of risk. For patients who have undergone total knee replacement, total hip replacement, or hip fracture repair, prophylaxis is recommended for a minimum of 10 to 14 days; however, extending it up to 35 days is recommended due to continued VTE risk up to 1 month postsurgery.[5-7]

TREATMENT

Desired Therapeutic Outcomes

The goal of VTE treatment is to prevent short- and long-term complications of the disease. The aim of initial therapy is to prevent propagation or local extension of the clot, embolization, hemodynamic collapse, and death. The goal of long-term and extended therapy is to prevent complications such as PTS, pulmonary hypertension, and recurrent VTE.[2,12]

General Treatment Principles

Anticoagulant drugs are considered the mainstay of therapy for patients with VTE, and the therapeutic strategies for DVT and PE are similar.[2,12] Management decisions are guided by balancing the risks and benefits of various treatment options. The treatment of VTE can be divided into three phases: acute (first 5–10 days), long term (first 3 months), and extended (beyond 3 months).[12] The acute treatment phase of VTE is typically accomplished by administering a fast-acting parenteral or a DOAC (Table 10–8). The long-term and extended phase treatments of VTE are usually accomplished using oral anticoagulant agents such as warfarin, or one of the DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban).[2,12] In certain populations, such as patients with cancer and women who are pregnant, the LMWHs are the preferred agents during long-term and extended treatment phases due to better safety or efficacy.[2] The etiology of VTE will guide the duration of therapy. VTE can be provoked (by transient risk factors), unprovoked (or idiopathic), and cancer associated. Patients with unprovoked or cancer-associated VTE have a significantly higher risk of recurrence compared to patients with provoked VTE.[2,12]

KEY CONCEPT In the absence of contraindications, the treatment of VTE should initially include a rapid-acting injectable anticoagulant (eg, UFH, LMWH, fondaparinux) or a rapidly acting DOAC (eg, apixaban, rivaroxaban). If warfarin is used for oral anticoagulation, it should be initiated on the same day as the parenteral anticoagulant, and the parenteral agent should be overlapped for a minimum of 5 days and until the INR is greater than or equal to 2 for at least 24 hours. If dabigatran or edoxaban are used for oral anticoagulation, they should be initiated after 5 to 10 days of initial treatment with a parenteral anticoagulant. Anticoagulation therapy should be continued for a minimum of 3 months. However, the duration of anticoagulation therapy should be based on the patient's risk of VTE recurrence and major bleeding.[2,12]

Pharmacologic Therapy

▶ *Thrombolytics*

The role of thrombolysis in the treatment of VTE is controversial.[2,12,31] Compared with anticoagulants, thrombolytics restore venous patency more quickly; however, the bleeding risk associated with their use is significantly higher. In patients with DVT, thrombolytics decrease short-term pain and swelling and prevent destruction of the venous valves. While they may decrease the incidence and severity of PTS, clinical trials have failed to show reduction in recurrent DVT, PE, or death;[31] therefore, their use in most patients is not recommended.[2,12] In a select group of high-risk patients with massive iliofemoral DVT who are at risk of venous gangrene and limb loss, thrombolysis may be considered. See Table 10–9.

In patients with acute PE, the use of thrombolytics provides short-term benefits such as restoring pulmonary artery patency and hemodynamic stability.[2,12,31] However, systemic thrombolysis does not reduce mortality and is associated with a greater risk

Table 10–8

Pharmacologic Options for the Acute Phase Treatment of Venous Thromboembolism

Parenteral Anticoagulants

UFH

IV administration:[a] use weight-based dosing nomogram (Table 10–10)
Or
SC administration: 17,500 units (250 units/kg) given every 12 hours (an initial 5000 unit IV bolus dose is recommended to obtain rapid anticoagulation)
Adjust subsequent doses to attain a goal aPTT based on the institution-specific therapeutic range
Or
SC administration: 333 units/kg followed by 250 units/kg given every 12 hours (fixed-dose unmonitored dosing regimen)

LMWHs

Dalteparin: 200 units/kg SC once daily *or* 100 units/kg SC twice daily
Enoxaparin: 1.5 mg/kg SC once daily *or* 1 mg/kg SC twice daily; if CrCl < 30 mL/min (0.50 mL/s): 1 mg/kg SC once daily

Factor Xa Inhibitor

Fondaparinux[b]:
For body weight ≤ 50 kg (110 lb), use 5 mg SC once daily
For body weight 50–100 kg (110–220 lb), use 7.5 mg SC once daily
For body weight ≥ 100 kg (220 lb), use 10 mg SC once daily

Direct Oral Anticoagulants

Apixaban: 10 mg PO twice daily for the initial 7 days, then 5 mg PO twice daily[c]
Dabigatran: 150 mg PO twice daily after 5–10 days of parenteral anticoagulation[d]
Edoxaban: 60 mg PO once daily or 30 mg[e] PO once daily after 5–10 days of parenteral anticoagulation
Rivaroxaban: 15 mg PO twice daily for the initial 21 days, then 20 mg PO daily[d]

[a]IV administration preferred due to improved dosing precision.

[b]Contraindicated in patients with CrCl < 30 mL/min (0.50 mL/s).

[c]After the initial 6 months of therapy, the dose is reduced to 2.5 mg PO twice daily.

[d]Avoid in patients with CrCl < 30 mL/min (0.50 mL/s).

[e]Reduced dose for CrCl 15–50 mL/min (0.25–0.83 mL/s), body weight ≤ 60 kg (132 lb), or concomitant use of P-glycoprotein inhibitors.

aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; IV, intravenous; LMWHs, low molecular weight heparins; SC, subcutaneous; UFH, unfractionated heparin.

of major bleeding.[12] Given the relative lack of data to support their routine use, thrombolytics should be reserved for select high-risk circumstances. Candidates for thrombolytic therapy are patients with acute massive **embolism** who are hemodynamically unstable (systolic blood pressure [SBP] < 90 mm Hg) and at low risk for bleeding. Current guidelines recommend a short infusion time (2 hours) over a prolonged infusion time (24 hours) and administration through a peripheral vein over a pulmonary artery catheter.[2,12]

▶ *Unfractionated Heparin*

UFH has traditionally been the drug of choice for indications requiring a rapid anticoagulation including the acute treatment

Patient Encounter 2

A 62-year-old woman with a new diagnosis of ovarian cancer is admitted to the hospital for debulking surgery.

PMH: Depression × 19 years; history of hip fracture 3 years ago with subsequent lower left extremity DVT, treated with LMWH and warfarin for 3 months.

FH: Brother 55 years old with type 2 diabetes; maternal grandmother died at 65 years due to breast cancer.

SH: Smoked half a pack per day for 25 years, quit 15 years ago; occasional alcohol use. Lives alone and expects to be discharged to a rehabilitation facility postoperatively before returning home.

Home Meds: Sertraline 100 mg by mouth daily; oxycodone 5–10 mg by mouth every 5 hours as needed for pain; St. John's Wort 2 capsules daily.

Allergies: NKDA

VS: BP 110/60 mm Hg, HR 55 beats/min, RR 18 breaths/min, T 37.0°C (98.6°F), Wt 127 kg (280 lb), BMI 41 kg/m^2.

Labs: All withinnormal limits; eGFR 96 mL/min/1.73 m^2; CrCl 94 mL/min (1.57 mL/s).

Which risk factor(s) predispose this patient to VTE?

How should postoperative VTE be prevented?

How long should she receive VTE prophylaxis?

What education about VTE prophylaxis should she receive?

of VTE. Unlike thrombolytics, UFH and other anticoagulants will not dissolve a formed clot but prevent its propagation and growth.[2,9] Heparin exerts its anticoagulant effect by augmenting the natural anticoagulant, AT. See **Figure 10–4**.

UFH can be administered via the intravenous (IV) or subcutaneous (SC) route.[2,9] See Table 10–8. When rapid anticoagulation is required, UFH should be administered IV and an initial bolus dose should be given. For the treatment of VTE, UFH is generally given as a continuous IV infusion. The half-life of UFH is dose dependent and ranges from 30 to 90 minutes but may be significantly longer, up to 150 minutes, with high doses. UFH is eliminated by two mechanisms: (a) enzymatic degradation via a saturable zero-order process, and (b) renally via a first-order process. Lower UFH doses are primarily cleared via enzymatic processes, whereas higher doses are primarily renally eliminated. Clearance of UFH can be impaired in patients with renal and hepatic dysfunction. Patients with active thrombosis may require higher UFH doses due to a more rapid elimination or variations in the plasma concentrations of heparin-binding proteins.

Certain patient-specific situations may require UFH higher doses to achieve a therapeutic anticoagulant effect. AT deficiency and elevated factor VIII levels are common in pregnant patients. AT deficiency has been linked to higher UFH dose requirements. The requirement of these higher UFH doses is termed *heparin resistance*. Factor VIII elevations can result in altered activated partial thromboplastin time (aPTT) response to UFH, and monitoring with antifactor Xa levels is recommended.[2,9,10]

The dose of UFH required to achieve a therapeutic anticoagulant response is correlated to the patient's weight.[2,9] Weight-based

Table 10–9

Thrombolysis for the Treatment of Venous Thromboembolism

- Thrombolytic therapy should be reserved for patients who present with PE with shock, hypotension, or massive DVT with limb gangrene
- Diagnosis must be objectively confirmed before initiating thrombolytic therapy
- Thrombolytic therapy is most effective when administered as soon as possible after PE diagnosis, but benefit may extend up to 14 days after symptom onset

FDA-Approved PE Thrombolytic Regimens

- Streptokinase 250,000 units IV bolus over 30 minutes followed by 100,000 units/hour for 12–24 hours[a]
- Urokinase 4400 units/kg IV bolus over 10 minutes followed by 4400 units/kg/hour for 12–24 hours[a]
- Alteplase (rt-PA) 100 mg IV over 2 hours

Non-FDA Approved Thrombolytic Regimens

- Reteplase two 10-unit IV boluses given 30 minutes apart
- Tenecteplase weight-adjusted IV bolus over 5 seconds (30–50 mg with a 5-mg step every 10 kg from < 60 to > 90 kg)

- Factors that increase the risk of bleeding must be evaluated before thrombolytic therapy is initiated (ie, recent surgery, trauma or internal bleeding, uncontrolled hypertension, recent stroke, or intracranial hemorrhage)
- Baseline labs should include CBC and blood typing in case transfusion is needed
- IV UFH should not be used during IV thrombolytic therapy. Neither the aPTT nor any other anticoagulation parameter should be monitored during the thrombolytic infusion
- aPTT should be measured following the completion of thrombolytic therapy:
  - If aPTT < 2.5 times the control value, UFH infusion should be started and adjusted to maintain aPTT in therapeutic range
  - If aPTT > 2.5 times the control value, remeasure every 2–4 hours and start UFH infusion when aPTT is < 2.5
- Avoid phlebotomy, arterial puncture, and other invasive procedures during thrombolytic therapy to minimize the risk of bleeding

[a]Two-hour infusions of streptokinase and urokinase are as effective and safe as alteplase; 2-hour infusion times are preferred over longer infusion times.

aPTT, activated partial thromboplastin time; CBC, complete blood count; DVT, deep vein thrombosis; FDA, Food and Drug Administration; IV, intravenous; PE, pulmonary embolism; rt-PA, recombinant tissue plasminogen activator; UFH, unfractionated heparin.

dosing regimens should be used to exceed the therapeutic threshold in the first 24 hours after initiating treatment.[9,10] Achieving a therapeutic aPTT in the first 24 hours after initiating UFH is critical because it has been shown to lower the risk of recurrent VTE. For nonobese patients, the actual body weight should be used to calculate the initial UFH dose (Table 10–10). For obese patients, using the actual body weight to calculate the initial dose is also generally recommended; however, data are limited in morbidly obese patients, that is, weight more than 150 kg (330 lb). Some experts recommend using an adjusted body weight (ABW) in these patients instead. The infusion rate is then adjusted based on laboratory monitoring of the patient's response.[9,10] (See Table 10–10.)

KEY CONCEPT Due to significant interpatient variability and changes in patient response over time, UFH requires close monitoring and periodic dose adjustment. The response to UFH can be monitored using a variety of laboratory tests including the aPTT, the whole blood clotting time, activated clotting time (ACT), antifactor Xa activity, and the plasma heparin concentration.[9,10] Although it has several limitations, the aPTT is the most widely used test in clinical practice to monitor UFH. Traditionally, therapeutic aPTT range is defined as 1.5 to 2.5 times the control aPTT value. However, due to variations in reagents and instruments used to measure the aPTT in different laboratories, each institution should establish a therapeutic range for UFH. The institution-specific therapy range should correlate with a plasma heparin concentration of 0.2 to 0.4 units/mL (kU/L) by protamine titration or 0.3 to 0.7 units/mL (kU/L) by an amidolytic antifactor Xa assay.[4,27] An aPTT should be obtained at baseline, 6 hours after initiating the heparin infusion, and 6 hours after each dose change because this is the time required to reach steady state. UFH dose is then adjusted based on the aPTT measurement and institutional-specific therapeutic range (Table 10–10). In patients with heparin resistance, antifactor Xa concentrations may be a more accurate method of monitoring the patient's response.[9,10]

LO 5

Side effects associated with UFH include bleeding, thrombocytopenia, hypersensitivity reactions, and with prolonged use, alopecia, hyperkalemia, and osteoporosis.[9,10]

KEY CONCEPT Bleeding is the most common adverse effect associated with antithrombotic drugs including UFH therapy.[8] A patient's risk of major hemorrhage is related to the intensity and stability of therapy, age, concurrent drug use, history of gastrointestinal bleeding, risk of falls or trauma, and recent surgery. Several risk factors can increase the risk of UFH-induced bleeding (Table 10–11). The risk of bleeding is related to intensity of anticoagulation. Higher aPTT values are associated with an increased risk of bleeding. The risk of major bleeding is 1% to 5% during the first few days of treatment.[2,9,10] In addition to the aPTT, hemoglobin, hematocrit, and blood pressure should be monitored. Concurrent use of UFH with other antithrombotic agents, such as thrombolytics and antiplatelet agents, also increases bleeding risk. Patients receiving UFH therapy should be closely monitored for signs and symptoms of bleeding, including epistaxis, hemoptysis, hematuria, hematemesis, **hematochezia**, **melena**, severe headache, and joint pain. If major bleeding occurs, UFH should be stopped immediately and the source of bleeding treated.[9,10] If necessary, use protamine sulfate as an antidote to reverse the effects of UFH. The usual dose is 1 mg protamine sulfate per 100 units of UFH, up to a maximum of 50 mg, given as a slow IV infusion over 10 minutes. The effects of UFH are neutralized in 5 minutes, and the effects of protamine persist for 2 hours. If bleeding is not controlled or the anticoagulant effect rebounds, repeated doses of protamine may be administered.[9,10]

LO 6

Heparin-induced thrombocytopenia (HIT) is a very serious adverse effect associated with UFH use. Platelet counts should be monitored every 2 to 3 days throughout the course of UFH therapy.[9,10] HIT should be suspected if the platelet count drops by more than 50% from baseline or to below $150 \times 10^3/mm^3$ ($150 \times 10^9/L$). HIT should also be suspected if thrombosis occurs despite UFH use. Immediate discontinuation of all heparin-containing products including the use of LMWHs and heparin-based flushes is required. Alternative anticoagulation with parenteral DTIs should be initiated. In patients with contraindications to anticoagulation therapy, UFH should not be administered (Table 10–12).

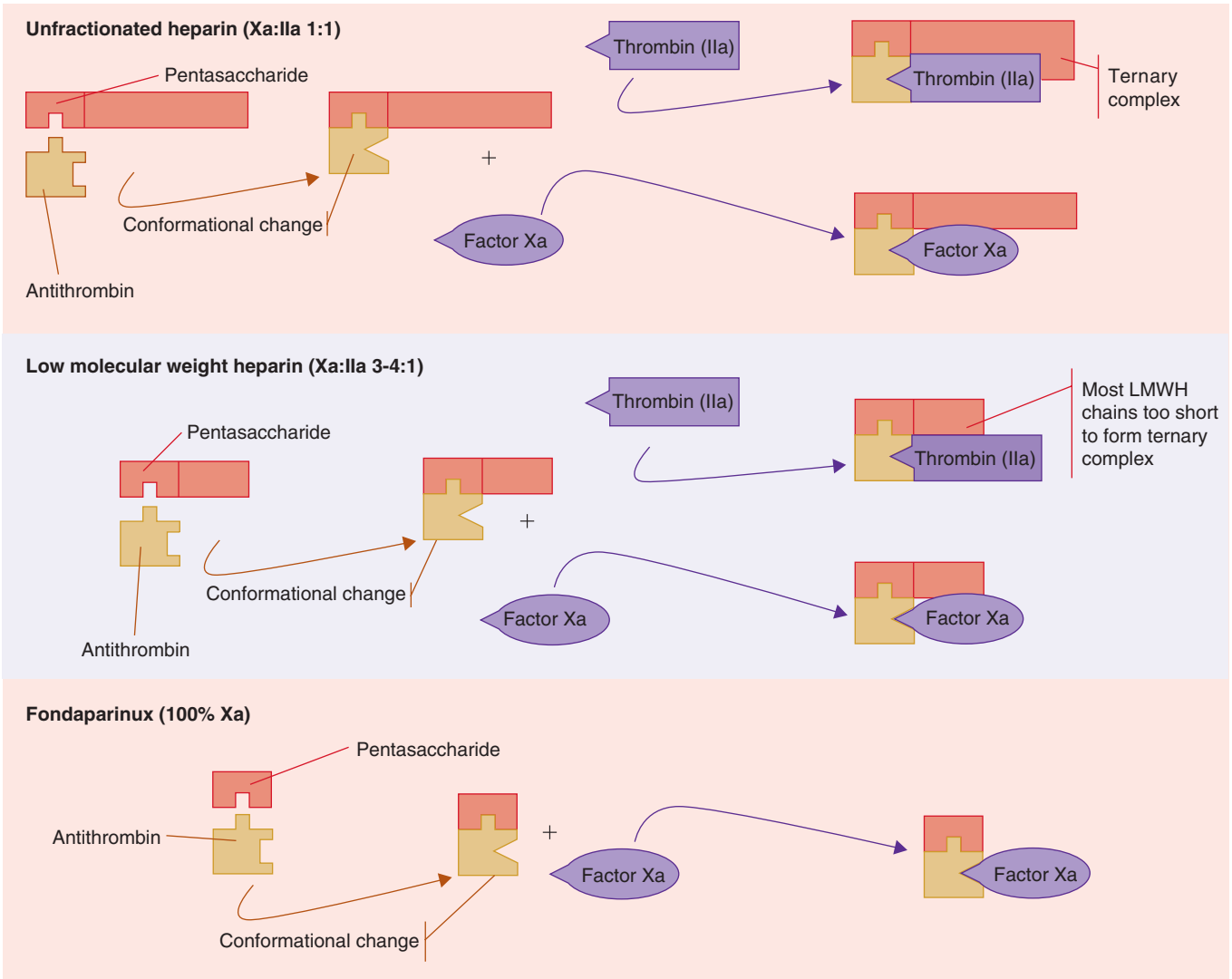

FIGURE 10–4. Mechanism of action of unfractionated heparin, low molecular weight heparin (LMWH), and fondaparinux. (From Witt DM, Clark NP. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014:266.)

UFH may be used to treat VTE during pregnancy. UFH should be used with caution in the peripartum period due to risk of maternal hemorrhage. UFH is not secreted into breast milk and is safe for use by women who wish to breastfeed.[2,9,10,20] For treatment of VTE in children, the UFH dose is 50 units/kg bolus followed by an infusion of 20,000 units/m^2 per 24 hours. Alternatively, a loading dose of 75 units/kg followed by an infusion of 28 units/kg/hour if younger than 12 months old and 20 units/kg/hour if older than 1 year may be considered.[32]

► *Low Molecular Weight Heparins*

LO 7

Compared with UFH, LMWHs have improved pharmacodynamic and pharmacokinetic properties.[9,10,12] They exhibit less binding to plasma and cellular proteins, resulting in a more predictable anticoagulant response. Consequently, routine monitoring of anticoagulation activity and dose adjustments are not required in most patients. LMWHs have longer plasma half-lives, allowing once- or twice-daily administration, improved SC bioavailability, and dose-independent renal clearance. In addition, LMWHs have a more favorable side-effect profile than UFH. They are also associated with a lower incidence of HIT and osteopenia. Two LMWHs are currently available in the United States: dalteparin and enoxaparin.

Like UFH, LMWHs prevent the propagation and growth of formed thrombi.[9] The anticoagulant effect is mediated through a specific pentasaccharide sequence that binds to AT. The primary difference in the pharmacologic activity of UFH and LMWH is their relative inhibition of thrombin (factor IIa) and factor Xa. Smaller heparin fragments (as in LMWHs) cannot bind AT and thrombin simultaneously (Figure 10–4). The SC bioavailability of the LMWHs is greater than 90%. Peak anticoagulant effect of the LMWHs is reached 3 to 5 hours after an SC dose. The elimination half-life is 3 to 6 hours and is agent specific. In patients with renal impairment, the half-life of LMWHs is prolonged.[9,10,12]

The dose of LMWHs for the treatment of VTE is determined based on the patient's weight and is administered SC once or twice daily (Table 10–8). Due to their predictable anticoagulant effect, routine monitoring is not necessary in most patients.[9] LMWHs have been evaluated in many randomized trials and

Table 10–10

Weight-Based[a] Dosing for UFH Administered by Continuous IV Infusion for Venous Thromboembolism

Initial Loading Dose	Initial Infusion Rate
80 units/kg (maximum = 10,000 units)	18 units/kg/hour (maximum = 2300 units/hour)
	Maintenance Infusion Rate
aPTT (seconds)	*Dose Adjustment*
< 37 (or < 12 seconds below institution-specific therapeutic range)	80 units/kg bolus then increase infusion by 4 units/kg/hour
37–47 (or 1–12 seconds below institution-specific therapeutic range)	40 units/kg bolus then increase infusion by 2 units/kg/hour
48–71 (within institution-specific therapeutic range)	No change
72–93 (or 1–22 seconds above institution-specific therapeutic range)	Decrease infusion by 2 units/kg/hour
> 93 (or > 22 seconds above institution-specific therapeutic range)	Hold infusion for 1 hour then decrease by 3 units/kg/hour

[a]Use actual body weight for all calculations. Adjusted body weight (ABW) may be used for morbidly obese patients (> 130% of ideal body weight [IBW]).

ABW = IBW + (Actual body weight – IBW) × 0.7

aPTT, activated partial thromboplastin time; IV, intravenous; UFH, unfractionated heparin.

have been shown to be at least as safe and effective as UFH for the treatment of VTE.[2,12] Indeed, the rate of mortality was lower in patients treated with an LMWH in clinical trials. This mortality benefit was primarily seen in patients with cancer.[33]

LO 5

Prior to initiating treatment with an LMWH, baseline laboratory tests should include PT/INR, aPTT, CBC, and serum creatinine (SCr). Monitor the CBC with platelet count every 3 to 5 days during the first 2 weeks of therapy, and every 2 to 4 weeks with extended use.[9,10] Use LMWHs cautiously in patients with renal impairment due to the potential of drug accumulation and risk of bleeding. Specific dosing recommendations for patients with a CrCl less than 30 mL/min (0.50 mL/s) are currently available for enoxaparin but are lacking for other LMWH agents (Table 10–8). Current guidelines recommend the use of UFH over LMWH in patients with severe renal dysfunction (CrCl < 30 mL/min [0.50 mL/s]).[2]

Table 10–11

Risk Factors for Major Bleeding While on Anticoagulation

- Increased anticoagulation intensity (eg, INR > 5, aPTT > 120 seconds)
- Initiation of therapy (first few days and weeks)
- Unstable anticoagulation response (eg, variable INR response)
- Age older than 65 years
- Concurrent antiplatelet drug use
- Concurrent NSAID or aspirin use
- History of gastrointestinal bleeding
- Recent surgery or trauma
- High risk for fall/trauma (eg, elderly, sedentary/bedbound, high risk medications)
- Heavy alcohol use
- Renal failure
- Cerebrovascular disease
- Active malignancy

aPTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug.

Table 10–12

Contraindications to Anticoagulation Therapy

General
- Active bleeding
- Hemophilia or other hemorrhagic tendencies
- Severe liver disease with elevated baseline PT/INR
- Severe thrombocytopenia (platelet count < 20×10^3/mm^3 [20×10^9/L])
- Malignant hypertension
- Inability to meticulously supervise and monitor treatment

Drug-Specific Contraindications
- UFH
  - Hypersensitivity to UFH
  - History of HIT
- LMWHs
  - Hypersensitivity to LMWH, UFH, pork products, methylparaben, or propylparaben
  - History of HIT or suspected HIT
- Fondaparinux
  - Hypersensitivity to fondaparinux
  - Severe renal insufficiency (CrCl < 30 mL/min [0.50 mL/s])
  - Body weight < 50 kg (110 lb) for prophylaxis
  - Bacterial endocarditis
  - Thrombocytopenia with a positive in vitro test for antiplatelet antibodies in the presence of fondaparinux
- Lepirudin
  - Hypersensitivity to hirudins
- Argatroban
  - Hypersensitivity to argatroban
- Warfarin
  - Hypersensitivity to warfarin
  - Pregnancy
  - History of warfarin-induced skin necrosis
  - Inability to obtain follow-up PT/INR measurements
  - Inappropriate medication use or lifestyle behaviors
- Dabigatran
  - Mechanical prosthetic heart valves
  - Hypersensitivity to dabigatran
- Apixaban
  - Hypersensitivity to apixaban
- Rivaroxaban
  - Hypersensitivity to rivaroxaban

CrCl, creatinine clearance; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; LMWHs, low molecular weight heparins; PT, prothrombin time; UFH, unfractionated heparin.

KEY CONCEPT Most patients with an uncomplicated DVT and PE can be managed safely at home.[2] LMWHs can be easily administered in the outpatient setting, thus enabling the treatment of VTE at home. Several large clinical trials have demonstrated the efficacy and safety of LMWHs for outpatient treatment of DVT and PE, and this approach is commonly utilized in clinical practice.[2,33] Patients with DVT with normal vital signs, low bleeding risk, no other comorbid conditions requiring hospitalization, and who are stable may have anticoagulant initiated at home. Although the treatment of patients with PE

in the outpatient setting is more controversial, patients with submassive PE who are hemodynamically stable can be safely treated in the outpatient setting as well.[12] Patients considered for outpatient therapy must be reliable or have adequate caregiver support and must be able to strictly adhere to the prescribed treatment regimen and recommended follow-up visits. Close patient follow-up is critical to the success of any outpatient DVT treatment program. Home DVT treatment results in cost savings and improved patient satisfaction and quality of life.[2,12,33]

LO 5 Laboratory methods of measuring a patient's response to LMWH may be warranted in certain situations.[9,34] Although controversial, measurement of antifactor Xa activity has been the most widely used method in clinical practice. Monitoring of antifactor Xa activity may be considered in adult patients who are morbidly obese (weight > 150 kg [330 lb] or body mass index [BMI] > 50 kg/m^2), weigh less than 50 kg (110 lb), or have significant renal impairment (CrCl < 30 mL/min [0.50 mL/s]). Laboratory monitoring may also be useful in children, and pregnant women and those on long-term therapy.[34]

As with UFH, bleeding is the major complication associated with LMWHs. The incidence of major bleeding reported in clinical trials is less than 3%.[8,9] Minor bleeding, especially bruising at the injection site, occurs frequently. Protamine sulfate will partially reverse the anticoagulant effects of the LMWHs and should be administered in the event of major bleeding. Due to its limited binding to LMWH chains, protamine only neutralizes 60% of their antithrombotic activity. If the LMWH was administered within the previous 8 hours, give 1 mg protamine sulfate per 1 mg of enoxaparin or 100 antifactor Xa units of dalteparin. If bleeding is not controlled, give another 0.5 mg of protamine sulfate for every antifactor Xa 100 units of LMWH. Give smaller protamine doses if more than 8 hours have lapsed since the last LMWH dose.

The incidence of HIT is lower with LMWHs than with UFH.[9,10] However, LMWHs cross-react with heparin antibodies in vitro and should not be given as an alternative anticoagulant in patients with a diagnosis or history of HIT. Monitor platelet counts every few days during the first 2 weeks and periodically thereafter.

In patients undergoing spinal and epidural anesthesia or spinal puncture, spinal and epidural hematomas have been linked to the use of LMWHs. In patients with in-dwelling epidural catheters, concurrent use of LMWHs and all other agents that impact hemostasis should be avoided. When inserting and removing the in-dwelling epidural catheters, the timing of LMWH administration around catheter manipulation should be carefully coordinated. Catheter manipulation should only occur at minimal or trough anticoagulant levels.[9,10]

LMWHs are an excellent alternative to UFH for the treatment of VTE in pregnant women.[9,20] The LMWHs do not cross the placenta. Because the pharmacokinetics of LMWHs may change during pregnancy, monitoring of antifactor Xa activity every 4 to 6 weeks to make dose adjustments is recommended.[34] LMWHs have also been used to treat VTE in pediatric patients. Children younger than 1 year require higher doses (eg, enoxaparin 1.5 mg/kg SC every 12 hours). Monitor antifactor Xa activity to guide dosing in children.[32]

LO 5

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▶ *Factor Xa Inhibitors*

Parenteral Fondaparinux is an indirect inhibitor of factor Xa and exerts its anticoagulant activity by accelerating AT.[9,35,36] Due to its small size, fondaparinux exerts inhibitory activity specifically against factor Xa and has no effect on thrombin (Figure 10–4). After SC administration, fondaparinux is completely absorbed, and peak plasma concentrations are reached within 2 to 3 hours.[9,35,36] It has a half-life of 17 to 21 hours, permitting once-daily administration, but the anticoagulant effects of fondaparinux will persist for 2 to 4 days after stopping the drug. In patients with renal impairment, the anticoagulant effect persists even longer. Fondaparinux does not require routine coagulation monitoring or dose adjustments.

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Fondaparinux is not metabolized in the liver and therefore has few drug interactions.[9,35,36] However, concurrent use with other antithrombotic agents increases the risk of bleeding. Unlike the heparins, factor Xa inhibitors do not affect platelet function and do not react with the heparin platelet factor (PF)-4 antibodies seen in patients with HIT. Thus, they have a theoretical role in treatment and prevention of HIT. A few small observational studies report fondaparinux use in the management of patients with HIT. Based on these data some centers use fondaparinux in patients with subacute HIT or a history of HIT who require anticoagulation therapy.[9,35,36]

Fondaparinux is as safe and effective as IV UFH for the treatment of PE and SC LMWH for the treatment of DVT.[9,35,36] The recommended dose for fondaparinux in the treatment of VTE is based on the patient's weight (Table 10–8). Fondaparinux is renally eliminated, and accumulation can occur in patients with renal dysfunction. Due to the lack of specific dosing guidelines, fondaparinux is contraindicated in patients with severe renal impairment (CrCl < 30 mL/min [0.50 mL/s]). Baseline renal function should be measured and monitored closely throughout therapy. Based on limited data at this time, monitoring antifactor Xa activity to guide fondaparinux dosing is not recommended.[9,35,36]

LO 5

As with other anticoagulants, the major side effect associated with fondaparinux is bleeding. Fondaparinux should be used with caution in elderly patients because their risk of bleeding is higher. Patients receiving fondaparinux should be carefully monitored for signs and symptoms of bleeding. A CBC should be obtained at baseline and monitored periodically to detect the possibility of occult bleeding. In the event of major bleeding, fresh-frozen plasma and factor concentrates should be given. Fondaparinux is not reversed by protamine.[9,35,36]

LO 5

There are very limited data regarding the use of fondaparinux during pregnancy and its use in pediatric patients has not been studied.[35]

Oral Apixaban, rivaroxaban, edoxaban, and betrixaban are direct inhibitors of factor Xa, part of a newer generation of oral anticoagulants also referred to as direct oral anticoagulants (DOACs).[29,30,36,37] Apixaban and rivaroxaban have been evaluated and approved by the Food and Drug Administration (FDA) for the treatment of VTE (DVT and PE) and reduction in the risk of recurrence of DVT and PE. Edoxaban is also approved for VTE treatment. Rivaroxaban had similar efficacy and safety when compared to traditional therapy with LMWH and a vitamin K antagonist in the treatment of patients with VTE. Apixaban was noninferior in preventing recurrent VTE or VTE-related death but resulted in lower major bleeding events when compared to LMWH and warfarin therapy. Therefore, both agents can be used as monotherapy without parenteral anticoagulation overlap, allowing for a single oral regimen approach in the treatment and prevention of recurrent VTE. Edoxaban was noninferior to warfarin in recurrent VTE and associated with less major or clinically relevant nonmajor bleeding. Unlike the other oral factor Xa inhibitors, edoxaban is initiated after completing 5 to 10 days of initial treatment with a parenteral anticoagulant. See Table 10–13.

Table 10–13

Dosing of the Direct Oral Anticoagulants in the Treatment of Venous Thromboembolism (VTE)

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Acute VTE	150 mg BID after 5–10 days of parenteral anticoagulation	15 mg BID × 3 weeks then 20 mg once daily with food	10 mg BID for 7 days, then 5 mg BID	60 mg once daily
Prevention of VTE recurrence	150 mg BID	20 mg once daily with food	2.5 mg BID	n/a
Dosage adjustments and/or thresholds for avoidance	Any P-gp *inducer*: avoid concurrent use Any P-gp *inhibitor* with CrCl < 50 mL/min (0.83 mL/s): avoid concurrent use CrCl < 30 mL/min (0.50 mL/s): avoid use	CrCl 30–50 mL/min (0.50–0.83 mL/s): use with caution CrCl < 30 mL/min (0.50 mL/s): avoid use	Dual strong CYP3A4 and P-gp inhibitors: If dose > 2.5 mg BID, decrease by 50% If already taking 2.5 mg BID and dual strong CYP3A4 and P-gp inhibitor: avoid use No dose adjustment in renal impairment required	CrCl 15–50 mL/min (0.25–0.83 mL/s) or body weight ≤ 60 kg (132 lb), or concurrent use with certain P-gp inhibitors: 30 mg once daily

CrCl, creatinine clearance; CYP, cytochrome P-450; P-gp, P-glycoprotein.

LO 7

The DOACs inhibit a serine protease single target within the common pathway of the coagulation cascade during the final stages of clot formation. See Figure 10–5. This specificity provides a linear dose response and wider therapeutic index that allows for fixed dosing and precludes the need for routine coagulation monitoring.[4,12,29,30,36,37] Apixaban, rivaroxaban, edoxaban, and betrixaban are competitive, selective, and potent direct inhibitors of factor Xa that bind in a reversible manner to the active site of both free-floating factor Xa and factor Xa within the prothrombinase complex, thereby attenuating thrombin generation. These agents have intrinsic anticoagulant activity, and do not require a cofactor to exert their effect as with UFH and the LMWHs.[4,12,29,30,36,37]

The pharmacokinetic and pharmacodynamic properties of DOACs are significantly different than those of warfarin. See Table 10–14. They have a more rapid onset and offset of action and shorter half-lives compared to warfarin. However, missed doses may be more prone to result in therapeutic complications than longer half-life therapies such as warfarin. They are all eliminated renally to varying degrees (see Table 10–14), and dose adjustment or avoidance in patients with renal impairment may be needed.[4,12,29,30,36,37] See Table 10–13. All DOACs are substrates of the P-gp transport system, and the Xa inhibitors are also substrates of the hepatic cytochrome P-450 (CYP) isoenzyme system. Any inhibition or induction of these metabolic systems will alter their absorption.[38] There are currently no readily available standardized laboratory assays to measure the anticoagulant effect of the DOACs, nor are there currently any FDA-approved specific antidotes to reverse the factor Xa inhibitors. This can cause challenges in situations where rapid

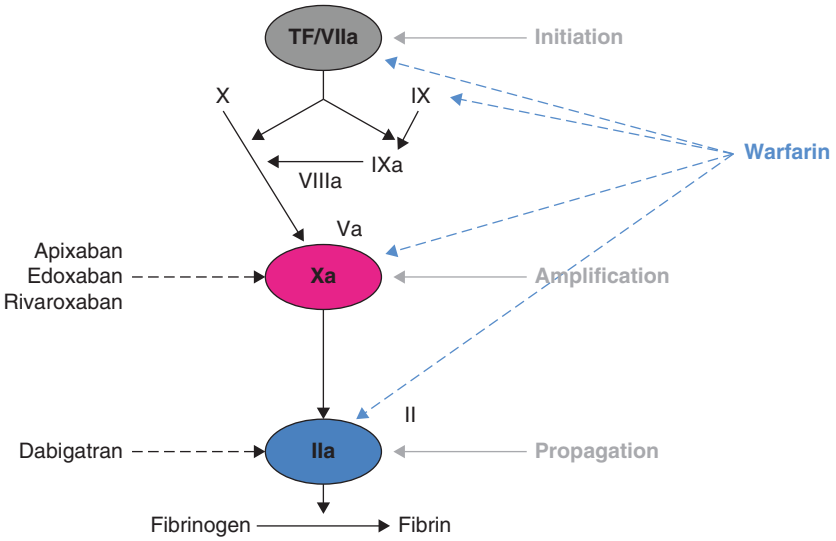

FIGURE 10–5. Mechanism of action of the oral anticoagulants. (TF, tissue factor.) (From Weitz JI, Bates SM. New anticoagulants. J Thromb Haemost. 2005;3:1843–1853.)

Table 10–14

Pharmacologic and Pharmacokinetic Characteristics of Direct Oral Anticoagulants

Property	Apixaban	Dabigatran	Rivaroxaban	Edoxaban	Betrixaban
Mechanism of action	Factor Xa inhibitor	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Bioavailability (%)	50%	3%–7%	80%–100% for 10-mg dose 66% for 20-mg dose[a]	62%	34%
T_{max} (hours)	1–3	1–3	2–4	1–2	3–4
Onset of effect	Within 3 hours	Within 3 hours	Within 4 hours	Within 2 hours	NA
Half-life (hours)	8–15	12–17	5–13	10–14	19–27
Renal excretion	27%	80%	35%	50%	11%
CYP-mediated metabolism	25% CYP3A4/5, CYP2J2 (minor), CYP1A2 (minor)	No	30% CYP3A4/5, CYP2J2 (equal)	CYP3A4	Minor: CYP1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 3A4
Drug transporter	P-gp, BCRP	P-gp	P-gp, BCRP	P-gp	P-gp
Drug–drug interactions	Potent CYP3A4 and P-gp inhibitors; affecting absorption, metabolism, and excretion	Potent P-gp inhibitors; affecting absorption	Potent CYP3A4 and P-gp inhibitors; affecting absorption, metabolism, and excretion	P-gp inducers (eg, rifampin): affecting absorption	P-gp inhibitors: affecting absorption
Food effect	No effect reported	Delayed absorption with food but no influence on bioavailability	Delayed absorption with food with increased (+39%) bioavailability Take with largest meal of the day (usually dinner)	No effect reported	Reduced absorption by 61%–70% (low-fat meal) and 48%–50% (high-fat meal)
Age	Lower clearance as age increases	Lower clearance as age increases	No effect reported	No effect reported	No effect reported
Body weight	Higher exposure with low body weight (< 50 kg [110 lb])	No effect reported	No effect reported	13% higher exposure with median low body weight (55 kg [121 lb]) compared to high body weight (84 kg [185 lb])	NA
Sex	Lower clearance in women	Lower clearance in women	No effect reported	No effect reported	No effect reported
Ethnicity	No effect reported	No effect reported	Lower dose in Japanese patients	No effect reported	NA
Gastrointestinal tolerability	No effect reported	Dyspepsia 5%–10%	No effect reported	No effect reported	No effect reported
Coagulation measurement	Anti-FXa	ECT > dTT	Anti-FXa	Anti-FXa	Anti-FXa

[a]Bioavailability is dependent on food intake for doses > 10 mg. Rivaroxaban doses > 10 mg should be administered with food.

BCRP, breast cancer resistance protein; CYP, cytochrome P-450; dTT, diluted thrombin time; ECT, ecarin clotting time; FXa, factor Xa; P-gp, P-glycoprotein; T_{max}, time to maximum plasma concentration.

reversal of anticoagulation is required such as in cases of major bleeding or need for emergency surgery.[12,29,30,36,37,39] Fresh-frozen plasma, factor concentrates, or recombinant factor VIIa may be given in the event of a major life-threatening bleed.

Apixaban has dual pathways of elimination, with approximately 27% being cleared renally and the remainder eliminated via the fecal route. Elderly, low weight (< 50 kg [110 lb]), and patients with renal impairment can have increased exposure to apixaban, while gender and race do not appear to have clinically relevant influence. Apixaban pharmacokinetics are not significantly altered in patients with mild (Child Pugh A) to moderate (Child Pugh B) hepatic impairment. However, apixaban has not been studied in patients with severe hepatic impairment and is not recommended for use in these patients. There are no adequate studies in pregnant women, and its use during pregnancy is likely to increase bleeding risk. Use in pediatric patients has not been studied.[29]

Apixaban is a substrate of both the CYP 3A4/5 and P-gp systems, and it may be subject to a number of drug interactions (Table 10–15).[29,38] See Tables 10–13, 10–14, and 10–15 for pertinent drug interactions, monitoring, and dosing recommendations.

LO 5

While routine anticoagulation monitoring is not required, there may be clinical scenarios where knowing the patient's degree of anticoagulation may be necessary.[39] A drug-specific chromogenic anti-Xa assay may be used to measure apixaban plasma concentrations; however, this assay is not readily available in most laboratories. Other tests such as the PT, aPTT, and INR are not recommended to assess the anticoagulant effects of apixaban.[29,39] Baseline and periodic patient assessment including

Table 10–15

Drug Interactions and Monitoring Recommendations for Direct Oral Anticoagulants

	Apixaban	Rivaroxaban	Dabigatran	Edoxaban	Betrixaban
Drug interactions	Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (eg, ketoconazole, ritonavir, erythromycin) or reduce apixaban dose Avoid concomitant use with strong dual inducers of CYP3A4 and P-gp (eg, rifampin, phenytoin, carbamazepine) Concomitant use with antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID increases bleeding risk	Avoid concomitant use with strong dual inhibitors of CYP3A4 and P-gp (eg, ketoconazole, ritonavir, erythromycin) Avoid concomitant use with strong dual inducers of CYP3A4 and P-gp (eg, rifampin, phenytoin, carbamazepine) Avoid concomitant use with other anticoagulants	Avoid concomitant use with P-gp inducers (eg, rifampin) P-gp inhibitors and impaired renal function can lead to increased exposure to dabigatran: Avoid concomitant use with severe renal impairment (CrCl < 30 mL/min [0.50 mL/s]) For moderate renal impairment, reduce dose to 75 mg twice daily when used concomitantly with dronedarone or systemic ketoconazole or avoid concomitant use	Avoid concomitant use with P-gp inducers (eg, rifampin) Concomitant use with coagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding.	For concomitant use of P-gp inhibitors (eg, amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin): reduce dose to 80 mg × 1 then 40 mg daily Concomitant use of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding.
Monitoring	Baseline laboratory assessment: Hemoglobin/hematocrit, liver function, renal function, PT/INR At every visit: Adherence, signs/symptoms of bleeding or thromboembolism, side effects, concomitant medications (including over-the-counter) Annual laboratory assessment: Hemoglobin/hematocrit, renal function, liver function If CrCl 30–60 mL/min (0.50–1.0 mL/s), > 75 years, or fragile: renal function every 6 months If CrCl 15–30 mL/min (0.25–0.50 mL/s): renal function every 3 months If condition changes that might impact anticoagulation therapy: check renal and/or liver function				

CrCl, creatinine clearance; CYP, cytochrome P-450; INR, International Normalized Ratio; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein; PT, prothrombin time.

adherence, side effects, and renal and liver function should be conducted (Table 10–15).[40]

Rivaroxaban's bioavailability is dose dependent.[30] At a dose of 10 mg, bioavailability is 80% to 100% and may be taken without regard for food. At higher doses, bioavailability is approximately 66% in the fasted state, which is increased to greater than 80% by food intake. Thus, rivaroxaban 15 mg and 20 mg tablets should be taken with the largest meal of the day. See Table 10–14. Like apixaban, rivaroxaban does not induce or inhibit CYP isoenzymes, but may be affected by medications that are substrates for this enzymatic pathway.[30,38] Rivaroxaban has a dual mode of elimination, with approximately 35% excreted unchanged in the urine and the remaining two-thirds (in the form of inactive metabolites) excreted fairly equally between the renal and hepatobiliary route.[30] Rivaroxaban is a P-gp substrate, not only at the level of gut absorption, but also at the level of elimination in the kidney. Medications that are substrates for the P-gp transport system may impact plasma concentrations of rivaroxaban.[38,40]

While patients with renal impairment can have increased exposure to rivaroxaban, gender, race, age, and extremes of weight (< 50 kg [110 lb] or > 120 kg [265 lb]) have not been shown to significantly impact its pharmacokinetics or pharmacodynamics. Rivaroxaban should be avoided in patients with CrCl less than 30 mL/min (0.50 mL/s) when used in VTE treatment.[30] See Table 10–13. Mild hepatic impairment has minimal impact on the pharmacokinetics and pharmacodynamics of rivaroxaban. Patients with moderate hepatic impairment (Child-Pugh B) have significantly increased exposure to rivaroxaban and its use in patients with severe liver disease has not been studied.[30] There are no well controlled studies in pregnant women and pediatric patients and dosing of rivaroxaban in these patients has not been established.

Rivaroxaban should not be used concomitantly with medications that are dual P-gp and strong CYP3A4 inhibitors or inducers.[38,40] See Table 10–15. Use with weaker combined P-gp and CYP3A4 substrates should be undertaken with caution and only if benefit of use outweighs risk. Concomitant use of rivaroxaban with antiplatelet and nonsteroidal anti-inflammatory agents should be done with extreme caution due to the additive antithrombotic effects and heightened risk of bleeding. As with apixaban, a drug-specific chromogenic anti-Xa assay may be used to measure rivaroxaban activity. Rivaroxaban prolongs the aPTT and PT in a dose-dependent manner, but the PT is more sensitive to rivaroxaban than the aPTT.[29,39,40] Because it is widely available and has a low level of complexity, the PT may be used in a qualitative manner to quickly determine the presence of rivaroxaban. A normal result with most PT reagents would exclude clinically significant anticoagulant activity. The PT and INR are not suitable for measurement of rivaroxaban activity.

LO 5

Edoxaban is 62% orally bioavailable and dose dependent and is 55% bound to plasma protein. Edoxaban undergoes minimal CYP3A4 metabolism, hydrolysis, and conjugation, although an active primary metabolite is formed via hydrolysis

with renal elimination accounting for approximately half of edoxaban elimination. Edoxaban should not be used in those with moderate or severe hepatic impairment (Child-Pugh B and C). Individuals weighing 60 kg (132 lb) or less should receive a reduced dose of 30 mg daily. Similar to apixaban and rivaroxaban, chromogenic antifactor Xa can be considered to evaluate the presence of edoxaban. Edoxoban may affect PT and aPTT, but these measures should not be considered reliable measures of serum concentrations or anticoagulation intensity. Similar to the other DOACs, concomitant use of edoxaban with P-gp inducers, particularly rifampin, should be avoided.[36,39,40]

Betrixaban is 34% orally bioavailable and unlike rivaroxaban, administration with a low or high-fat meal leads to reduced betrixaban exposure. Betrixaban should thus be administered with food. Bextrixaban is mainly excreted through feces (85%), 11% through urine, and 1% metabolized via CYP1A1, 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4. A reduced dose is recommended if severe renal impairment (CrCl 15–30 mL/min [0.25–0.50 mL/s]) or concomitant use of P-gp inhibitors is present. Betrixaban has not been evaluated in the setting of hepatic impairment, and its use in this patient population should be avoided. The recommended duration of treatment for betrixaban is 35 to 42 days.[37]

Reversal agents for oral factor Xa inhibitors are undergoing evaluation and approval.[41] Andexanet alfa, a recombinant modified human factor Xa decoy protein that binds to the active site of factor Xa inhibitors with high affinity thereby preventing DOAC-mediated factor Xa inhibition, has been found to effectively reverse the effects of rivaroxaban and apixaban utilizing DOAC-specific doses. Ciraparantag is a small synthetic molecule that utilizes noncovalent hydrogen bonds and charge–charge interactions to release factor Xa from a DOAC and has been studied with edoxaban use. Ciraparantag has also been proposed as a reversal agent for DTIs, UFH, and LMWH.

▶ *Direct Thrombin Inhibitors*

Given that thrombin is the central mediator of coagulation and amplifies its own production, it is a natural target for pharmacologic intervention.[9,42,43] DTIs bind thrombin and prevent interactions with their substrates (Figure 10–6).

Parenteral Parenteral DTIs are considered the drugs of choice for the treatment of VTE in patients with a diagnosis or history of HIT.[9,42,43] Several injectable DTIs are approved for use in the United States including lepirudin, bivalirudin, argatroban, and desirudin. All have been used to treat thrombosis in patients with HIT, but only lepirudin and argatroban are FDA approved for this indication. However, as of 2012, lepirudin is no longer commercially available in the United States. Data with some of the DTIs (desirudin, bivalirudin) in the treatment of HIT is limited and there are no high-quality studies that directly compare one DTI with another. DTIs differ in terms of their chemical structure, binding to the thrombin molecule and pharmacokinetic profiles. See Table 10–16. Unlike heparins, DTIs do not require AT as a cofactor and do not bind to plasma proteins. Therefore, they produce a more predictable anticoagulant effect. DTIs have a targeted specificity for thrombin, the ability to inactivate clot-bound thrombin, and an absence of platelet interactions that can lead to HIT.[9,42,43]

LO 7

Oral Small molecule DTIs have been structurally modified for oral administration.[42] One agent, dabigatran, is currently approved in the United States for treatment of VTE.[44] Dabigatran was found to be as effective and safe as warfarin in the treatment and prevention of recurrent VTE.[12,44] Like edoxaban, patients should be anticoagulated with UFH or LMWH for the initial 5 to 10 days of therapy and then transitioned to dabigatran for VTE treatment.[2,12,44] See Table 10–13. Similar to other DOACs, dabigatran can be given in fixed doses without the need for routine coagulation monitoring and has a fast onset and offset of action, offering more convenient anticoagulation options for patients and providers.[44]

LO 7

Dabigatran is a direct reversible, competitive inhibitor of thrombin and an oral prodrug of dabigatran etexilate.[42-44] Dabigatran is converted to its active form dabigatran etexilate by serum esterases that are independent of CYP pathways. See Table 10–14. Dabigatran has an oral bioavailability of approximately 3% to 7% and requires an acidic environment for absorption. The prodrug is contained in small pellets coated with an acid core. These pellets are enclosed in a capsule shell. This specific capsule formulation improves the dissolution and absorption of the prodrug, independent of gastric pH. Therefore, the capsules should not be broken, chewed, or opened before administration. Dabigatran demonstrates 35% protein binding and is a substrate of the efflux transporter P-gp. Although the absence of CYP metabolism decreases potential for many drug interactions, coadministration with P-gp substrates, inhibitors, or inducers may affect the efficacy of dabigatran.[38,40] See Table 10–15.

Approximately 80% of dabigatran is eliminated in the urine, and its use is not recommended in the treatment of VTE in patients with a CrCl less than 30 mL/min (0.50 mL/s) due to increased risk of drug exposure and bleeding.[44] Subjects with severe liver disease were excluded from clinical trials of dabigatran. In those with moderate hepatic impairment (Child-Pugh B), the pharmacokinetic profile of dabigatran is not affected. Gender, age, race, or extremes of weight (< 50 kg [110 lb] or > 110 kg [243 lb]) do not significantly impact dabigatran pharmacology.

Dabigatran prolongs the aPTT, PT, thrombin time (TT), and ecarin clotting time (ECT) assays in a dose-dependent manner.[39,44]

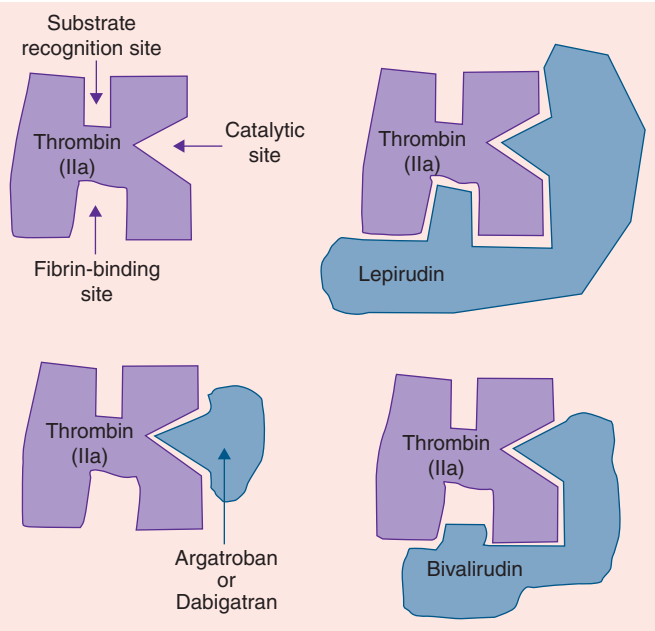

FIGURE 10–6. Mechanism of action of direct thrombin inhibitors. (From Witt DM, Nutescu EA, Haines S. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York, NY: McGraw-Hill; 2011:326.)

Table 10–16

Pharmacologic and Clinical Properties of Direct Thrombin Inhibitors Used in Treatment of Thrombosis in Patients with Heparin-Induced Thrombocytopenia (HIT)

	Lepirudin	Desirudin	Bivalirudin	Argatroban
Route of administration	IV	SC	IV	IV
FDA approved indication	Treatment of thrombosis in patients with HIT	VTE prevention after total hip arthroplasty	Patients with unstable angina undergoing percutaneous transluminal coronary angioplasty; PCI with provisional use of glycoprotein IIb-IIIa inhibitor; patients with or at risk of HIT or HITTS undergoing PCI	Prophylaxis or treatment of thrombosis in adult patients with HIT; patients with or at risk of HIT undergoing PCI
Binding to thrombin	Irreversible Catalytic site and exosite-1	Irreversible Catalytic site and exosite-1	Partially reversible Catalytic site and exosite-1	Reversible Catalytic site
Half-life in healthy subjects	80 minutes	2–3 hours	25 minutes	40–50 minutes
Monitoring	aPTT (IV) SCr/CrCl	aPTT SCr/CrCl	aPTT/ACT SCr/CrCl	aPTT/ACT Liver function
Elimination	Renal	Renal	Enzymatic (80%) and renal (20%)	Hepatobiliary
Antibody development	Anti-hirudin antibodies in up to 40%–60% of patients	Not reported	May cross-react with anti-hirudin antibodies	No
Effect on INR	+	+	++	+++

+ minimal effect

++ moderate effect

+++ significant effect

ACT, activated clotting time; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; FDA, Food and Drug Administration; HITTS, heparin-induced thrombocytopenia and thrombosis syndrome; INR, International Normalized Ratio; IV, intravenous; PCI, percutaneous coronary intervention; SC, subcutaneous; SCr, serum creatinine; VTE, venous thromboembolism.

Peak values greater than 2.5 times control may indicate supratherapeutic levels. A normal aPTT would indicate a lack of clinically relevant anticoagulant activity. The aPTT may be used in a qualitative manner to determine the presence of anticoagulation with dabigatran. It should not be used to quantitate dabigatran plasma concentrations. The PT is relatively insensitive to dabigatran, and the INR is not suitable for measurement of dabigatran due to significant variability. The TT, diluted thrombin time (dTT), and ECT exhibit a linear dose-response with therapeutic dabigatran plasma concentrations. Unfortunately, none of these assays are widely available in practice. It is important to note that quantitative thresholds beyond which a patient would be at increased risk of clotting or bleeding have not been established for any of the DOACs.[39,42,44]

LO 5

Contraindications to the use of DTIs and risk factors for bleeding are similar to those of other antithrombotic agents (Tables 10–11 and 10–12). Bleeding is the most common side effect reported. Concurrent use of DTIs with thrombolytics or antiplatelet agents significantly increases bleeding complications.[41] Idarucizumab, a humanized monoclonal antibody fragment specific to dabigatran and its acyl glucuronide metabolites, binds free and thrombin-bound dabigatran with 350-time higher affinity compared to thrombin and is indicated for dabigatran reversal.[45] Idarucizumab is administered as two consecutive 2.5 gram infusions or as a single bolus 5 gram IV injection. Serious adverse reactions include thromboembolic risk accompanying dabigatran reversal, hypersensitivity reactions, and serious adverse events in those with hereditary fructose intolerance. Fresh-frozen plasma, factor concentrates, or recombinant factor VIIa may also be given in the event of a major life-threatening bleed; however, their efficacy for this use has not been established. DTIs can increase PT/INR and interfere with the accuracy of monitoring and dosing of warfarin therapy. Data on use of DTIs in pregnancy are very limited. Use of DTIs in pediatric patients has not been established.[44]

LO 6

▶ *Warfarin*

KEY CONCEPT Warfarin has been the primary oral anticoagulant used in the United States when long-term or extended anticoagulation is required, but its use is gradually being supplanted in favor of DOACs. Warfarin is FDA approved for prevention and treatment of VTE.[46] Although very effective, warfarin has a narrow therapeutic index, requiring frequent dose adjustments and careful patient monitoring.[4,10,11,46]

Warfarin exerts its anticoagulant effect by inhibiting production of the vitamin K–dependent coagulation factors II (prothrombin), VII, IX, and X, as well as the anticoagulant proteins C and S (Figure 10–7). Warfarin has no effect on circulating coagulation factors that have been previously formed and its therapeutic antithrombotic activity is delayed for 5 to 7 days (potentially longer in slower metabolizers). This delay is related to half-lives of the clotting factors: 60 to 100 hours for factor II (prothrombin), 6 to 8 hours for factor VII, 20 to 30 hours for factor IX, and 24 to

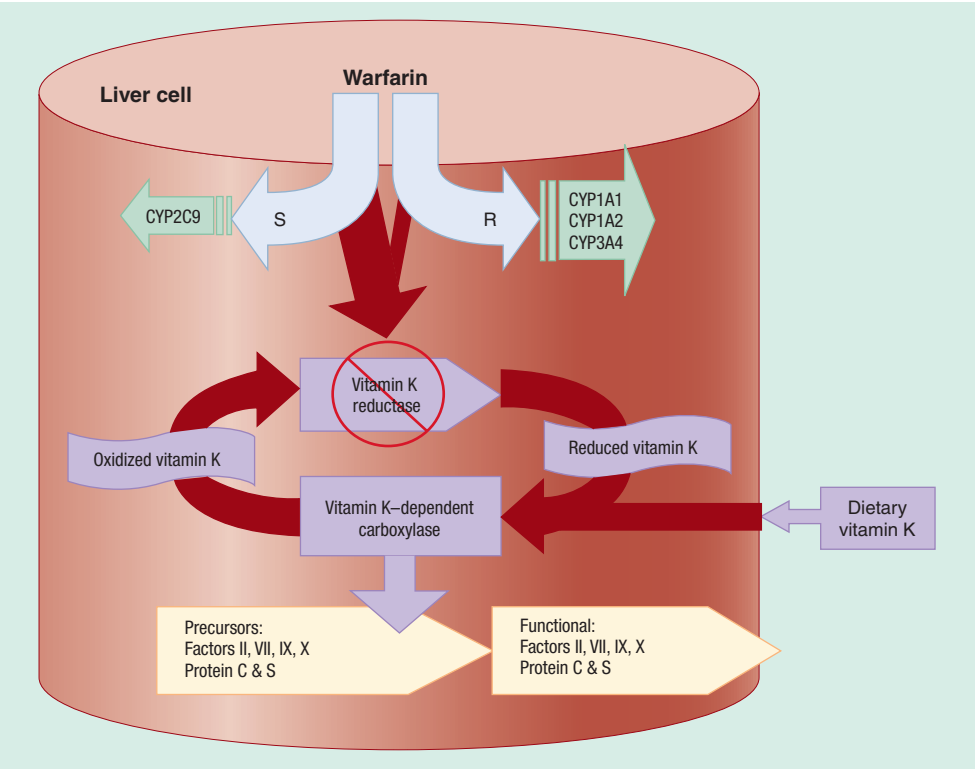

FIGURE 10–7. Pharmacologic activity and metabolism of warfarin. (CYP, cytochrome P-450 isoenzyme.) (From Witt DM, Nutescu EA, Haines S. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York, NY: McGraw-Hill; 2011:328.)

40 hours for factor X. Proteins C and S, the natural anticoagulants, are inhibited more rapidly due to their shorter half-lives, 8 to 10 hours and 40 to 60 hours, respectively. Reductions in the concentration of natural anticoagulants before the clotting factors are depleted can lead to a paradoxical hypercoagulable state during the first few days of warfarin therapy. It is for this reason that patients with acute thrombosis should receive a fast-acting anticoagulant (heparin, LMWH, or fondaparinux) while transitioning to warfarin therapy. The use of DOACs as a bridging agent has not been well evaluated or approved.[4,10,11,46]

Warfarin is metabolized in the liver via several isoenzymes including CYP 1A2, 3A4, 2C9, 2C19, 2C8, and 2C18 (Figure 10–7).[4,10,11,46] Hepatic metabolism of warfarin varies greatly among patients, leading to large interpatient differences in dose requirements and genetic variations in these isoenzymes. Multiple studies have demonstrated that VKORC1 and CYP2C9 genotypes influence the interpatient variability in warfarin dose requirements, together explaining up to 45% of overall dose variance. Several algorithms that incorporate CYP2C9 genotype and VKORC1 haplotype with other patient characteristics to predict warfarin maintenance dosing requirements have been developed and showed efficacy in better predicting warfarin stable doses when compared to clinical algorithms. Based on these data, the FDA recommends incorporating patient's genotype information in guiding warfarin dosing when such information is available.[46] See Table 10–17.[46] Guidelines published by the Clinical Pharmacogenetics Implementation Consortium are available to guide and apply CYP2C9 and VKORC1 genotype result interpretation to warfarin dosing.[47] Although randomized studies to date showed mixed results of pharmacogenomic-based warfarin dosing on clinical and health utilization outcomes, careful analyses of study design and single nucleotide polymorphisms tested in relation to the study patient population are necessary to appropriately interpret the implications and validity of genotype-guided dosing study outcomes. Therefore, pharmacogenomic-based dosing has not yet been widely adopted in clinical practice and some guidelines recommend against routine ordering of preemptive genetic testing.[2,4]

Warfarin displays nonlinear kinetics. Small-dose adjustments can lead to large changes in anticoagulant response.[4,10,11,46] The dose of warfarin is determined by each patient's individual response to therapy and the desired intensity of anticoagulation. In addition to hepatic metabolism and genotype, warfarin dose requirements are influenced by diet, drug–drug interactions, and health status. LO 5 Therefore, warfarin dose must be determined by frequent clinical and laboratory monitoring. Although there are conflicting data regarding the optimal warfarin induction regimen, when the patient's genotype is unknown, most patients can start with 5 mg daily and subsequent doses are determined based on INR response (Figure 10–8). When initiating therapy, it is difficult to predict the precise warfarin maintenance dose a patient will require. Patients who are younger (< 55 years) and otherwise healthy can safely use higher warfarin "initiation" doses (eg, 7.5–10 mg). A more conservative "initiation" dose (eg, 4 mg or less) should be given to patients older than 75 years, patients with heart failure, liver disease, or poor nutritional status, and patients who are taking interacting medications or are at high risk of bleeding. Loading doses of warfarin (eg, 15–20 mg) are not recommended. These large doses can lead to the false impression that a therapeutic INR has been achieved in 2 to 3 days and lead to potential future

Table 10–17

Food and Drug Administration Recommended Warfarin Initial Daily Doses Based on CYP2C9 and VKORC1 Genotypes[46]

	CYP2C9					
VKORC1	***1/*1**	***1/*2**	***1/*3**	***2/*2**	***2/*3**	***3/*3**
GG	5–7 mg	5–7 mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg
AG	5–7 mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg
AA	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg

CYP, cytochrome P450.

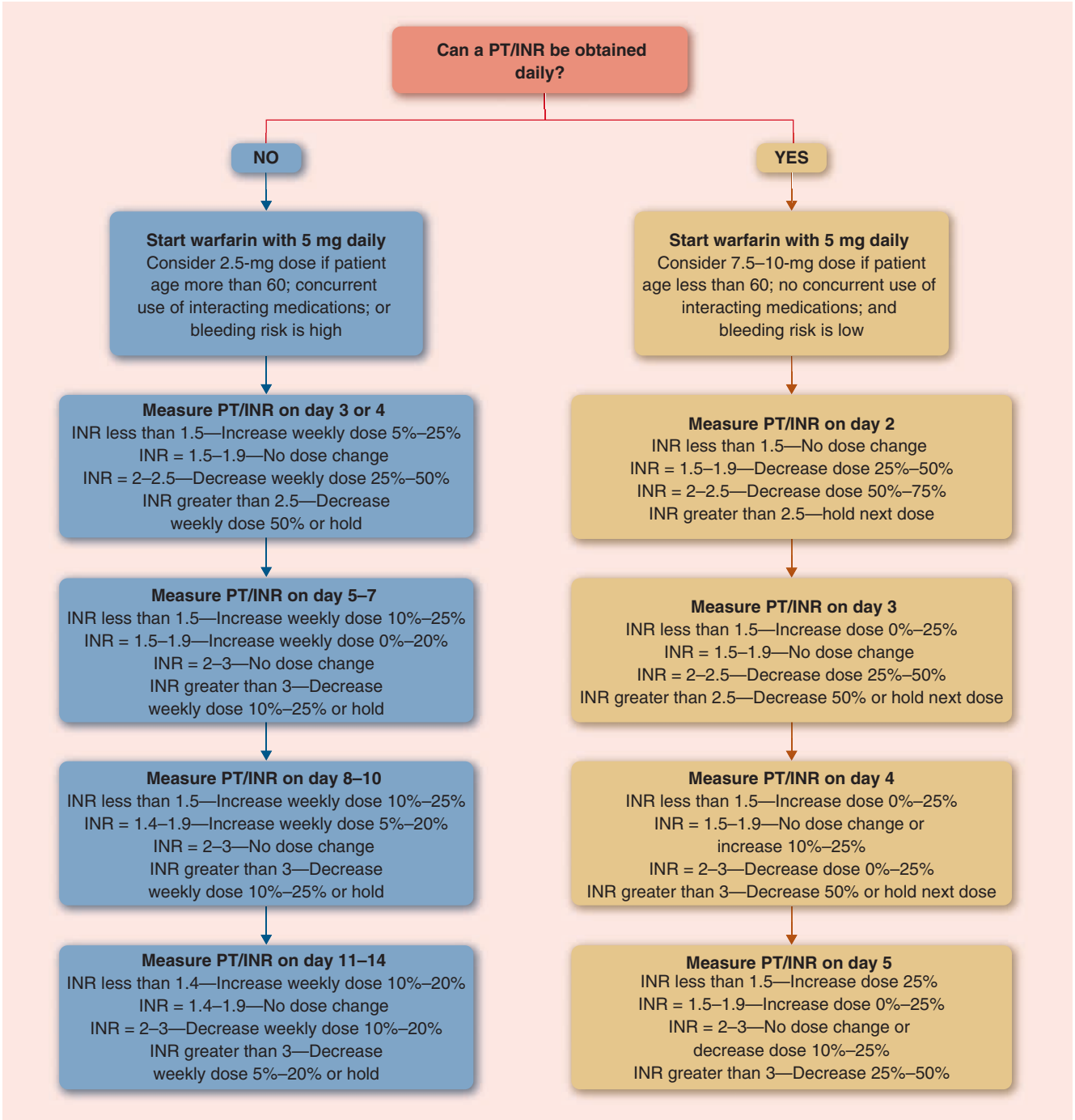

FIGURE 10–8. Initiation of warfarin therapy. (INR, international normalized ratio; PT, prothrombin time.) (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:248.)

Patient Encounter 3, Part 1

A 48-year-old woman presents to the emergency department complaining of shortness of breath, chest pain, and dizziness. She was in a car accident a week ago and injured her left leg. She started having left calf pain approximately 5 days ago and feeling short of breath and experiencing chest pain (7/10) last evening. She could not sleep, and her shortness of breath has gotten progressively worse in the last several hours. She was hospitalized because she was suspected to have a PE.

PMH: Obesity × 20 years; Asthma

FH: Mother died of an MI; paternal grandmother had clots (deep vein thrombosis) in her legs

SH: Full-time bus driver

Current Meds: Albuterol (salbutamol) metered-dose inhaler as needed; Ortho-Tri-Cyclen Lo by mouth daily; Ginseng one to two tablets by mouth daily as needed; multivitamin one tablet by mouth daily

Allergies: NKDA

PE:

VS: BP 104/64 mm Hg, HR 102 beats/min, RR 20 breaths/min, T 38.0°C (100.4°F), Wt 96 kg (211 lb; BMI 35.3 kg/m^2), Ht 65 in (165 cm)

Labs: Within normal limits; eGFR 101 mL/min/1.73 m^2; CrCl 99 mL/min (1.65 mL/s)

Procedures/Tests

ECG: Normal sinus rhythm; no ischemic changes

CXR: Cardiomegaly present

V/Q scan: High probability of PE

What symptoms are consistent with the diagnosis of PE? What are the most likely etiologies for PE in this case?

What are appropriate initial acute phase treatment and long-term and extended treatment options for PE in this patient?

If UFH is chosen as the initial acute phase anticoagulation treatment option for this patient's PE, what is the goal aPTT?

What is patient's goal INR for warfarin therapy?

How long should she remain on anticoagulation therapy?

Given the list of medications the patient took prior to hospitalization, should any of these be discontinued or changed? If changed, what alternative therapy would you recommend?

LO 6 overdosing.[4,10,11,46] Before initiating therapy, screen the patient for any contraindications to anticoagulation therapy and risk factors for major bleeding (Tables 10–11 and 10–12). Conduct a thorough medication history including the use of prescription and nonprescription drugs, and any herbal supplements to detect interactions that may affect warfarin dosing requirements.

In patients with acute VTE, a rapid-acting anticoagulant (UFH, LMWH, or fondaparinux) should be overlapped with warfarin for a minimum of 5 days and until the INR is greater than 2 and stable. This is important because the full antithrombotic effect will not be reached until 5 to 7 days or even longer after initiating warfarin therapy. The typical maintenance dose of warfarin for most patients will be between 25 and 55 mg per week, although some patients require higher or lower doses stemming from their genotype or other clinical factors. Adjustments in the maintenance warfarin dose should be determined based on the total weekly dose and by reducing or increasing the weekly dose by increments of 5% to 25%. When adjusting the maintenance dose, wait at least 7 days to ensure a steady state has been attained on the new dose before checking the INR again. Checking the INR too soon can lead to inappropriate dose adjustments and unstable anticoagulation status.[4,10,11,46]

LO 5 LO 8 KEY CONCEPT Warfarin requires frequent laboratory monitoring to ensure optimal outcomes and minimize complications. PT is the most frequently used test to monitor warfarin's anticoagulant effect. PT measures biological activity of factors II, VII, and X. Due to wide variation in reagent sensitivity, different **thromboplastins** will result in different PT results, potentially leading to inappropriate dosing decisions.[4,10,11,46] To standardize result reporting, the World Health Organization developed a reference thromboplastin and recommended the INR to monitor warfarin therapy. The INR corrects for the differences in thromboplastin reagents. Goal or target INR for each patient is based on the indication for warfarin therapy. For treatment and prevention of VTE, the INR target is 2.5 with an acceptable range of 2 to 3. Before initiating warfarin therapy, a baseline PT/INR and CBC should be obtained. After initiating warfarin therapy, the INR should be monitored at least every 2 to 3 days during the first week of therapy. Once a stable response to therapy is achieved, INR monitoring is performed less frequently, weekly for the first 1 to 2 weeks, then every 2 weeks, and every 4 to 6 weeks thereafter if the warfarin dose and the patient's health status are stable.[4,10,11,46,48] At each encounter, the patient should be carefully questioned regarding any factors that may influence the INR result. These factors include adherence to therapy, the use of interacting medications, consumption of vitamin K-rich foods, alcohol use, and general health status. Patients should also be questioned about symptoms related to bleeding and thromboembolic events. Warfarin dose adjustments should take into account not only the INR result but also patient-related factors that influence the result. Structured anticoagulation therapy management services (anticoagulation clinics) have been demonstrated to improve the efficacy and safety of warfarin therapy. Some patients engage in self-testing and self-management by using a point-of-care PT/INR device approved for home use. Highly motivated and well-trained patients are good candidates for self-testing or self-management.[48]

KEY CONCEPT Similar to other anticoagulants, warfarin's primary side effect is bleeding.[8] Warfarin can unmask an existing lesion. Incidence of warfarin-related bleeding appears to be highest during the first few weeks of therapy. The annual incidence of major bleeding ranges from 1% to 10% depending on the quality of warfarin therapy management. Bleeding in the gastrointestinal tract is most common. Intracranial hemorrhage (ICH) is one of the most serious complications because it often causes severe disability and death. The intensity of anticoagulation therapy is related to bleeding risk. Higher INRs result in higher bleeding risk, and risk of ICH increases when the INR exceeds 4.[4,10,11] Instability and wide fluctuations in the INR are also associated with higher bleeding risk. In cases of warfarin overdose or overanticoagulation, vitamin K may be used to reverse warfarin's effect. Vitamin K can

LO 8

Patient Encounter 3, Part 2

The patient is discharged home on warfarin therapy. She was referred to a local area antithrombosis center for monitoring of her oral anticoagulation therapy and has been maintained on warfarin 6 mg daily for the last 3 months. The patient presents today for a routine visit for anticoagulation monitoring and her INR is 10.5. She reports that 6 days ago she was started on Bactrim DS twice daily, which was prescribed by her primary care physician for a urinary tract infection. In addition, the primary care physician told the patient that her thyroid gland was enlarged and ordered some lab tests to determine if she has a thyroid problem. The patient has not heard what the results are. She also reports that she is trying to lose weight and her intake of vitamin K-rich foods (kale, turnip greens, brussels sprouts) has increased significantly over the last month. She has no other complaints today and denies any signs or symptoms of bleeding.

What is the most likely explanation for elevated INR?

Should she be given vitamin K? If yes, discuss the dose, route of administration, and an appropriate patient monitoring plan.

How will you manage the patient's warfarin therapy? Outline a plan including specific dose changes, timing of monitoring, and patient education.

be given by IV or oral route; the SC route is not recommended as vitamin K is erratically absorbed and frequently ineffective. The IV route is reserved for cases of severe warfarin overdose and when patients are actively bleeding. Anaphylactoid reactions have been reported with rapid IV administration; therefore, slow infusion is recommended. An oral dose of vitamin K will reduce INR within 24 hours. If INR is still elevated after 24 hours, another dose of oral vitamin K can be given. The dose of vitamin K should be based on the degree of INR elevation and whether bleeding is present. A dose of 2.5 to 5 mg orally is recommended when INR is greater than 10 and there is no active bleeding, while a higher dose 5 to 10 mg given via slow IV is recommended in cases when bleeding is present. Higher doses (eg, 10 mg) can lead to prolonged warfarin resistance. In cases of life-threatening bleeding, fresh-frozen plasma or clotting factor concentrates should also be administered, in addition to IV vitamin K. In patients in whom INR is less than 10 and there is no active bleeding or imminent risk of bleeding, simply withholding warfarin until INR decreases to within therapeutic range and reducing the weekly dose with more frequent monitoring is appropriate.[4,10,11,46]

Nonhemorrhagic side effects related to warfarin are rare but can be severe when they occur. Warfarin-induced skin necrosis (incidence < 0.1%) presents as an eggplant-colored skin lesion or a maculopapular rash that can progress to necrotic gangrene. It usually manifests in fatty areas such as the abdomen, buttocks, and breasts, and generally appears during the first week of therapy. Patients with protein C or S deficiency or those who receive large loading doses of warfarin are at greatest risk.[46] The mechanism is thought to be due to imbalances between procoagulant and anticoagulant proteins early in the course of warfarin therapy. Warfarin-induced purple toe syndrome is another rare side effect; patients present with a purplish discoloration of their toes. If these side effects are suspected, warfarin therapy should be discontinued immediately, and an alternative anticoagulant should be started.

Table 10–18

Clinically Significant Drug Interactions with Warfarin

Increase Anticoagulation Effect (↑ INR)	Decrease Anticoagulation Effect (↓ INR)	Increase Bleeding Risk
Acetaminophen	Amobarbital	Argatroban
Acute alcohol ingestion	Butabarbital	Aspirin
Allopurinol	Carbamazepine	Clopidogrel
Amiodarone	Cholestyramine	Danaparoid
Cephalosporins (with MTT side chain)	Chronic alcohol ingestion	Dipyridamole
Chloral hydrate	Dicloxacillin	Low molecular weight heparins
Chloramphenicol	Griseofulvin	Nonsteroidal anti-inflammatory drugs
Cimetidine	Nafcillin	Ticlopidine
Ciprofloxacin	Phenobarbital	Unfractionated heparin
Clofibrate	Phenytoin	
Danazol	Primidone	
Disulfiram	Rifampin	
Doxycycline	Secobarbital	
Erythromycin	Sucralfate	
Fenofibrate	Vitamin K	
Fluconazole		
Fluorouracil		
Fluoxetine		
Fluvoxamine		
Gemfibrozil		
Influenza vaccine		
Isoniazid		
Itraconazole		
Lovastatin		
Metronidazole		
Miconazole		
Moxalactam		
Neomycin		
Norfloxacin		
Ofloxacin		
Omeprazole		
Phenylbutazone		
Piroxicam		
Propafenone		
Propoxyphene		
Quinidine		
Sertraline		
Sulfamethoxazole		
Sulfinpyrazone		
Tamoxifen		
Testosterone		
Vitamin E		
Zafirlukast		

INR, international normalized ratio; MTT, methyl-tetrazole-thiomethyl.

There is a theoretical risk that warfarin may cause accelerated bone loss with long-term use, but to date there is no evidence to support this concern. Warfarin is teratogenic, it should be avoided during pregnancy, and women of childbearing potential should be instructed to use an effective form of contraception.

LO 9 KEY CONCEPT Warfarin is prone to numerous clinically significant drug–drug and drug–food interactions (Tables 10–18, 10–19, and 10–20).[10,11,46] Patients on warfarin should be questioned at every encounter to assess for any potential interactions with foods, drugs, herbal products, and nutritional supplements. When an interacting

Table 10–19

Potential Warfarin Interactions with Herbal and Nutritional Products

Increase Anticoagulation Effect (Increase Bleeding Risk or ↑ INR)		Decrease Anticoagulation Effect (↓ INR)
Amica flower	Ginkgo	Coenzyme Q_{10}
Angelica root	Horse chestnut	Ginseng
Anise	Licorice root	Green tea
Asafoetida	Lovage root	St. John's wort
Bogbean	Meadowsweet	
Borage seed oil	Onion	
Bromelain	Papain	
Capsicum	Parsley	
Celery	Passionflower herb	
Chamomile	Poplar	
Clove	Quassia	
Cranberry	Red clover	
Danshen	Rue	
Devil's claw	Sweet clover	
Dong quai	Turmeric	
Fenugreek	Vitamin E	
Feverfew	Willow bark	
Garlic		
Ginger		

INR, international normalized ratio.

drug is initiated or discontinued, more frequent monitoring should be instituted. In addition, the dose of warfarin can be modified (increased or decreased) in anticipation of the expected impact on the INR.[10,11,46] Warfarin-related drug interactions can generally be divided into two major categories: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions are most commonly due to changes in hepatic metabolism or binding to plasma proteins. Drugs that affect the CYP2C9, CYP3A4, and CYP1A2 have the greatest impact on warfarin metabolism. Interactions that impact the metabolism of the S-isomer result in greater changes in the INR than interactions affecting the R-isomer. Pharmacodynamic drug interactions enhance or diminish the anticoagulant effect of warfarin, increasing the risk of bleeding or clotting, but may not alter the INR. There are increasing reports regarding dietary supplements, nutraceuticals, and vitamins that can interact with warfarin. Patients on warfarin may experience changes in the INR due to fluctuating intake of dietary vitamin K. Patients should be instructed to maintain a consistent diet and avoid large fluctuations in vitamin K intake rather than strictly avoiding vitamin K-rich foods.[4,10,11,46]

Nonpharmacologic Therapy

▶ *Thrombectomy*

Most cases of VTE can be successfully treated with anticoagulation. In some cases, removal of the occluding thrombus by surgical intervention may be warranted. Surgical or mechanical thrombectomy can be considered in patients with massive iliofemoral DVT when there is a risk of limb gangrene due to venous occlusion.[2,12] The procedure can be complicated by recurrence of thrombus formation. In patients who present with massive PE, pulmonary embolectomy can be performed in patients with contraindications to thrombolytic therapy, when thrombolysis has failed clinically, or when thrombolysis will not have sufficient time to take effect. The usual practice is to administer heparin by IV infusion to achieve a therapeutic aPTT during the operation, and postoperatively and thereafter give warfarin for the usual recommended duration.[2,12]

▶ *Inferior Vena Cava Filters*

An inferior vena cava (IVC) filter is indicated in patients with newly diagnosed proximal DVT or PE who have a contraindication to anticoagulation therapy.[2,12] IVC interruption is accomplished

Table 10–20

Vitamin K Content of Select Foods[a]

Very High (> 200 mcg)	High (100–200 mcg)	Medium (50–100 mcg)	Low (< 50 mcg)
Brussels sprouts	Basil	Apple, green	Apple, red
Chickpea	Broccoli	Asparagus	Avocado
Collard greens	Canola oil	Cabbage	Beans
Coriander	Chive	Cauliflower	Breads and grains
Endive	Coleslaw	Mayonnaise	Carrot
Kale	Cucumber (unpeeled)	Pistachios	Celery
Lettuce, red leaf	Green onion/scallion	Squash, summer	Cereal
Parsley	Lettuce, butterhead		Coffee
Spinach	Mustard greens		Corn
Swiss chard	Soybean oil		Cucumber (peeled)
Tea, black			Dairy products
Tea, green			Eggs
Turnip greens			Fruit (varies)
Watercress			Lettuce, iceberg
			Meats, fish, poultry
			Pasta
			Peanuts
			Peas
			Potato
			Rice
			Tomato

[a]Approximate amount of vitamin K per 100 g (3.5 oz) serving.

through minimally invasive means by inserting a filter through the internal jugular vein or femoral vein and advancing it into the IVC using ultrasound or fluoroscopic guidance. One of the risks associated with these filters is development of thrombosis on the filter itself. Therefore, anticoagulation therapy should be resumed as soon as contraindications resolve. Temporary or removable filters are increasingly used, and filters should be removed once therapy is completed.[15]

APPROACH TO TREATING PATIENTS WITH VTE

LO 10

A treatment algorithm for VTE is presented in Figure 10–9. Note that LMWH or fondaparinux are preferred over UFH for acute VTE treatment; however, in patients with CrCl less than 30 mL/min (0.50 mL/s), UFH is the preferred treatment approach. For the long-term and extended treatment phases, DOACs are recommended over warfarin to prevent recurrent thrombosis not associated with a cancer diagnosis. However, in patients with cancer-associated thrombosis, the LMWHs are recommended for the acute, long-term, and extended phases of treatment due to better efficacy in preventing recurrent thromboembolic events.[2,33]

Anticoagulation therapy is continued for a minimum of 3 months but should be given longer depending on the underlying etiology of the VTE, thrombus location, and the patient's risk factors.[2,12] Determining the optimal duration of anticoagulation involves weighing the risk of recurrent VTE against the risk of bleeding associated with anticoagulation therapy and determining patient preference regarding treatment duration. Patients with provoked VTE by transient risk factors (eg, surgery, trauma) or an isolated distally located DVT require therapy for 3 months. Patients with unprovoked VTE have a recurrence risk of at least 10% after 1 year and at least 30% at 5 years, thus most such patients require extended if not indefinite anticoagulation, particularly in those with PE or proximally located DVT and PE, and if the patient carries low to moderate bleeding risk. Patients with low to moderate bleeding risk who have a second unprovoked VTE should receive extended or indefinite anticoagulation and those at high bleeding risk should be treated for three months. Patients who are recommended to receive indefinite anticoagulation should have periodic visits to assess bleeding risk and patient preference/quality of life to determine if anticoagulation should continue.

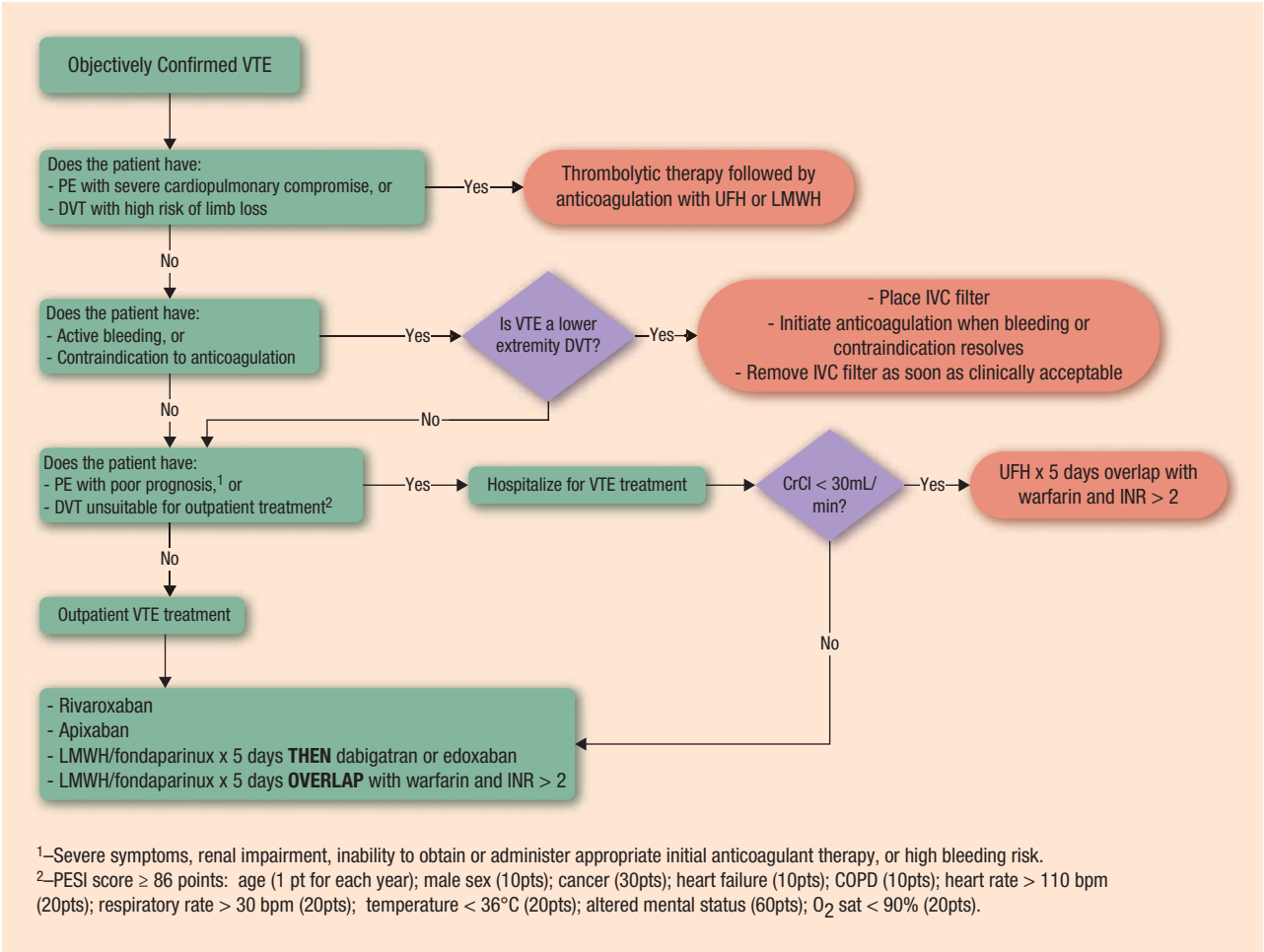

FIGURE 10–9. Treatment of VTE. (bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance [30 mL/min is equivalent to 0.50 mL/s]; DVT, deep vein thrombosis; INR, international normalized ratio; IVC, inferior vena cava; LMWH, low molecular weight heparin; O_2 sat, oxygen saturation [90% is equivalent to 0.90 when expressed as a fraction]; PE, pulmonary embolism; PESI, pulmonary embolism severity index; UFH, unfractionated heparin; VTE, venous thromboembolism.) (From Witt DM, Clark NP, Vazquez SR. Venous thromboembolism. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:240.)

Patient preference should always be a strong consideration when deciding on extended duration anticoagulation.[2,12]

OUTCOME EVALUATION

- KEY CONCEPT Achieve optimal outcomes by: (a) preventing the occurrence of VTE in patients who are at risk, (b) administering effective treatments in a timely manner to patients who develop VTE, (c) preventing treatment-related complications, and (d) reducing the likelihood of long-term complications including recurrent events.
- Given that VTE is often clinically silent and potentially fatal, strategies to increase widespread use of prophylaxis have the

Patient Care Process

Collect Information:

- Obtain and review from the medical record the medical history, family history, social history, physical assessment findings, and laboratory and diagnostic testing results.
- Complete a medication history for use of prescription and nonprescription medications and dietary supplements. Identify any allergies to medications and other substances.
- Interview the patient and review records to identify lifestyle habits such as dietary patterns, alcohol and illicit drug use, smoking status, medication use–related preferences and beliefs, and socioeconomic factors that affect access to medications and health care.

Assess the Information:

- Based on clinical assessment and physical examination, determine whether the patient is experiencing signs or symptoms of VTE (Table 10–1 and Clinical Presentation and Diagnosis of DVT and PE).
- Apply the Wells criteria to determine the probability that the patient's signs, symptoms, and risk factors are the result of DVT and/or PE (Tables 10–2 and 10–3).
- Review relevant laboratory (eg, D-dimer, PT/INR, aPTT, antifactor Xa activity, SCr, CrCl, blood urea nitrogen [BUN], serum albumin, liver function tests, CBC with platelets) and diagnostic tests (eg, venous ultrasound, V/Q, or CT scan). See Clinical Presentation and Diagnosis of DVT and PE.
- Screen for pertinent family history (ie, hypercoagulable disorders, pregnancy loss, DVT, PE).
- Determine if diagnosis of VTE is confirmed based on clinical criteria and/or diagnostic testing.
- Assess whether the VTE is a new or recurrent event and whether the VTE is an idiopathic or triggered event.
- Assess severity of VTE and whether patient is a candidate for outpatient therapy.
- Assess risk of bleeding and check for any contraindications to anticoagulation therapy (Tables 10–6, 10–11, and 10–12).
- Screen dietary and medication profile including over-the-counter medications and herbal therapies used at home for potential drug–drug and drug–food interactions with anticoagulation therapy (Tables 10–15, 10–18, and 10–19).
- If patient is already receiving anticoagulation therapy, assess efficacy, safety, and adherence to therapy.

Develop a Care Plan:

- Once diagnosis of VTE has been confirmed with an objective test, initiate anticoagulation therapy in full therapeutic doses. If there is high clinical suspicion of VTE, anticoagulation therapy may be initiated while waiting for results of diagnostic tests (Figure 10–9).
- Determine the most appropriate anticoagulant therapy and dose options based on patient clinical characteristics, insurance coverage, plans for outpatient therapy, complexity of anticoagulation management, and patient preferences (Tables 10–8, 10–9, 10–10, and 10–13).
- Determine optimal duration of anticoagulation therapy by weighing the risk of recurrent VTE against the risk of bleeding and considering patient preferences regarding treatment duration.

Implement the Care Plan:

- Educate the patient on purpose of therapy and importance of proper monitoring, potential drug–drug and drug–food interactions, dietary consistency with vitamin K-containing foods if treated with warfarin, taking appropriate birth control measures in females, adherence with anticoagulants and with laboratory monitoring, potential side effects, and procedures to follow in case of emergency.
- Address any patient concerns about anticoagulation treatment and its management.
- Devise a structured plan for long-term monitoring of anticoagulation therapy; if treated with warfarin, determine if patient is candidate for anticoagulation self-testing.
- Refer the patient to a specialized anticoagulation monitoring service if available or another designated specialized provider.
- Evaluate patient's medical insurance status and assess coverage level for oral and injectable anticoagulant medications and coverage for follow-up monitoring visits and/or anticoagulation self-testing devices and supplies.

Follow-up: Monitor and Evaluate:

- Follow a structured plan for periodic long-term monitoring of anticoagulation therapy.
- Reevaluate risks and benefits of continuing anticoagulation therapy beyond the initial 3 months; patients who are recommended to receive indefinite anticoagulation should have periodic visits to assess bleeding risk and patient preference/quality of life to determine if anticoagulation should continue.
- Periodically reassess patient adherence, concurrent medications to screen for drug interactions, dietary habits to screen for drug–diet interactions, and renal and liver function tests.
- Monitor the patient to determine if there is worsening or new symptoms related to VTE.
- Evaluate the patient to determine if he/she is experiencing any side effects such as overt bruising or bleeding, as well as changes in stool or urine color.

greatest potential to improve patient outcomes. Thus, relying on early diagnosis and treatment of VTE is unacceptable because many patients will die before treatment can be initiated.

- Effective VTE prophylaxis programs screen all patients admitted to the hospital for VTE risk factors, determine each patient's level of risk, and select and implement prevention strategies that provide sufficient protection for the level of risk.
- Periodically evaluate patients who are receiving VTE prophylaxis for signs and symptoms of DVT, such as swelling, pain, warmth, and redness of lower extremities, and for signs and symptoms of PE, such as chest pain, shortness of breath, palpitations, and hemoptysis.
- Providing effective treatment in a timely manner is the primary goal for patients who develop VTE. Treat DVT and PE quickly and aggressively with effective doses of anticoagulant drugs.
- Short-term aims of therapy are to prevent propagation or local extension of the clot, embolization, and death.
- Regularly monitor patients for development of new symptoms or worsening of existing symptoms.
- All anticoagulant drugs require precise dosing and meticulous monitoring. Closely monitor patients receiving anticoagulant therapy for signs and symptoms of bleeding including epistaxis, hemoptysis, hematuria, hematemesis, bright red blood per rectum, tarry stools, severe headache, and joint pain. If major bleeding occurs, stop therapy immediately and treat the source of bleeding. In addition, closely monitor patients for potential drug–drug and drug–food interactions and adherence with the prescribed regimen.
- Long-term goals of therapy are to prevent complications such as PTS, pulmonary hypertension, and recurrent VTE.
- Continue long-term anticoagulation therapy for an appropriate duration based on etiology of the initial clot and presence of ongoing risk factors.

Abbreviations Introduced in This Chapter

ABW	Adjusted body weight
ACCP	American College of Chest Physicians
ACT	Activated clotting time
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AT	Antithrombin
BCRP	Breast cancer resistance protein
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CBC	Complete blood count
CrCl	Creatinine clearance
CT	Computed tomography
CYP	Cytochrome P-450
DOAC	Direct oral anticoagulant
DTI	Direct thrombin inhibitor
dTT	Diluted thrombin time
DVT	Deep vein thrombosis
ECT	Ecarin clotting time
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FXa	Factor Xa
GCS	Graduated compression stockings
GP	Glycoprotein
HIT	Heparin-induced thrombocytopenia
HITTS	Heparin-induced thrombocytopenia and thrombosis syndrome
IBW	Ideal body weight
ICH	Intracranial hemorrhage
INR	International normalized ratio
IPC	Intermittent pneumatic compression (device)
IV	Intravenous
IVC	Inferior vena cava
LDH	Lactate dehydrogenase
LDUH	Low-dose unfractionated heparin
LMWH	Low molecular weight heparin
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
PAI-1	Plasminogen activator inhibitor-1
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PF	Platelet factor
P-gp	P-glycoprotein
PT	Prothrombin time
PTS	Postthrombotic syndrome
rt-PA	Recombinant tissue plasminogen activator (alteplase)
SCr	Serum creatinine
SBP	Systolic blood pressure
SC	Subcutaneous
SGOT	Serum glutamic-oxaloacetic transaminase
SERM	Selective estrogen receptor modulator
TT	Thrombin time
UFH	Unfractionated heparin
V/Q	Ventilation/perfusion (scan)
VTE	Venous thromboembolism
vWF	von Willebrand factor
WBC	White blood cell

REFERENCES

1. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet. 2012;379(9828):1835–1846.
2. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest. 2016;149(2):315–352.
3. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e351S–e418S.
4. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e44S–e88S.
5. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e278S–e325S.
6. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e227S–e277S.
7. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141 (2 suppl):e195S–e226S.

8. Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th ed. Chest. 2008;133:257S–298S.
9. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141 (2 suppl):e24S–e43S.
10. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e152S–e184S.
11. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th ed. Chest. 2008;133:160S–198S.
12. Wells PS, Forgie MA, Rodger MA. Treatment of venous thromboembolism. JAMA. 2014;311(7):717–728.
13. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). Am J Med. 2014;127(9):829–839.
14. Tagalakis V, Patenaude V, Kahn SR, Suissa S. Incidence of and mortality from venous thromboembolism in a real-world population: the Q-VTE Study Cohort. Am J Med. 2013;126(9):e13–e21.
15. Reitsma PH, Versteeg HH, Middeldorp S. Mechanistic view of risk factors for venous thromboembolism. Arterioscler Thromb Vasc Biol. 2012;32(3):563–568.
16. Kearon C. Natural history of venous thromboembolism. Circulation. 2003;107(23 suppl 1):I22–I30.
17. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008;359(9):938–949.
18. Anderson JA, Weitz JI. Hypercoagulable states. Crit Care Clin. 2011;27(4):933–952, vii.
19. Rosendaal FR, Reitsma PH. Genetics of venous thrombosis. J Thromb Haemost. 2009;7(suppl 1):301–304.
20. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e691S–e736S.
21. Khorana AA. Cancer and coagulation. Am J Hematol. 2012;87(suppl 1):S82–S87.
22. Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. Brit Med J. 2008;336:1227–1231.
23. Aird WC. Coagulation. Crit Care Med. 2005;33:S485–S487.
24. Rijken DC, Lijnen HR. New insights into the molecular mechanisms of the fibrinolytic system. J Thromb Haemost. 2009;7(1):4–13.
25. Wells PS. Integrated strategies for the diagnosis of venous thromboembolism. J Thromb Haemost. 2007;5(suppl 1):41–50.
26. Sinert R, Foley M. Clinical assessment of the patient with a suspected pulmonary embolism. Ann Emerg Med. 2008;52:76–79.
27. Bauersachs RM. Clinical presentation of deep vein thrombosis and pulmonary embolism. Best Pract Res Clin Haematol. 2012;25(3):243–251.
28. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. N Engl J Med. 2016;375:534–554.
29. Apixaban Prescribing Information. Bristol-Myers Squibb Company, Princeton, NJ; April 2017. Available from: https://packageinserts.bms.com/pi/pi_eliquis.pdf. Accessed September 1, 2017.
30. Rivaroxaban Prescribing Information. Janssen Pharmaceuticals, Inc, Titusville, NJ; March 2017. Available from: https://www.xarelto-us.com/shared/product/xarelto/prescribing-information.pdf. Accessed September 1, 2017.
31. Watson LI, Armon MP. Thrombolysis for acute deep vein thrombosis. Cochrane Database Syst Rev. 2004:CD002783.
32. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e737S–e801S.
33. Segal JB, Streiff MB, Hofmann LV, et al. Management of venous thromboembolism: a systematic review for a practice guideline. Ann Intern Med. 2007;146(3):211–222.
34. Nutescu EA, Spinler SA, Wittkowsky AK, Dager WE. Low molecular weight heparins in renal impairment and obesity: available evidence and clinical practice recommendations across medical and surgical settings. Ann Pharmacother. 2009;43(6):1064–1083.
35. Arixtra [Prescribing Information]. GlaxoSmithKline. August 2009. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021345s019lbl.pdf Accessed October 29, 2017.
36. Savaysa [Prescribing Information]. Daiichi Sankyo Co, Inc., Parsippany, NJ; September 2016. Available from: http://dsi.com/prescribing-information portlet/getPIContent?productName=Savaysa&inline=true. Accessed September 1, 2017.
37. Bevyxxa [Prescribing Information]. Portola Pharmaceuticals, Inc, South San Francisco, CA; June 2017. Available from: http://www.bevyxxa.com/docs/Bevyxxa-Full-Prescribing-Information.pdf. Accessed September 1, 2017.
38. Nutescu E, Chuatrisorn I, Hellenbart E. Drug and dietary interactions of warfarin and novel oral anticoagulants: an update. J Thromb Thrombolysis. 2011;31(3):326–343.
39. Cuker A, Siegal DM, Crowther MA, Garcia DA. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants. J Am Coll Cardiol. 2017;64:1128–1139.
40. Heidbuchel H, Verhamme P, Alings M, et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2013;15(5):625–651.
41. Rogers KC, Shelton MP, Finks SW. Reversal agents for direct oral anticoagulants: understanding new and upcoming options. Cardiol Rev. 2016;24:310–315.
42. Weitz JI, Eikelboom JW, Samama MM. New antithrombotic drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl): e120S–e51S.
43. Nutescu EA, Shapiro NL, Chevalier A. New anticoagulant agents: direct thrombin inhibitors. Cardiol Clin. 2008;26(2):169–187.
44. Pradaxa [Prescribing Information]. Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT; July 2017. Available from: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. Accessed September 1, 2017.
45. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373:511–520.
46. Coumadin [Prescribing Information]. Bristol-Myers Squibb, Princeton, NJ; August 2017. Available from: http://packageinserts.bms.com/pi/pi_coumadin.pdf. Accessed September 1, 2017.
47. Johnson JA, Caudle KE, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther. 2017;102(3):397–404.
48. Garcia DA, Witt DM, Hylek E, et al. Delivery of optimized anticoagulant therapy: consensus statement from the Anticoagulation Forum. Ann Pharmacother. 2008;42(7): 979–988.

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11 Stroke

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LEARNING OBJECTIVES

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

LO

1. Differentiate types of cerebrovascular disease including transient ischemic attack (TIA), ischemic stroke (cerebral infarction), and hemorrhagic stroke.
2. Identify modifiable and nonmodifiable risk factors associated with ischemic stroke and hemorrhagic stroke.
3. Explain the pathophysiology of ischemic stroke and hemorrhagic stroke.
4. Describe the clinical presentation of TIA, ischemic stroke, and hemorrhagic stroke.
5. Formulate strategies for primary prevention of acute ischemic stroke.
6. Evaluate treatment options for acute ischemic stroke.
7. Determine whether fibrinolytic therapy is indicated in a patient with acute ischemic stroke.
8. Formulate strategies for secondary prevention of acute ischemic stroke.
9. Evaluate treatment options for acute hemorrhagic stroke.

INTRODUCTION

Cerebrovascular disease, or stroke, is the second most common cause of death worldwide, and is the fifth leading cause of death in the United States. Stroke can be either ischemic or hemorrhagic and is an acute medical emergency. Rapid treatment dependent on the type of stroke is critical. Treatment of risk factors and preventive measures are also paramount in the management of stroke. Decades of progress in treatment and prevention of stroke have resulted in a decrease in both stroke incidence and stroke case fatality rates.[1] Stroke mortality rates are higher in women than men and geographic variability exists, with higher mortality rates observed in the Southeastern United States, termed the "stroke belt."

EPIDEMIOLOGY

Approximately 795,000 strokes occur in the United States each year. New strokes account for 610,000 of this total; recurrent strokes account for the remaining 185,000. Stroke incidence increases with age, especially after age 55 years, resulting in an increased incidence in the elderly population.[2] Stroke is the leading cause of long-term disability in adults, with 90% of survivors having residual deficits. Moderate to severe disability is seen in 70% of survivors and 15% to 30% of stroke survivors are permanently disabled. The American Heart Association estimates there are currently over 7 million stroke survivors in the United States. Societal impact and economic burden is great, with total costs of $33.9 billion reported in the United States in 2013.

ETIOLOGY AND CLASSIFICATION

Strokes can either be ischemic (87% of all strokes) or hemorrhagic (13% of all strokes). KEY CONCEPT Ischemic stroke, which may be thrombotic or embolic, is the abrupt development of a focal neurological deficit that occurs due to inadequate blood supply to an area of the brain. A thrombotic occlusion occurs when a **thrombus** forms inside an artery in the brain. An embolic stroke typically occurs when a piece of thrombus, originating either inside or outside of the cerebral vessels, breaks loose and is carried to the site of occlusion in the cerebral vessels. An extracerebral source of emboli is often the heart, leading to cardioembolic stroke.

KEY CONCEPT Hemorrhagic stroke is a result of bleeding into the brain and other spaces within the central nervous system (CNS) and includes subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), and subdural **hematomas**. SAH results from sudden bleeding into the space between the inner and middle layers of the meninges, most often due to trauma or rupture of a cerebral **aneurysm** or **arteriovenous malformation** (AVM). ICH is bleeding directly into the brain parenchyma, often as a result of chronic uncontrolled hypertension. Subdural hematomas result from bleeding under the dura that covers the brain and most often occur as a result of head trauma. For hemorrhagic events associated with stroke, refer to the Clinical Presentation and Diagnosis of Stroke textbox.

Cerebral Ischemic Events

LO 1

There are two main classifications of cerebral ischemic events: transient ischemic attack (TIA) and ischemic stroke (cerebral infarction). A TIA is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. TIAs have a rapid onset and short duration, typically lasting less than 1 hour and often less than 30 minutes. The symptoms vary depending on the area of the brain affected; however, no deficit remains after the attack.[3] KEY CONCEPT TIAs are

a risk factor for acute ischemic stroke, preceding acute ischemic stroke in approximately 15% of cases; therefore, preventive measures are the same for both TIA and ischemic stroke.[4]

LO1 Ischemic stroke is similar to TIA; however, tissue injury and infarction are present, and in many patients, residual deficits remain after the event. A standardized tissue-based definition of cerebral infarction has been established defining cerebral infarction as brain, spinal cord, or retinal cell death attributable to ischemia, based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.[5]

Risk Factors

Assessment of risk factors for ischemic stroke and hemorrhagic stroke is an important component of stroke prevention, diagnosis, and treatment. Major goals in the long-term management of ischemic stroke involve primary prevention (prevention of first stroke) and secondary prevention (prevention of a recurrent stroke). Risk factors for ischemic stroke are divided into modifiable and nonmodifiable (Table 11–1). Hypertension is one of the major risk factors for both ischemic and hemorrhagic stroke. Other risk factors for hemorrhagic stroke include trauma, cigarette smoking, cocaine use, heavy alcohol use, anticoagulant use, and cerebral aneurysm and AVM rupture.[6,7] Every patient should have risk factors assessed and treated, if possible, because management can decrease the occurrence and/or recurrence of stroke.[6,8]

LO2

Table 11–1

Nonmodifiable and Modifiable Risk Factors for Ischemic Stroke

Nonmodifiable Risk Factors
- Age (> 55 years)
- Gender (males more than females)
- Race and ethnicity (American Indian/Alaska Natives, African American, Asian/Pacific Islander, Hispanic)
- Genetic predisposition
- Low birth weight

Well Documented and Modifiable Risk Factors
- Hypertension (most important risk factor)
- Cardiac disease
  - Atrial fibrillation (most important and treatable cardiac cause of stroke)
  - Mitral stenosis
  - Mitral annular calcification
  - Left atrial enlargement
  - Structural abnormalities such as atrial-septal aneurysm
  - Acute myocardial infarction
- Transient ischemic attacks or prior stroke (major independent risk factor)
- Diabetes (independent risk factor)
- Dyslipidemia
- Asymptomatic carotid stenosis
- Oral contraceptive use (with estrogen content > 50 mcg)
- Postmenopausal hormone therapy
- Sickle cell disease
- Lifestyle factors
  - Cigarette smoking
  - Excessive alcohol use
  - Physical inactivity
  - Obesity
  - Diet
  - Cocaine and intravenous drug use
  - Low socioeconomic status

Less Well Documented or Potentially Modifiable Risk Factors
- Increased hematocrit
- Metabolic syndrome
- Hyperhomocysteinemia
- Migraine (risk not clear)
- Sleep disordered breathing (ie, sleep apnea)

PATHOPHYSIOLOGY

Ischemic Stroke

LO3 In ischemic stroke, there is an interruption of the blood supply to an area of the brain either due to thrombus formation or an embolism. Loss of cerebral blood flow results in tissue hypoperfusion, tissue hypoxia, and cell death. Thrombus formation usually starts with lipid deposits in the vessel wall that cause turbulent blood flow. This leads to vessel injury and vessel collagen becoming exposed to blood. This vessel injury initiates the platelet aggregation process due to the exposed subendothelium. Platelets release adenosine diphosphate (ADP), which causes platelet aggregation and consolidation of the platelet plug. Thromboxane A_2 is released, contributing to platelet aggregation and vasoconstriction. The vessel injury also activates the coagulation cascade, which leads to thrombin production. Thrombin converts fibrinogen to fibrin, leading to clot formation as fibrin molecules, platelets, and blood cells aggregate. Refer to Figures 7–3, 10–3, and 10–4 for a depiction of these processes.

After the initial event, secondary events occur at the cellular level that contribute to cell death. Regardless of the initiating event, the cellular processes that follow may be similar. Excitatory amino acids such as glutamate accumulate within the cells, causing intracellular calcium accumulation. Inflammation occurs and oxygen free radicals are formed resulting in the common pathway of cell death.

There is often a core of ischemia containing unsalvageable brain cells. Surrounding this core is an area termed the **ischemic penumbra**. In this area, cells are still salvageable; however, this is time-sensitive. Without restoration of adequate perfusion, cell death continues throughout a larger area of the brain, ultimately leading to neurological deficits.

Hemorrhagic Stroke

LO3 The pathophysiology of hemorrhagic stroke is not as well studied as that of ischemic stroke; however, it is more complex than previously thought. Much of the process is related to the presence of blood in the brain tissue and/or surrounding spaces resulting in compression. The hematoma that forms may continue to grow and enlarge after the initial bleed, and early growth is associated with a poor outcome. Brain tissue swelling and injury is a result of inflammation caused by thrombin and other blood products. This can lead to increased intracranial pressure (ICP) and **herniation**.[7] Delayed cerebral ischemia, or vasospasm, is a potential consequence of aneurysmal SAH that results in vasoconstriction of cerebral vessels and clinical symptoms of ischemia.

PRIMARY PREVENTION OF ISCHEMIC STROKE

Aspirin

LO5 Use of aspirin (ASA) in patients with no history of stroke or ischemic heart disease reduced the incidence of nonfatal myocardial infarction (MI) but not stroke. Primary prevention guidelines recommend ASA for general cardiovascular prophylaxis (not specific to stroke) in men and women with a

Clinical Presentation and Diagnosis of Stroke

General

- Patient may not be able to reliably report history due to cognitive or language deficits. A reliable history may have to come from a family member or another witness.

Symptoms of Ischemic Stroke

LO 4

- The patient may complain of weakness on one side of the body, inability to speak, loss of vision, vertigo, headache, or falling.

Signs of Ischemic Stroke

- Patients usually have multiple signs of neurologic dysfunction, and specific deficits are determined by the area of the brain involved.
- Hemiparesis or monoparesis occur commonly, as does a hemisensory deficit.
- Patients with vertigo and double vision are likely to have posterior circulation involvement.
- Aphasia is seen commonly in patients with anterior circulation strokes.
- Patients may also suffer from dysarthria, visual field defects, and altered levels of consciousness.

Signs and Symptoms of Hemorrhagic Stroke

- A sudden severe headache, nausea, vomiting, and photophobia may be the first signs and symptoms. Patients may complain the headache is "the worst headache of my life."
- Neck pain and nuchal rigidity (stiffness) may also be experienced.

**It is important to note that a diagnosis of type of stroke cannot be made solely on signs and symptoms because overlap occurs between types of stroke.

Laboratory Tests

- There are no specific laboratory tests for stroke.
- Tests for hypercoagulable states, such as protein C deficiency and antiphospholipid antibody, should be done only when cause of stroke cannot be determined based on presence of well-known risk factors.

Other Diagnostic Tests

- Computed tomography (CT) scan of the head will reveal an area of hyperintensity (white) identifying that a hemorrhage has occurred. CT scan will either be normal or hypointense (dark) in an area where an infarction has occurred. It may take 24 hours (and rarely longer) to reveal the area of infarction on a CT scan.
- Magnetic resonance imaging (MRI) of the head will reveal areas of ischemia earlier and with better resolution than a CT scan. Diffusion-weighted imaging can reveal an evolving infarct within minutes.
- Carotid Doppler studies will determine whether the patient has a high degree of stenosis (blockage of an artery) in the carotid arteries, which are the vessels that supply blood to the brain (extracranial disease).
- Electrocardiogram (ECG) will determine whether the patient has atrial fibrillation (AF), a major risk factor for cardioembolic stroke.
- Transthoracic echocardiogram will identify whether there are heart valve abnormalities or problems with wall motion of the heart resulting in emboli to the brain.

10-year cardiovascular risk of greater than 10% and in women who are at high risk for stroke. ASA may be considered for prevention of a first stroke in patients with chronic kidney disease, and cilostazol may be considered for prevention of a first stroke in patients with peripheral arterial disease. The benefits must be weighed against the risk of major bleeding. Due to lack of benefit observed in clinical trials, ASA is not recommended for primary prevention in patients with diabetes and asymptomatic peripheral arterial disease, or in those at low risk.[8]

Patient Encounter Part 1

An 83-year-old, 86.4 kg (190 lb), 5'4" (163 cm) white woman presents to the emergency department with weakness in her left arm and difficulty "getting the words out." She was last seen well by her neighbor approximately 3 hours prior to her neighbor noticing her symptoms. Her neighbor called 911 immediately after observing her symptoms. Her past medical history is significant for hypertension, dyslipidemia, and a previous stroke 3 years ago. She has experienced transient ischemic attacks in the past and has had two TIAs in the past week. Social history includes alcohol use of 3 to 4 drinks per week and obesity. Current medications include perindopril 4 mg once daily, atorvastatin 20 mg daily, aspirin 81 mg daily, and a multivitamin tablet once daily.

What signs and symptoms does the patient have that are suggestive of stroke?

What nonmodifiable and modifiable risk factors does she have for acute ischemic stroke?

▶ *Diabetes*

LO 5

Diabetes is an independent risk factor for stroke. Intensive glycemic control has not been shown to reduce stroke risk in either type 1 or type 2 diabetes mellitus. Adequate control of blood pressure (BP) to a target level of less than 130/80 mm Hg and management of dyslipidemia are recommended in individuals with diabetes. The use of a statin is also recommended to prevent a first stroke.[8,9] Hypertension guidelines recommend initial therapy that includes a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACE-I), or angiotensin receptor blocker (ARB).[9] The guidelines suggest that in black patients with diabetes, initial antihypertensive therapy should include a thiazide-type diuretic or a CCB.[9]

▶ *Dyslipidemia*

LO 5

Clinical studies have found a relationship between total cholesterol levels and stroke rate. Statin use, in addition to lifestyle modifications, is recommended for primary prevention

of ischemic stroke in patients estimated to have a high 10-year risk of cardiovascular events.[8] Treatment recommendations are based on current guidelines for treatment of blood cholesterol.[10] The benefit of other lipid-lowering therapies on stroke risk has not been established.[8]

▶ *Hypertension*

LO 5

Hypertension is the most important and well-documented risk factor for stroke. Lowering BP in hypertensive patients reduces the relative risk of both ischemic and hemorrhagic stroke. All patients should have BP monitored and controlled appropriately based on current guidelines for BP management released by the American College of Cardiology/American Heart Association in 2017.[9] In patients without cardiovascular disease (CVD), treatment with BP-lowering medications is recommended in patients with an estimated 10-year atherosclerotic CVD (ASCVD) risk of 10% or greater and systolic blood pressure (SBP) greater than or equal to 130 mm Hg or diastolic blood pressure (DBP) greater than or equal to 80 mm Hg, or in those patients with an estimated 10-year ASCVD risk less than 10% and an SBP greater than or equal to 140 mm Hg or a DBP greater than or equal to 90 mm Hg.[9] A recent meta-analysis of multiple trials found that more intensive BP lowering reduced the risk of stroke by 20% over a less-intensive BP-lowering strategy.[11] Many patients require two or more drug therapies to achieve BP control. For primary prevention of stroke, reduction in BP is the main goal because one antihypertensive agent has not been clearly shown to be more beneficial than any other. Refer to Chapter 5, "Hypertension."

▶ *Smoking Cessation*

LO 5

The relationship between smoking and both ischemic and hemorrhagic stroke is clear. Smoking status should be assessed at every patient visit. Patients should be assisted and encouraged in smoking cessation as stroke risk after cessation declines over time. Effective treatment options are available including counseling, nicotine replacement products, and oral agents.

▶ *Other Treatments*

A number of other disease states and lifestyle factors should be addressed as primary prevention of stroke. AF is an important and well-documented risk for stroke. See Chapter 9, "Arrhythmias," for information on stroke prevention in AF. Asymptomatic carotid stenosis, cardiac disease, sickle cell disease, obesity, excessive alcohol use, and physical inactivity are other risks that should be assessed and managed appropriately.

TREATMENT

Desired Outcomes

The short-term treatment goals for acute ischemic stroke include reducing secondary brain damage by reestablishing and maintaining adequate perfusion to marginally ischemic areas of the brain and protecting these areas from the effects of ischemia (ie, neuroprotection). KEY CONCEPT Long-term treatment goals for acute ischemic stroke include prevention of a recurrent stroke through reduction and modification of risk factors and by use of appropriate treatments.

Short-term treatment goals for hemorrhagic stroke include rapid neurointensive care to maintain adequate oxygenation, breathing, and circulation. Management of increased ICP and BP are important in the acute setting. Long-term management includes prevention of complications and of a recurrent bleed and delayed cerebral ischemia. Prevention of long-term disability and death related to stroke is important regardless of stroke type.

General Approach

KEY CONCEPT All patients should have a brain CT or MRI scan to differentiate an ischemic stroke from a hemorrhagic stroke because treatment differs and fibrinolytic therapy must be avoided until hemorrhagic stroke is ruled out. A CT or MRI scan is the most important initial diagnostic test in patients with acute stroke. For those with an ischemic stroke, an evaluation should be done to determine the appropriateness of reperfusion therapy. In hemorrhagic stroke, a surgical evaluation should be completed to assess the need for surgical clipping of an aneurysm or other procedure to control the bleeding and prevent rebleeding and other complications. Figure 11–1 provides an algorithm for initial management of the acute stroke patient.

Early Management of Acute Ischemic Stroke

Acute ischemic stroke is a medical emergency. Identification of the time of symptom onset and symptom presentation are important determinants in treatment. The time the patient was last without symptoms is used as the time of stroke onset. Because patients typically do not experience pain, determining the onset time can be difficult. It is also important to document risk factors, previous functional status, and the National Institutes of Health Stroke Scale (NIHSS) to assess stroke severity and current disability due to stroke. The NIHSS is a 42-point scale that quantifies neurological deficits in stroke patients. It is easy to perform and is used as a measure of daily functioning.

▶ *Supportive Measures*

LO 6

Acute complications of ischemic stroke include cerebral edema, increased ICP, seizures, and hemorrhagic conversion (ie, conversion of ischemic stroke into a hemorrhagic stroke). In the acute setting, supportive interventions and treatments to prevent acute complications should be initiated. Continuous cardiac monitoring, most commonly with a Holter monitor, should be continued for the first 24 hours to screen for AF and other cardiac diseases. Improved AF detection rates have been seen with extended monitoring times.[12] Tissue oxygenation should be maintained acutely. Measure the oxygen saturation using pulse oximetry and supplement the patient with oxygen if necessary. Oxygen saturation should be maintained at 94% (0.94) or greater.[13] Volume status and electrolytes should be corrected. If required, blood glucose should be corrected because both hyperglycemia and hypoglycemia may worsen brain ischemia. When blood glucose less than 60 mg/dL (3.3 mmol/L) is present, bolus with 25 mL of 50% dextrose immediately. Patients with elevated blood glucose poststroke have been documented to have worse outcomes; therefore, lowering blood glucose to between 140 and 180 mg/dL (7.8–10.0 mmol/L) with subcutaneous insulin is a reasonable approach.[14,15] If the patient is febrile, treat with acetaminophen because fever is associated with brain ischemia and increased morbidity and mortality after stroke. Alternatively, cooling devices can be used.[14,16] Low-dose unfractionated heparin (UFH) or low-dose low molecular weight heparin (LMWH) administered subcutaneously significantly decrease the risk of developing venous thromboembolism (VTE) poststroke. Low-dose UFH or LMWH should be initiated for VTE prophylaxis in patients who are not candidates for intravenous (IV) fibrinolytic therapy. In patients receiving fibrinolytic therapy, VTE prophylaxis with low-dose UFH or LMWH should be delayed until 24 hours after fibrinolytic administration to avoid bleeding complications.

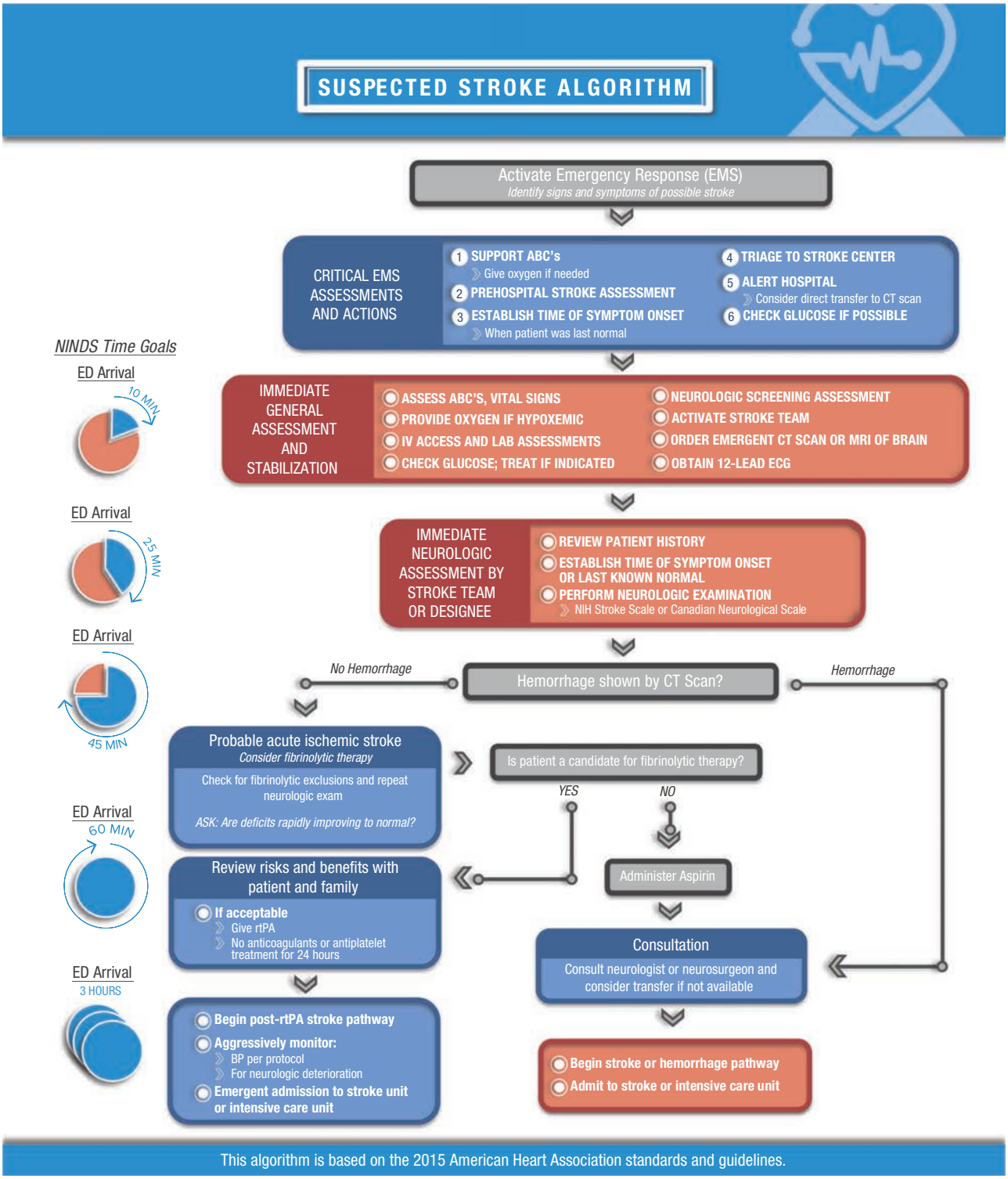

FIGURE 11–1. Suspected stroke treatment algorithm. (ABC, airway, breathing, and circulation; BP, blood pressure; CT, computed tomography; ECG, electrocardiogram; ED, emergency department; EMS, emergency medical services; IV, intravenous; MRI, magnetic resonance imaging; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke; rtPA, alteplase.) (Reproduced with permission from Professional Medical Certifications. Suspected Stroke Algorithm. © 2018 Professional Medical Certifications. Available at https://promedcert.com/acls-algorithms/algorithm-acls-suspected-stroke.)

In the setting of acute ischemic stroke, up to 80% of patients have an elevated BP in the first 24 to 48 hours.[9] BP should be checked three times with each reading taken 5 minutes apart.

BP should be optimized; however, hypertension should generally not be treated in the acute period (12–24 hours) because it may cause decreased blood flow in ischemic areas, potentially increasing the infarction size. The cautious use of antihypertensive medications may be necessary in patients with severely elevated BP (SBP > 220 mm Hg or DBP > 120 mm Hg) who are otherwise candidates for fibrinolytic therapy. Antihypertensive therapy may also be used in patients with stroke and other medical disorders, including aortic aneurysm

Table 11–2

Blood Pressure (BP) Recommendations for Ischemic Stroke (Eligible for Alteplase)

Before treatment: If systolic BP > 185 mm Hg or diastolic BP > 110 mm Hg	May use either labetalol 10–20 mg IV over 1–2 minutes (may repeat after 10 minutes) or nicardipine infusion 5 mg/hour (titrate up by 2.5 mg/hour every 5–15 minutes; maximum dose 15 mg/hour) or may consider other agents (hydralazine, enalaprilat)
During and after treatment to maintain BP ≤ 180/105 mm Hg:	
If systolic BP > 180–230 mm Hg or diastolic BP > 105–120 mm Hg	Use either labetalol 10 mg IV over 1–2 minutes followed by labetalol infusion 2–8 mg/min or nicardipine infusion 5 mg/hour (titrate up by 2.5 mg/hour every 5–15 minutes; maximum dose 15 mg/hour)
If BP not controlled or diastolic BP > 140 mm Hg	Nitroprusside 0.3–0.5 mcg/kg/min titrated by 0.5 mcg/kg/min to response; maximum dose 10 mcg/kg/min

IV, intravenous.

rupture, MI and heart failure, requiring immediate lowering of BP. Tables 11–2 and 11–3 provide recommendations on BP management in those eligible and not eligible for fibrinolytic therapy. In those not eligible for fibrinolytic therapy, if BP reduction is necessary, aim for a 15% reduction in SBP and DBP in the first 24 hours after stroke onset.

▶ *Fibrinolytic Therapy*

Alteplase American Stroke Association guidelines recommend alteplase (rt-PA; Activase) as the only Food and Drug Administration (FDA)-approved acute treatment for ischemic stroke and strongly encourage early diagnosis and treatment of appropriate patients.[14] Alteplase is an IV fibrinolytic that was approved for acute ischemic stroke treatment within 3 hours of symptom onset based on the results of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial.[17] Patients treated with alteplase were 30% more likely to have minimal or no disability at 3 months. Alteplase treatment resulted in an 11% to 13% absolute increase in patients with excellent outcomes at 3 months, independent of patient age, stroke subtype, stroke severity, or prior use of ASA.[18] ICH within 36 hours after stroke onset occurred in 6.4% of those given alteplase versus 0.6% in those given placebo. There was no significant difference in mortality between the two groups at 3 months or 1 year. A dose of 0.9 mg/kg (maximum 90 mg) is recommended; the first 10% is given as an IV bolus, and the remainder is infused over 1 hour.

Subsequent studies that followed the NINDS trial protocol have supported alteplase use in acute ischemic stroke and have shown similar rates for both response and ICH occurrence. When clinical trials are pooled, study results show that the sooner alteplase is given after onset of stroke symptoms, the greater the benefit seen in neurological outcome.[18-20] Alteplase has been shown to provide a benefit when administered from 3 to 4.5 hours after stroke onset in select patients. Additional exclusion criteria for alteplase use between 3 and 4.5 hours after symptom onset include age greater than 80, use of oral anticoagulants regardless of international normalized ratio (INR), NIHSS greater than 25, and the combination of stroke and diabetes.[20,21] KEY CONCEPT

LO 7 Current guidelines recommend alteplase use within 3 hours after stroke onset in appropriate patients and within 3 to 4.5 hours in patients meeting additional criteria. The guidelines recommend that alteplase be started as soon as possible within this window of time.[14,18,21] A **door-to-needle** time of 60 minutes is recommended. Alteplase is commonly withheld in patients with minor or rapidly improving stroke symptoms and in patients with stroke symptoms upon awakening. As many as one-third of patients with minor stroke may go on to have a poor outcome.[22] Although a recent observational study demonstrated a benefit to alteplase treatment in minor stroke, further research is underway in an effort to improve outcomes after ischemic stroke.[23,24] Table 11–4 LO 7 details the inclusion and exclusion criteria for administration of alteplase in acute ischemic stroke.

Efficacy is measured by elimination of existing neurological deficits and long-term improvement in neurological status and functioning based on neurological examinations and other outcome measures. BP measurements and neurological examinations should be completed every 15 minutes during and after the infusion of alteplase for 2 hours, every 30 minutes for the next 6 hours, and then every hour until 24 hours after alteplase administration. Patients should be assessed using the NIHSS at baseline and 24 hours after the administration of alteplase.

The major adverse effects of fibrinolytic therapy are bleeding, including ICH and serious systemic bleeding. Mental status changes and a severe headache may indicate ICH. Signs of systemic bleeding include easy bruising; hematemesis; guaiac-positive stools; black, tarry stools; hematoma formation; hematuria; bleeding gums; and nosebleeds. Angioedema is a potential side effect that may cause airway obstruction.

Antiplatelet agents, anticoagulants, and invasive procedures such as insertion of a central line, placement of a nasogastric tube, and bladder catheterization should be avoided for 24 hours after infusion of alteplase to prevent bleeding complications. A CT scan should be obtained 24 hours after IV infusion of alteplase before initiating anticoagulants or antiplatelet agents.

Other Fibrinolytics Aside from alteplase, no other fibrinolytics are FDA indicated for use in acute ischemic stroke. Trials evaluating streptokinase were stopped early due to a high

Table 11–3

Blood Pressure (BP) Recommendations for Ischemic Stroke (Not Eligible for Alteplase)

Systolic BP < 220 mm Hg and diastolic BP < 120 mm Hg	Observe unless other end-organ involvement
Systolic BP > 220 mm Hg or diastolic BP 121–140 mm Hg	Labetalol 10–20 mg IV over 1–2 minutes (may repeat every 10–20 minutes; maximum dose 300 mg) or nicardipine infusion 5 mg/hour titrated to response
Diastolic BP > 140 mm Hg	Nitroprusside 0.3–0.5 mcg/kg/min titrated by 0.5 mcg/kg/min to response; maximum dose 10 mcg/kg/min

IV, intravenous.

Table 11–4

Inclusion and Exclusion Criteria for Alteplase (rt-PA) Use in Acute Ischemic Stroke

Inclusion Criteria
- 18 years of age or older
- Clinical diagnosis of ischemic stroke causing a measurable neurological deficit
- Time of symptom onset well established to be < 4.5 hours before treatment would begin

Exclusion Criteria
- Evidence of multilobar infarction on CT scan of the brain (> 1/3 cerebral hemisphere) prior to treatment
- Clinical presentation suggestive of SAH even with a normal head CT
- Active internal bleeding
- Known bleeding diathesis, including but not limited to: (a) platelet count less than $100 \times 10^3/mm^3$ ($100 \times 10^9/L$); (b) heparin within 48 hours with an elevated aPTT; or (c) current oral anticoagulant use (eg, warfarin) or recent use with an elevated PT (> 15 seconds) or INR (> 1.7)
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration < 50 mg/dL (2.8 mmol/L)
- Recent intracranial or intraspinal surgery, significant head trauma, or previous stroke within 3 months
- Recent arterial puncture at a noncompressible site in previous 7 days
- Lumbar puncture within 7 days
- History of previous intracranial hemorrhage
- Intracranial neoplasm, known AVM or aneurysm
- SBP > 185 mm Hg or DBP > 110 mm Hg at time of treatment, or patient requires aggressive treatment to reduce BP to within these limits

Relative Exclusion Criteria
- Consider risk to benefit of IV rt-PA if any relative contraindications are present:
  - Only minor or rapidly improving stroke symptoms
  - Pregnancy
  - Witnessed seizure at onset of stroke symptoms with postictal residual neurological impairments
  - Major surgery or serious trauma within 14 days
  - Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
  - Recent acute MI (within previous 3 months)

Additional Exclusion Criteria for Treatment Between 3 and 4.5 Hours
- Age > 80 years
- Use of oral anticoagulants regardless of INR
- NIHSS > 25
- Combination of ischemic stroke and diabetes

aPTT, activated partial thromboplastin time; AVM, arteriovenous malformation; BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; ECT, ecarin clotting time; INR, international normalized ratio; IV, intravenous; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; PT, prothrombin time; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; TT, thrombin time.

incidence of hemorrhage in streptokinase-treated patients. Desmoteplase has not demonstrated a clinical benefit when administered 3 to 9 hours after stroke onset.[25] Tenecteplase has demonstrated positive initial results. Trials evaluating extended treatment windows with tenecteplase and in comparison to alteplase are currently ongoing.[14,24] Fibrinolytic agents other than alteplase and the defibrinogenating agents are not recommended for treatment unless associated with a clinical trial.[14]

Intraarterial Fibrinolytics Early clinical trials evaluating intraarterial (IA) fibrinolytics evaluated pro-urokinase (r-pro UK) with heparin or heparin alone within 6 hours of symptom onset. Results from the first trial were not statistically significant, whereas results of the second trial showed a statistically significant benefit to r-pro UK.[26] Pro-urokinase is not FDA-approved for acute stroke treatment and is not available in the United States; however, this early work paved the way for continued advancements in acute stroke treatment. Progress has been made utilizing IA fibrinolytic therapy with alteplase administered via a catheter into the affected cerebral artery combined with embolectomy devices (ie, **endovascular** therapy) to remove the clot. Three randomized clinical trials comparing IA alteplase, first-generation embolectomy devices (ie, coil retrievers or aspiration devices using suction) or a combination to IV alteplase did not demonstrate a benefit.[27] Use of IA fibrinolytics without endovascular therapy is not recommended as first-line therapy in patients with acute ischemic stroke.[27]

Patient Encounter Part 2

The patient arrives in the emergency department 4 hours after the onset of her symptoms. In the emergency department, an IV line is placed, a physical and neurological examination is completed, and she is moved to the stroke unit. A head CT scan is negative for hemorrhagic stroke and reveals a diffuse hypodensity on the right. Her BP on admission to the stroke unit is 182/104 mm Hg. The patient denies other exclusions to IV alteplase. The neurologist is evaluating her for alteplase administration.

Identify your acute treatment goals for the patient.

Is she a candidate for IV alteplase at this time?

What acute management would be appropriate for the patient in the stroke unit?

▶ *Heparin*

Full-dose IV UFH has been previously used in acute stroke therapy; however, no adequately designed trials have been conducted to establish its efficacy and safety. Current acute ischemic stroke treatment guidelines do not recommend routine, urgent full-dose anticoagulation with UFH due to lack of a proven benefit in improving neurological function and the risk of intracranial bleeding.[14,18,28] The major complications of heparin include conversion of ischemic stroke into hemorrhagic stroke, bleeding, and thrombocytopenia. Occurrence of severe headache and mental status changes may indicate ICH. Signs of bleeding mirror those listed for alteplase therapy.

▶ *LMWHs and Heparinoids*

Full-dose LMWHs and heparinoids are not recommended in the treatment of acute ischemic stroke.[14,18,29] Studies with these agents have generally been negative, with no convincing evidence of improved outcomes after ischemic stroke. Increased risks of bleeding complications and hemorrhagic transformation have been observed.

▶ *Thrombin Inhibitors*

Several thrombin inhibitors have been approved for stroke prevention in patients with AF and may have a potential benefit in acute stroke treatment. Currently, use of these agents in acute stroke treatment is not well established, and it is recommended that their use be in conjunction with a clinical trial.[14] One recent clinical trial evaluated the use of dabigatran within 24 hours of stroke onset to prevent early stroke recurrence in patients without AF.[30] Further clinical trials are needed to establish the role of these agents in the acute setting.

▶ *Antiplatelet Agents*

ASA use in acute ischemic stroke has been studied in two large randomized trials. Patients who received ASA within 48 hours of onset of acute ischemic stroke symptoms were less likely to suffer early recurrent stroke, death, and disability. KEY CONCEPT ASA therapy with an initial dose of 160 to 325 mg is recommended in most patients with acute ischemic stroke within 24 to 48 hours after stroke symptom onset. ASA dose may then be decreased to 75 to 100 mg daily to reduce bleeding complications.[18] Administration should not replace other acute stroke treatments and should be delayed for 24 hours in patients receiving alteplase. In minor stroke or TIA, ASA plus clopidogrel has been compared to ASA alone started within 24 hours of stroke onset. Patients in the combination group demonstrated a reduced risk of recurrent stroke up to the 1-year follow-up.[31]

▶ *Nonpharmacologic Therapy*

Carotid Endarterectomy It is not well established whether carotid endarterectomy (CEA; removal of a thrombus from the carotid artery) is of value when performed emergently or urgently after stroke, meaning within the first 24 hours after symptom onset.[14] Recent trials have concluded that patients with TIA or mild to moderate stable stroke undergoing CEA within 48 hours may have an acceptable surgical risk. However, patients with unstable neurological status and more severe strokes demonstrated worse outcomes.[14,32] More research is needed to delineate the role of CEA in acute treatment.

Endovascular Treatment A focused update of the current stroke treatment guidelines was recently published to provide guidelines on the role of endovascular therapy in acute ischemic stroke.[27] These guidelines provide additional data on the safety and efficacy of endovascular therapy based on the results of recent clinical trials. IV alteplase should not be withheld if indicated, even if endovascular treatments are being considered. The majority of patients in these trials received IV alteplase initially followed by endovascular therapy. Patients meeting specific criteria should receive endovascular therapy, with new-generation **stent retrievers** preferred over the coil retriever and aspiration devices. Stent retrievers provide immediate restoration of blood flow through expansion of the stent at the site of occlusion and clot removal as the stent is removed. Criteria include a prestroke modified Rankin Score of 0 to 1, IV alteplase use within 4.5 hours of symptom onset, age 18 years and older, causative occlusion of the internal carotid artery or proximal middle cerebral artery, NIHSS score of 6 or greater, Alberta Stroke Program Early CT (ASPECT) score 6 or greater, and treatment within 6 hours of symptom onset. Endovascular therapy using stent retrievers plus standard care with IV alteplase, when appropriate, may improve outcomes in select patients with acute ischemic stroke due to large vessel occlusion, if administered within 6 hours of symptom onset. More rapid endovascular treatment has also shown better clinical outcomes.[27]

Secondary Prevention Following an Ischemic Stroke

Secondary prevention is aimed at preventing another stroke in patients that have had an initial stroke and is an important component of treatment. Once the acute ischemic stroke has been managed, typically within the first 24 to 48 hours after symptom onset, the focus shifts to secondary prevention and developing plans to prevent another stroke and manage risk factors. Antiplatelet and anticoagulant agents should be held for 24 hours following alteplase administration.

▶ *Nonpharmacologic Therapy*

LO 8

Carotid Endarterectomy The benefit of CEA for prevention of recurrent stroke has been studied in major clinical trials including a meta-analysis.[33,34] CEA is recommended to prevent **ipsilateral** stroke in patients with symptomatic carotid artery stenosis of 70% or greater when the surgical risk is less than 6%. In patients with symptomatic stenosis of 50% to 69%, a moderate reduction in risk is seen in clinical trials. CEA is recommended when anesthesia risk is low based on patient factors including age, sex, and comorbidities, and surgical risk is less than 6%. CEA is not beneficial for symptomatic carotid stenosis less than 50% and should not be considered in these patients. Patients with asymptomatic carotid artery stenosis of 70% or more may benefit from CEA if surgical complication rates for stroke, MI, and death are low.[35]

LO 8

Carotid Angioplasty Carotid angioplasty with **stenting** has evolved as a less invasive procedure with shorter recovery times for appropriate patients. Several trials have compared carotid angioplasty with stenting to CEA in symptomatic patients. Carotid angioplasty with stenting is an alternative to CEA in high-risk surgical candidates with greater than 50% stenosis by angiography and greater than 70% stenosis by noninvasive imaging when performed by skilled clinicians.[10] Age is an important factor when deciding between carotid angioplasty with stenting and CEA. Patients older than 70 years may have improved outcomes with CEA compared to carotid angioplasty with stenting. In patients younger than 70 years, CEA and carotid angioplasty with stenting have similar risks for stroke, MI, and death and also similar rates for ipsilateral stroke.[36]

▶ *Pharmacologic Therapy*

LO 8

Aspirin ASA decreases risk of subsequent stroke by approximately 22% in both men and women with previous TIA or stroke.[37] Therefore, ASA is an option for initial therapy for secondary prevention of ischemic stroke. A wide range of doses have been used (50–1500 mg/day); however, the FDA has approved doses of 50 to 325 mg for secondary ischemic stroke prevention. Current guidelines recommend varying ASA doses including 75 to 100 mg daily and 50 to 325 mg daily.[18,36] Lower ASA doses are currently recommended to decrease the risk of bleeding complications.[18] Adverse effects of ASA include gastrointestinal (GI) intolerance, GI bleeding, and hypersensitivity reactions.

Clopidogrel Clopidogrel is slightly more effective than ASA and similar in efficacy to the combination of extended-release (ER) dipyridamole plus ASA.[38,39] The usual dose is 75 mg orally taken once daily. There have been 11 case reports of **thrombotic thrombocytopenic purpura** (TTP) occurring secondary to clopidogrel. Most occurred within the first 2 weeks of therapy; therefore, clinicians need to be aware of the potential for the development of TTP with clopidogrel. Proton pump inhibitors may decrease the effectiveness of clopidogrel. An H_2-blocker

may be preferred in patients who require both acid suppression and clopidogrel.[40] Patients with a genetic variant of cytochrome P450 (CYP) 2C19 classified as poor metabolizers may have a decrease in the active metabolite of clopidogrel, potentially requiring increased doses.[41] Clopidogrel is an option for initial monotherapy for secondary prevention of ischemic stroke and is considered first-line therapy in patients who also have peripheral arterial disease or are allergic to ASA.

LO 8

Extended-Release Dipyridamole Plus Aspirin Combination therapy with ER dipyridamole plus ASA has been found to be more effective in preventing stroke than either agent alone.[42] Headache and diarrhea were common adverse effects of dipyridamole; bleeding was more common in all treatment groups that included ASA. A trial comparing the combination of ER dipyridamole plus ASA to clopidogrel found no difference in outcomes; however, adverse events occurred more frequently in the combination of ER dipyridamole plus ASA group.[38] The currently available formulation is a combination product containing 25 mg ASA and 200 mg ER dipyridamole. This combination is an option for initial therapy for secondary stroke prevention, but is not appropriate for patients who are intolerant to ASA.

LO 8

Current Clinical Trials Clinical trials have been completed to evaluate other combinations of antiplatelet agents and to compare them against one another. Low-dose ASA plus clopidogrel combination therapy did not show a significant benefit in reducing recurrent stroke compared with clopidogrel alone and increased the risk of major bleeding.[43]

More recently, two trials have evaluated early initiation (within 24 hours) of the combination of ASA and clopidogrel and its effect in the months following a TIA or minor stroke.[44,45] One trial demonstrated a trend toward a reduction in ischemic events; however, the trial was stopped early due to low enrollment.[44] The second trial demonstrated a reduced risk of stroke in the first 90 days after stroke onset in the combination group compared to ASA alone. Based on this trial, the combination of ASA and clopidogrel may be considered within 24 hours of a TIA or minor stroke and continued for 90 days.[45] Continuation beyond 90 days is not recommended due to an increased risk of hemorrhage and lack of benefits as seen in other trials.[43]

Summary of Antiplatelet Therapy for Secondary Stroke Prevention KEY CONCEPT Current stroke treatment guidelines recommend ASA or combination therapy with ER dipyridamole plus ASA as initial antiplatelet therapy for the secondary prevention of stroke. Clopidogrel is another option for initial treatment and is recommended in patients unable to tolerate ASA and those with peripheral arterial disease.[18,36] Initial choice of agent should be individualized based on patient factors and cost. Therapeutic failure in this patient population is challenging because no data are available to guide a treatment decision. When a patient is on therapeutic doses of ASA, yet experiences a recurrent TIA or stroke, switching to either clopidogrel or the combination of ER dipyridamole and ASA is a reasonable option. If failure occurs on either clopidogrel or the combination of ASA and ER dipyridamole, switching to the alternate drug may be appropriate.

Oral Anticoagulants Recent clinical trials have not found oral anticoagulation to be better than antiplatelet therapy in those patients without AF or carotid stenosis. In patients without AF, antiplatelet therapy is recommended over oral anticoagulants for secondary prevention of stroke. On the other hand, patients with AF and a previous TIA or stroke have the highest risk of recurrent stroke. Long-term anticoagulation with warfarin or other newer agents is effective and therefore recommended in the primary and secondary prevention of cardioembolic stroke.[18,36] The newer oral anticoagulants have only been studied for stroke prevention in nonvalvular AF. The goal INR when monitoring warfarin for this indication is 2 to 3. Refer to Chapter 9, "Arrhythmias," for more information on stroke prevention in AF.

Patient Encounter Part 3

The patient has been in the ICU for 24 hours and is still experiencing weakness in her left arm and continues to have difficulty speaking at times. She will be transferred out of the stroke unit and admitted to a medicine floor for medical management and discharge planning.

What treatments would you recommend to reduce the risk of another stroke in the next 24–48 hours?

What treatments would you recommend at discharge to reduce the risk of another stroke?

▶ *Blood Pressure Management*

Hypertension is a major risk factor for stroke, and BP control is an important strategy for secondary stroke prevention. Current stroke guidelines and the 2017 hypertension guidelines recommend initiation of antihypertensive treatment for untreated patients with TIA or stroke and an established BP of 140/90 mm Hg or greater. Patients previously treated with antihypertensives should be reinitiated on therapy several days after acute ischemic stroke. The optimal regimen to achieve the BP goal has not been established. Diuretics, either alone or in combination with an ACE-I, have been shown to be beneficial in reducing stroke recurrence.[9,36]

▶ *Other Recommendations*

Management of diabetes and lipids based on treatment guidelines, cessation of smoking, increased physical activity, and reducing alcohol use in heavy drinkers are additional recommendations for management of patients with previous stroke or TIA.[36] Statin therapy is recommended in patients with previous stroke or TIA, regardless of history of coronary heart disease. Table 11–5 provides drug and dosing recommendations for treatment of ischemic stroke.

Treatment of Acute Hemorrhagic Stroke

▶ *Supportive Measures*

Acute hemorrhagic stroke is considered to be a medical emergency due to ICH, SAH, or subdural hematoma. Initially, patients experiencing a hemorrhagic stroke should be transported to a neurointensive care unit. KEY CONCEPT There is no proven treatment for ICH. Management is based on neurointensive care treatment and prevention of complications. Treatment should be provided to manage the needs of the critically ill patient including management of increased ICP, seizures, infections, and prevention of rebleeding and delayed cerebral ischemia. In those with severely depressed consciousness, rapid endotracheal intubation and mechanical ventilation may be necessary. BP is often elevated after hemorrhagic stroke; appropriate management is important to prevent rebleeding and expansion of the hematoma. In patients presenting with SBP greater than 220 mm Hg, BP lowering using

LO 9

Table 11–5

Recommendations for Pharmacotherapy of Ischemic Stroke

	Primary Agents	Alternatives
Acute treatment	Alteplase 0.9 mg/kg IV (maximum dose 90 mg); 10% as IV bolus, remainder infused over 1 hour in select patients within 4.5 hours of onset	Alteplase (various doses) intraarterially within 6 hours after onset in select patients
	ASA 160–325 mg started within 48 hours of onset; hold for 24 hours if alteplase given (may reduce dose to 50–100 mg daily after 48 hours)	If minor stroke or TIA, ASA 75 mg plus clopidogrel 75 mg daily started within 24 hours of onset
Secondary prevention (noncardioembolic stroke)	ASA 50–325 mg daily ASA 25 mg + ER dipyridamole 200 mg twice daily	Clopidogrel 75 mg daily
Cardioembolic	Warfarin (INR 2–3) Dabigatran 150 mg twice daily; decrease to 75 mg twice daily if creatinine clearance is 15–30 mL/min (0.25–0.50 mL/s) Apixaban 5 mg twice daily; decrease to 2.5 mg twice daily if patient has at least two of the following: age ≥ 80 years, weight ≤ 60 kg (132 lb) or serum creatinine ≥ 1.5 mg/dL (133 µmol/L)	Rivaroxaban 20 mg daily with the evening meal; decrease to 15 mg daily with the evening meal if creatinine clearance 15–50 mL/min (0.25–0.83 mL/s)
All patients	BP control Statin therapy	

ASA, aspirin; BP, blood pressure; ER, extended-release; INR, international normalized ratio; IV, intravenous; TIA, transient ischemic attack.

continuous IV infusion is recommended.[9,46] When SBP is between 150 and 220 mm Hg, lowering of the SBP to less than 140 mm Hg does not improve outcomes and may cause harm compared to a less aggressive BP-lowering goal in the acute period.[9,47] BP can be controlled with IV boluses of labetalol 10 to 80 mg every 10 minutes up to a maximum of 300 mg or with IV infusions of labetalol (0.5–2 mg/min) or nicardipine (5–15 mg/hour). Deep vein thrombosis prophylaxis with intermittent compression stockings should be implemented early after admission. In those patients with SAH, once the aneurysm has been treated, heparin may be instituted. In ICH patients with lack of mobility after 1 to 4 days, heparin or LMWH may be started.[46,48]

► *Nonpharmacologic Therapy*

LO 9

Patients with hemorrhagic stroke are evaluated for surgical treatment of SAH and ICH. In SAH, either clipping of the aneurysm or coil embolization is recommended within 72 hours after the initial event to prevent rebleeding. Coil embolization, also called coiling, is a minimally invasive procedure in which a platinum coil is threaded into the aneurysm. The flexible coil fills up the space to block blood flow into the aneurysm thereby preventing rebleeding. Surgical removal of the hematoma in patients with ICH is controversial because trials have not consistently shown improved outcomes. Minimally invasive clot removal techniques have been evaluated; however, these procedures are considered investigational because outcomes are not certain. Current guidelines note that surgical treatment of ICH is uncertain and is not recommended except in specific patient situations.[46]

► *Pharmacologic Therapy*

LO 9

Calcium Antagonists Oral nimodipine is recommended in SAH to prevent delayed cerebral ischemia. It is recommended to begin oral nimodipine promptly after the initial event, but no later than 96 hours following SAH. Delayed cerebral ischemia occurs 4 to 14 days after the initial aneurysm rupture and is a common cause of neurological deficits and death. Nimodipine 60 mg orally every 4 hours for 21 days following aneurysmal SAH reduces the risk of a poor outcome and delayed cerebral ischemia.

Hemostatic Therapy A meta-analysis evaluating five clinical trials found that recombinant factor VIIa decreases the growth of the hematoma, but did not improve survival or functional outcome. A higher incidence of thromboembolic events was also seen.[49] Current guidelines do not recommend treatment with recombinant factor VIIa due to an uncertain benefit and increased risk of thromboembolic events.[46]

OUTCOME EVALUATION

- Stroke outcomes are measured based on neurological status and functioning of the patient after the acute event.
- Early rehabilitation can reduce functional impairment after a stroke. Stroke rehabilitation guidelines have been endorsed by the American Heart Association and American Stroke Association. These guidelines recommend that patients receive care in a multidisciplinary setting or stroke unit, receive early assessment using the NIHSS, and that rehabilitation is started as soon as possible after the stroke. Other recommendations include screening for dysphagia (difficulty in swallowing) and aggressive secondary stroke prevention treatments.[50]
- Continued effort has been placed on stroke systems of care and developing mechanisms for more urgent assessment and treatment of suspected stroke.
- Table 11–6 provides monitoring guidelines for the acute stroke patient.

Table 11–6

Monitoring the Stroke Patient

Treatment	Parameter(s)	Monitoring Frequency	Comments
Ischemic Stroke			
All stroke patients	CT scan	Upon arrival	
	Neurologic examination		
	BP	Every 5 minutes × 3	
Alteplase			
	CT scan	24 hours after alteplase infusion	
	BP	Every 15 minutes × 2 hours, every 30 min × 6 hours, every 1 hour × 16 hours; then every shift	
	Neurologic function	Neurological examination every 15 minutes × 2 hours, every 30 min × 6 hours, every 1 hour × 16 hours; NIHSS 24 hours after alteplase infusion and at discharge	
	Bleeding	Clinical signs of bleeding every 2 hours × 24 hours	
ASA	Bleeding Hb/Hct, platelets[a]	Daily	
Clopidogrel	Bleeding Hb/Hct, platelets[a]	Daily	
ASA/ER dipyridamole	Headache, bleeding Hb/Hct, platelets[a]	Daily	
Warfarin	Bleeding, INR, Hb/Hct[a]	INR daily × 3 days; weekly until stable; then monthly	
New oral anticoagulants	Bleeding Hb/Hct, renal and liver function	Each visit Yearly; if decreased renal function, every 3–6 months	
Hemorrhagic Stroke			
	BP, neurologic function, ICP	Every 2 hours in ICU	May require treatments to lower systolic BP to < 180 mm Hg
Nimodipine for SAH	BP, neurologic function, fluid status	Every 2 hours in ICU	

[a]Hb/Hct and platelets should be monitored at baseline and every 6 months for ASA, clopidogrel, ASA/ER dipyridamole, and warfarin treatment.

ASA, aspirin; BP, blood pressure; CT, computed tomography; ER, extended-release; Hb, hemoglobin; Hct, hematocrit; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalized ratio; NIHSS, National Institutes of Health Stroke Scale; SAH, subarachnoid hemorrhage.

Patient Care Process

Collect Information:

- Assess signs and symptoms including time of symptom onset and time of arrival in the emergency department, obtaining information from patient or family members. Time the patient was last known to be well is used as the stroke onset time.
- Review results of completed prehospital stroke screening tests.
- Review the neurological and physical examination findings, including the NIHSS, evaluating for potential causes of stroke.
- Perform a comprehensive medication history, obtaining information from patient or family members.
- Determine the patient's baseline functional status.
- Determine the patient's risk factors for stroke.

Assess the Information:

- Determine if patient is experiencing an acute ischemic stroke.
- Determine if thrombolytic therapy is indicated based on inclusion and exclusion criteria.
- Review relevant laboratory tests (eg, BP, temperature, glucose, oxygen saturation).
- Assess the patient's weight.
- Review CT or MRI scan results to rule out a hemorrhagic stroke.
- Review the results of other diagnostic tests (eg, ECG, Doppler studies).
- Evaluate the inclusion and exclusion criteria for fibrinolytic therapy.
- Evaluate patient for IV and endovascular treatment acutely.

(*Continued*)

Patient Care Process (*Continued*)

Develop a Care Plan:

- Manage the patient's airway, breathing, and circulation (ABCs) initially in the acute phase of treatment.
- Transfer the patient to a stroke center if available.
- Begin IV alteplase if patient is within 4.5 hours of the onset of symptoms and meets the inclusion and exclusion criteria.
- Hold other anticoagulants and antiplatelet agents for 24 hours after the infusion of alteplase.
- Begin antiplatelet therapy to prevent a recurrent stroke.
- Manage patient's stroke risk factors.

Implement the Care Plan:

- If fibrinolytic therapy is indicated, initiate treatment protocol for alteplase administration and follow recommended monitoring plan.
- Develop a plan for long-term management of risk factors to prevent a recurrent stroke.
- Educate the patient on risk factors and lifestyle factors to reduce the risk of stroke recurrence.
- Educate the patient on the importance of adherence to their medication regimen.

Follow-up: Monitor and Evaluate:

- Monitor the patient's BP and neurological status every 15 minutes × 2 hours, every 30 minutes × 6 hours and then every hour for 24 hours after alteplase infusion.
- Obtain a follow-up CT scan 24 hours after the alteplase infusion.
- Evaluate functional status 24 hours after the alteplase infusion.
- Monitor patient's risk factors poststroke.

Abbreviations Introduced in This Chapter

ABCs	Airway, breathing, and circulation
ACE-I	Angiotensin-converting enzyme inhibitor
ADP	Adenosine diphosphate
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
ASA	Aspirin
ASCVD	Atherosclerotic cardiovascular disease
ASPECT	Alberta Stroke Program Early CT
AVM	Arteriovenous malformation
BP	Blood pressure
CCB	Calcium channel blocker
CEA	Carotid endarterectomy
CNS	Central nervous system
CT	Computed tomography
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECT	Ecarin clotting time
ER	Extended-release
FDA	Food and Drug Administration
GI	Gastrointestinal
HB	Hemoglobin
HCT	Hematocrit
IA	Intraarterial
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
INR	International normalized ratio
IV	Intravenous
LMWH	Low molecular weight heparin
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PT	Prothrombin time
rt-PA	Alteplase
r-pro UK	Pro-urokinase
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
TIA	Transient ischemic attack
TTP	Thrombotic thrombocytopenic purpura
TT	Thrombin time
UFH	Unfractionated heparin
VTE	Venous thromboembolism

REFERENCES

1. Lackland DT, Roccella EJ, Deutsch, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research, and Council on Functional Genomics and Translational Biology. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. Stroke. 2014;45: 315–353.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017; 135(10):e146–e603.
3. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke. 2009;40:2276–2293.
4. Rothwell PM, Warlow CP. Timing of TIAs preceding stroke: time window for prevention is very short. Neurology. 2005;64:817–820.
5. Sacco RL, Kasner SE, Broderick JP, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke

Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064–2089.
6. Grysiewicz RA, Thomas D, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality and risk factors. Neurol Clin. 2008;26:871–895.
7. Connelly ES, Rabinstein AA, Carhuapoma JR, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, and Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:1711–1737.
8. Meschia JF, Bushnell C, Boden-Albala B, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(12):3754–3832.
9. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 13. [Epub ahead of print.]
10. Stone NJ, Robinson JG, Lichtenstein AH, et al; on behalf of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 suppl 2):S1–S45.
11. Verdecchia P, Angeli F, Gentile G, Reboldi G. More versus less intensive blood pressure–lowering strategy: cumulative evidence and trial sequential analysis. Hypertension. 2016;68:642–653.
12. Suissa L, Lachaud S, Mahagne MH. Optimal timing and duration of continuous electrocardiographic monitoring for detecting atrial fibrillation in stroke patients. J Stroke Cerebrovasc Dis. 2013;22(7):991–995.
13. Jauch EC, Cucchiara B, Adeoye O, et al. Part 11: adult stroke: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care [published correction appears in Circulation. 2011;124:e404]. Circulation. 2010;122(suppl 3):S818–S828.
14. Jauch EC, Saver JL, Adams HP, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association. Stroke. 2013;44:870–914.
15. Kirkman MA, Citerio G, Smith M. The intensive care management of acute ischemic stroke: an overview. Intensive Care Med. 2014;40(5):640–653.
16. Kallmunzer B, Kollmar R. Temperature management in stroke—an unsolved, but important topic. Cerebrovasc Dis. 2011;31:532–543.
17. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–1587.
18. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. Antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines, 9th ed. Chest. 2012;141(2 supp):e601S–e636S.
19. Emberson J, Lees KR, Lyden P, et al; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384(9958):1929–1935.
20. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014;7:CD000213.
21. del Zoppo GJ, Saver JL, Jauch ED, Adams HP, Jr.; on behalf of the American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. Stroke. 2009;40:2945–2948.
22. Rajajee V, Kidwell C, Starkman S, et al. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. Neurology. 2006;67:980–984.
23. Greisenegger S, Seygang L, Kiechl S, et al; on behalf of the Austrian Stroke Unit Registry Collaborators. Thrombolysis in patients with mild stroke: results from the Austrian Stroke Unit Registry. Stroke. 2014;45:765–769.
24. Marshall RS. Progress in intravenous thrombolytic therapy for acute stroke. JAMA Neurol. 2015;72(8):928–934.
25. von Kummer R, Mori E, Truelsen T, et al. DIAS-4 investigators. Stroke. 2016;47(12):2880–2887.
26. Kidwell CS, Jahan R. Endovascular treatment of acute ischemic stroke. Neurol Clin. 2015;33:401–420.
27. Powers WJ, Derdeyn CP, Biller J, et al; on behalf of the American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46:3020–3035.
28. Sandercock PA, Counsell C, Kane EJ. Anticoagulants for acute ischaemic stroke. Cochrane Database Syst Rev. 2015;3:CD000024.
29. Sandercock PA, Leong TS. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. Cochrane Database Syst Rev. 2017;4:CD000119.
30. Kate M, Gioia L, Buck B, et al. Dabigatran therapy in acute ischemic stroke patients without atrial fibrillation. Stroke. 2015;46:2685–2687.
31. Wang Y, Pan Y, Zhao X, et al; on behalf of the CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack (CHANCE) trial: one-year outcomes. Circulation. 2015;132:40–46.
32. Barbetta I, Carmo M, Mercandalli G. Outcomes of urgent carotid endarterectomy for stable and unstable acute neurologic deficits. J Vasc Surg. 2014;59(2):440–446.
33. Rothwell PM, Eliasziw M, Fox AJ, et al; for the Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet. 2003;361:107–116.
34. Orrapin S, Rerkasem K. Carotid endarterectomy for symptomatic carotid stenosis. Cochrane Database Syst Rev. 2017;6:CD001081.
35. Brott TG, Halperin JL, Abbara S, et al; American College of Cardiology; American Stroke Association; American Association

of Neurological Surgeons; American College of Radiology; American College of Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation. 2011;124(4): e54–e130.

36. Kernan WN, Ovbiagele B, Black HR, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:2160–2236.
37. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71–86.
38. Sacco RL, Deiner HC, Yusuf S, et al; PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med. 2008;359:1238–1251.
39. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. The Lancet. 1996;348(9038):1329–1339.
40. Ho PM, Maddox TM, Wang L, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA. 2009;301(9):937–944.
41. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009;360:354–362.
42. The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomized controlled trial. Lancet. 2006;367:1665–1673.
43. Deiner HC, Bogousslavsky J, Brass LM, et al; for the MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004;364:331–337.
44. Kennedy J, Hill MD, Ryckborst KJ, et al; FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomized controlled pilot trial. Lancet Neurol. 2007;6(11):961–969.
45. Wang Y, Zhao X, Liu L, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369:11–19.
46. Hemphill CJ 3rd, Greenberg SM, Anderson CS, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015;46: 2032–2060.
47. Qureshi AI, Palesch YY, Barsan WG; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375(11):1033–1043.
48. Connelly ES, Rabinstein AA, Carhuapoma JR, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular Nursing, Council on Cardiovascular Surgery and Anesthesia, and Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:1711–1737.
49. Yuan ZH, Jiang JK, Huang WD, et al. A meta-analysis of the efficacy and safety of recombinant activated factor VII for patients with acute intracerebral hemorrhage without hemophilia. Clin Neurosci. 2010;17(6):685–693.
50. Winstein CJ, Stein J, Arena R, et al; and on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:e98–e169. Erratum in: Stroke. 2017;48(2):e78.

12 Dyslipidemias

Joel C. Marrs

LEARNING OBJECTIVES

LO

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

1. Identify the common types of lipid disorders.
2. Identify the statin-benefit groups and intensity of statin therapy according to the American College of Cardiology/American Heart Association.
3. Recommend appropriate therapeutic lifestyle changes (TLC) and pharmacotherapy interventions for dyslipidemia.
4. Determine a patient's atherosclerotic cardiovascular disease risk and corresponding treatment goals according to the National Lipid Association, American Association of Clinical Endocrinologist/American College of Endocrinology, and American College of Cardiology.
5. Identify patients who are indicated for nonstatin therapy according to the American College of Cardiology.
6. Describe components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for dyslipidemias.
7. Educate patients about the disease state, appropriate TLC, and drug therapy required for effective treatment.

INTRODUCTION

KEY CONCEPT

Hypercholesterolemia or dyslipidemia play a major role in atherosclerosis and plaque formation leading to coronary heart disease (CHD) as well as other forms of atherosclerotic cardiovascular disease (ASCVD), such as carotid and peripheral artery disease.[1] CHD is the leading cause of death in adults in the United States and most industrialized nations. It is also the chief cause of premature, permanent disability in the US workforce.

EPIDEMIOLOGY AND ETIOLOGY

It is estimated that 94.6 million US adults have high cholesterol with a value of 200 mg/dL (5.17 mmol/L) or greater.[2] Further, one out of every three US adults has a high level of low-density lipoprotein (LDL) cholesterol.[2] Elevated cholesterol values are a major risk factor for the development of ASCVD. Annually, approximately 580,000 Americans experience a new heart attack and 210,000 will have a recurrent event.[2] Lowering cholesterol reduces atherosclerotic progression and mortality from CHD and stroke. The development of CHD is a lifelong process. Except in rare cases of severely elevated serum cholesterol levels, years of poor dietary habits, sedentary lifestyle, and life-habit risk factors (eg, smoking, overweight/obesity) contribute to the development of atherosclerosis.[3]

PATHOPHYSIOLOGY

Cholesterol and Lipoprotein Metabolism

Cholesterol, an essential substance manufactured by most cells in the body, is used to maintain cell wall integrity and for the biosynthesis of bile acids and steroid hormones. Cholesterol, triglycerides, and phospholipids circulate in the blood as lipoproteins (Figure 12–1). The major lipoproteins are chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and high-density lipoprotein (HDL). Each lipoprotein has various proteins called apolipoproteins (Apos) embedded on the surface (Figure 12–1) that serve four main purposes: (a) required for assembly and secretion of lipoproteins; (b) serve as major structural components of lipoproteins; (c) act as ligands for binding to receptors on cell surfaces; and (d) can be cofactors for inhibition of enzymes involved in the breakdown of triglycerides from chylomicrons and VLDL.[4]

A measured total cholesterol is the total cholesterol molecules in all these major lipoproteins. The estimated value of LDL cholesterol is found using the Friedewald equation (after fasting for 9–12 hours):

LDL cholesterol (mg/dL) = total cholesterol – (HDL cholesterol + triglycerides/5), when lipids are expressed in units of mg/dL;

or

LDL cholesterol (mmol/L) = total cholesterol – (HDL cholesterol + triglycerides/2.2), when lipids are expressed in units of mmol/L

Where triglycerides/5 or triglycerides/2.2 estimate VLDL cholesterol in units of mg/dL or mmol/L, respectively.

This formula becomes inaccurate if serum triglycerides are greater than 400 mg/dL (4.52 mmol/L), if chylomicrons are present, or the patient has familial dysbetalipoproteinemia.

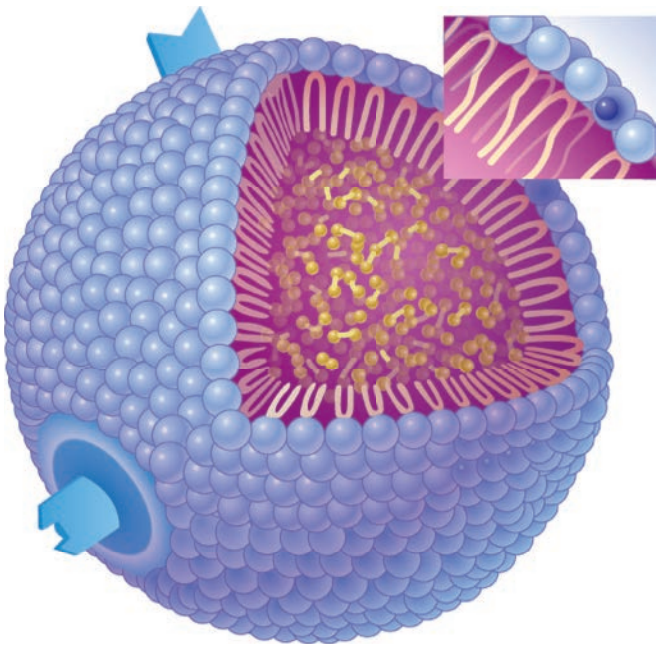

FIGURE 12–1. Lipoprotein structure. Lipoproteins are a diverse group of particles with varying size and density. They contain variable amounts of core cholesterol esters and triglycerides, and have varying numbers and types of surface apolipoproteins (Apos). The Apos function to direct the processing and removal of individual lipoprotein particles.

In each of these cases, LDL cholesterol must be directly measured, which can be done for any patient at most labs.[3] Non-HDL cholesterol is carried by all atherogenic Apos B-containing lipoproteins including VLDL, IDL, and LDL. It is calculated as:

Non-HDL cholesterol = total cholesterol – HDL cholesterol

Non-HDL cholesterol can be determined in a nonfasting state.

Cholesterol from the diet as well as from bile enters the small intestine and is emulsified by bile salts into micelles (Figure 12–2), which are microscopic particles of digested fat and cholesterol. These micelles interact with the **duodenal enterocyte** and **jejunal enterocyte** surfaces, and cholesterol is transported from the micelles into enterocytes by the Niemann-Pick C1 Like 1 (NPC1L1) transporter. Cholesterol within enterocytes is esterified and packaged into chylomicrons along with triglycerides, phospholipids, and Apos, which are then released into the **lymphatic** circulation. In the lymph and blood, chylomicrons are converted to chylomicron remnants. During this process, referred to as reverse cholesterol transport, chylomicrons also interact with HDL particles (Figure 12–3) and exchange triglyceride and cholesterol content (facilitated by cholesterol ester transfer protein, or CETP), and HDL particles acquire Apos A and C. Chylomicron remnant particles are then taken up by LDL-related protein (LRP).

In the liver, cholesterol and triglycerides are incorporated into VLDL along with phospholipids and Apo B-100 (Figure 12–4). VLDL loses its triglyceride content through interaction with

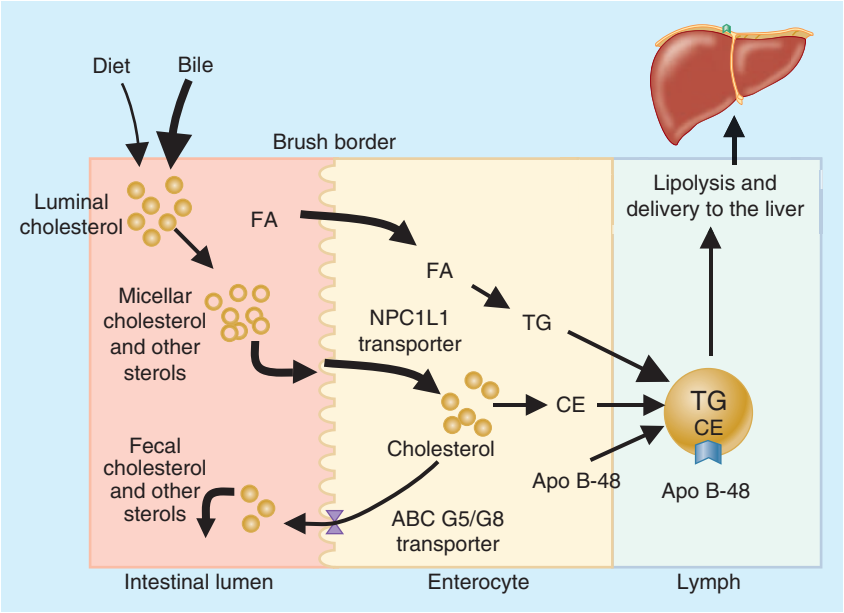

FIGURE 12–2. Intestinal cholesterol absorption and transport. Cholesterol from food and bile enters the gut lumen and is emulsified by bile acids into micelles. Micelles bind to the intestinal enterocytes, and cholesterol and other sterols are transported from the micelles into the enterocytes by a sterol transporter. Triglycerides synthesized by absorbed fatty acids, along with cholesterol and Apo B-48, are incorporated into chylomicrons. Chylomicrons are released into the lymphatic circulation and converted to chylomicron remnants (through loss of triglyceride), and then taken up by the hepatic LDL receptor-related protein (LRP). (ABC G5/G8, ATP-binding cassette G5/G8; Apo, apolipoprotein; CE, cholesterol ester; FA, fatty acid; LDL, low-density lipoprotein; NPC1L1, Niemann-Pick C1 Like 1; TG, triglyceride.)

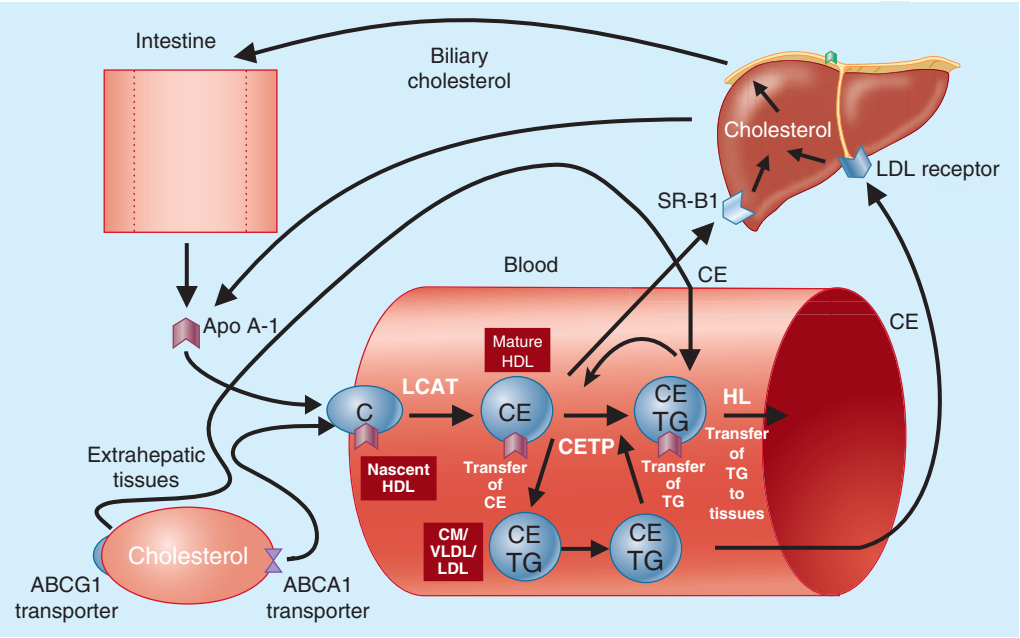

FIGURE 12–3. Reverse cholesterol transport. Cholesterol is transported from the arterial wall or other extrahepatic tissues back to the liver by HDL. Esterified cholesterol from HDL can be transferred to Apo B–containing particles in exchange for triglycerides. Cholesterol esters transferred from HDL to VLDL and LDL are taken up by hepatic LDL receptors or delivered back to extrahepatic tissue. (ABCA1, ATP-binding cassette A1; ABCG1, ATP-binding cassette G1; Apo, apolipoprotein; C, cholesterol; CE, cholesterol ester; CETP, cholesterol ester transfer protein; CM, chylomicrons; HDL, high-density lipoprotein; HL, hepatic lipase; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; SR-B1, scavenger receptors; TG, triglyceride; VLDL, very low-density lipoprotein.)

lipoprotein lipase (LPL) to form VLDL remnant and IDL. IDL can be cleared from the circulation by hepatic LDL receptors or further converted to LDL (by further depletion of triglycerides) through the action of hepatic lipases (HLs). Approximately 50% of IDL is converted to LDL. LDL particles are cleared from the circulation primarily by hepatic LDL receptors by interaction with Apo B-100. They can also be taken up by extrahepatic tissues or enter the arterial wall, contributing to atherogenesis. Biosynthesis of cholesterol is directly regulated by the amount of cholesterol present in an individual. Therefore, higher ingestion of cholesterol through food consumption results in decreased production of endogenous cholesterol in the liver. In the liver, cholesterol is produced through the mevalonate pathway (Figure 12–4) where the production of mevalonate is the rate-limiting and irreversible step in cholesterol synthesis. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) is converted to mevalonate by HMG-CoA reductase (site of action for statins).

Cholesterol is transported from the arterial wall or other extrahepatic tissues back to the liver by HDL (Figure 12–3). Triglyceride-rich HDL is hydrolyzed by HL, generating fatty acids (FA) and nascent (immature) HDL particles, or mature HDL can bind to scavenger receptors (SR-BI) on hepatocytes and transfer their cholesterol ester content for excretion in the bile.

LO 1

A variety of genetic mutations can occur during lipoprotein synthesis and metabolism that cause lipid disorders. The major genetic disorders and their effect on serum lipids are presented in Table 12–1. Disorders that increase serum cholesterol are generally those that affect the number or affinity of LDL receptors and are known as familial hypercholesterolemia (FH). These patients commonly present with **corneal arcus** of the eye, **xanthomas** of extensor tendons of the hand and Achilles tendon, premature CHD, and/or have a first or second degree relative with raised cholesterol and/or premature CHD. Elevations in triglycerides are generally associated with overproduction of triglyceride-rich VLDL, mutations in Apo E, or lack of LPL or Apo CII, which causes hyperchylomicronemia. Most individuals have mild to moderate elevations in cholesterol known as polygenic hypercholesterolemia, thought to be caused by various more subtle genetic defects as well as environmental factors such as diet, sedentary lifestyle, and overweight/obesity.[3]

Pathophysiology of Clinical Atherosclerotic Cardiovascular Disease

Lipoproteins are the "root cause" of atherosclerosis. The process begins when lipoproteins migrate between the **endothelial cells** into the arterial wall where they are modified by oxidation (Figure 12–5). Oxidized lipoproteins promote endothelial dysfunction by disturbing the production of nitric oxide, an endogenous vasodilator that maintains vasomotor tone, as well as increasing expression of cell-adhesion molecules on vascular endothelial cells leading to recruitment of monocytes (a variety of white blood cells) into the intima (inner layer of the wall of an artery or vein). Monocytes differentiate into macrophages (large scavenger cells) and express SR-BI, allowing enhanced uptake of these oxidized lipoproteins. The macrophages continue to accumulate lipoproteins and ultimately develop into lipid-laden **foam cells**. Accumulation of foam cells leads to formation of a lipid-rich core, which marks the transition to a more complicated atherosclerotic plaque. Such plaques may result in ischemic heart disease and **acute coronary syndromes**, further discussed in Chapters 7 and 8, respectively. Aggressive lipid lowering can restore endothelial function, decrease cardiovascular disease (CVD) risk, and improve patient cardiovascular (CV) outcomes.[3,5]

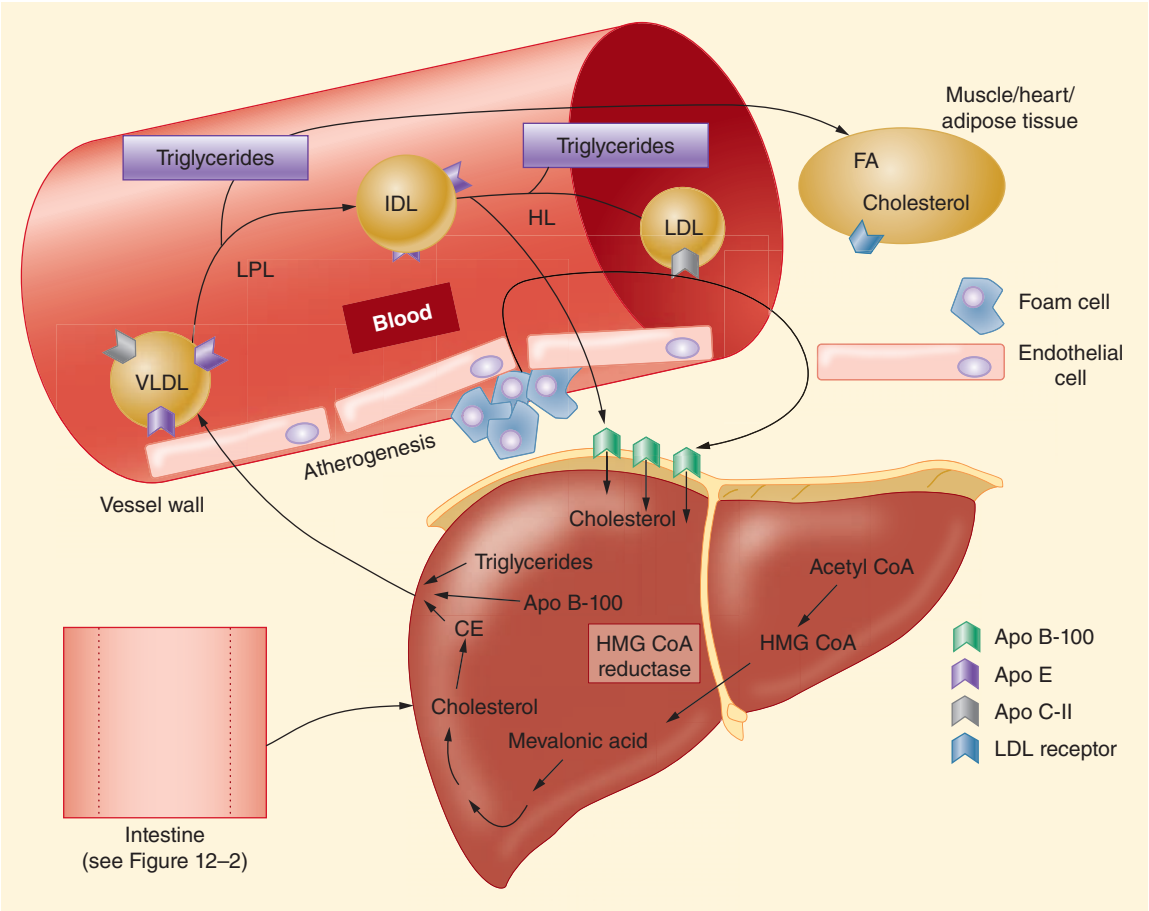

FIGURE 12–4. Endogenous lipoprotein metabolism. In liver cells, cholesterol and triglycerides are packaged into VLDL particles and exported into blood where VLDL is converted to IDL. Intermediate-density lipoprotein can be either cleared by hepatic LDL receptors or further metabolized to LDL. LDL can be cleared by hepatic LDL receptors or can enter the arterial wall, contributing to atherosclerosis. (Acetyl CoA, acetyl coenzyme A; Apo, apolipoprotein; CE, cholesterol ester; FA, fatty acid; HL, hepatic lipase; HMG-CoA, 3-hydroxy-3-methyglutaryl coenzyme A; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein.)

Table 12–1

Selected Characteristics of Primary Dyslipidemias

Disorder	Estimated Frequency	Metabolic Defect	Main Lipid Parameter
Autosomal dominant hypercholesterolemia			
Familial hypercholesterolemia homozygous	1/250,000–1/1 million	LDL-receptor negative	LDL-C > 500 mg/dL (12.93 mmol/L)
Heterozygous	1/250–1/500	Reduction in LDL receptors	LDL-C 250–500 mg/dL (6.47–12.93 mmol/L)
Familial defective Apo B-100	1/1000	Single nucleotide mutation	LDL-C 250–500 mg/dL (6.47–12.93 mmol/L)
PCSK9 gain of function mutations	Rare	Single nucleotide mutation	LDL-C 250–500 mg/dL (6.47–12.93 mmol/L)
Polygenic hypercholesterolemia	Common	Metabolic and environmental	LDL-C 160–250 mg/dL (4.14–6.47 mmol/L)
Familial combined dyslipidemia	1/200–300	Overproduction of VLDL and/or LDL	LDL-C 250–350 mg/dL (6.47–9.05 mmol/L) TG 200–800 mg/dL (2.26–9.04 mmol/L)
Familial hyperapobetalipoproteinemia	5%	Increase Apo B production	Apo B > 125 mg/dL (1.25 g/L)
Familial dysbetalipoproteinemia (Type III)	0.5%	Apo E2/2 phenotype	LDL-C 300–600 mg/dL (7.76–15.52 mmol/L)
Familial hypertriglyceridemia			
Type I	1/500,000–1/1 million	LPL-Apo CII system	TG > 1000 mg/dL (11.3 mmol/L)
Type IV	1/300	Unknown	TG 200–500 mg/dL (2.26–5.65 mmol/L)
Type V	1/205,000	Metabolic and environmental	TG > 1000 mg/dL (11.3 mmol/L)
Hypoalphalipoproteinemia	3%–5%	Defect in HDL catabolism	HDL-C < 35 mg/dL (0.91 mmol/L)

Apo, apolipoprotein; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; PCSK9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride; VLDL, very low-density lipoprotein.

Clinical Presentation and Diagnosis

Physical Findings

- Dyslipidemia is usually asymptomatic.
- Corneal arcus of the eye and xanthomas may be seen in patients with genetic disorders that cause a marked increase in serum LDL cholesterol (> 250 mg/dL [6.47 mmol/L]).
- Those with extremely elevated serum triglycerides (> 1000 mg/dL [11.3 mmol/L]) can develop pancreatitis (inflammation of the pancreas) and tuberoeruptive xanthomas.

Indications for Lipid Panel

- All adults more than 20 years of age should be screened at least every 5 years using a fasting blood sample to obtain a lipid profile (total cholesterol, non-HDL cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). A fasting lipid profile is preferred so an accurate assessment of LDL cholesterol can be performed, but non-HDL cholesterol can accurately be assessed irrespective of fasting state.
- Children between 2 and 20 years old should be screened for high cholesterol if their parents have premature CHD or if one of their parents has a total cholesterol greater than 240 mg/dL (6.21 mmol/L). Early screening will help identify children at highest risk of developing CHD in whom early education and dietary intervention are warranted.

Lipid Panel

- Non-HDL cholesterol exceeding 130 mg/dL (3.36 mmol/L) or LDL cholesterol exceeding 100 mg/dL (2.59 mmol/L) should have an assessment of ASCVD risk.
- Serum triglycerides exceeding 150 mg/dL (1.70 mmol/L) and serum HDL cholesterol less than 40 mg/dL (1.03 mmol/L) in men and less than 50 mg/dL (1.29 mmol/L) in women may increase risk of ASCVD and should be evaluated.

Indications for Other Tests

- Conditions that may produce lipid abnormalities (such as those listed in **Table 12–2**) should be screened for using appropriate tests. If present, these conditions should be properly addressed as these can be secondary causes for dyslipidemia.

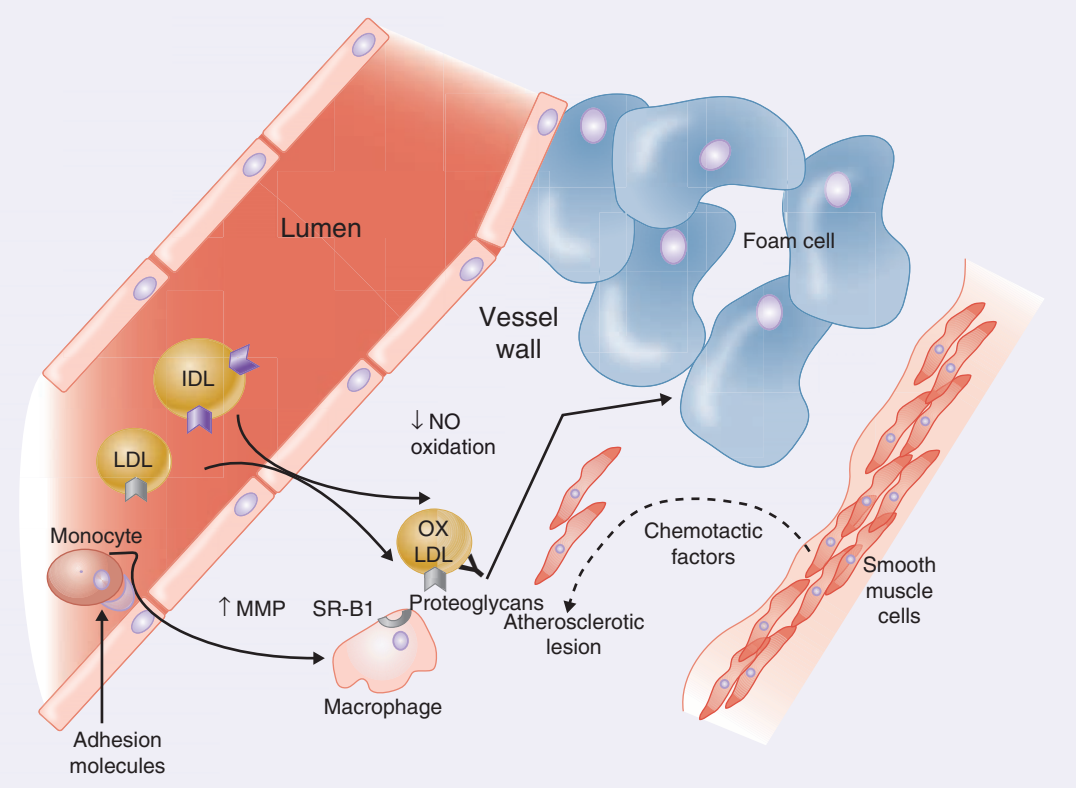

FIGURE 12–5. The process of atherogenesis. Atherosclerosis is initiated by the migration and retention of LDL and remnant lipoprotein particles into the vessel wall. These particles undergo oxidation and are taken up by macrophages in an unregulated fashion. The oxidized particles participate to induce endothelial cell dysfunction, leading to a reduced ability of the endothelium to dilate the artery and cause a prothrombotic state. The unregulated uptake of cholesterol by macrophages leads to foam cell formation and the development of a blood clot–favoring fatty lipid core. The enlarging lipid core eventually causes an encroachment of the vessel lumen. Early in the process, smooth muscle cells are activated and recruited from the media to the intima, helping to produce a collagen matrix that covers the growing clot protecting it from circulating blood. Later, macrophages produce and secrete matrix metalloproteinases that degrade the collagen matrix, leading to unstable plaque that may cause a myocardial infarction. (IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; MMP, matrix metalloproteinases; NO, nitric oxide; SR-B1, scavenger receptors.)

Table 12–2

Secondary Conditions and Drugs That May Cause Dyslipidemia

	↑ LDL Cholesterol	↑ Triglycerides	↓ HDL Cholesterol
Other Conditions			
Anorexia nervosa	√		
Chronic kidney disease	√	√	
Diabetes mellitus		√	√
Hemodialysis patients		√	
Hypothyroidism	√	√	
Nephrotic syndrome	√	√	√
Obesity		√	√
Obstructive liver disease/biliary cirrhosis	√		
Renal disease		√	
Drugs			
Anabolic steroids	√		√
Atypical antipsychotics		√	√
β-Blockers		√	√
Corticosteroids	√	√	
Cyclosporine	√		
Estrogen		√	
Isotretinoin		√	√
Progestins	√		√
Protease inhibitors		√	√
Thiazide diuretics	√	√	

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

TREATMENT

The rate-limiting enzyme in cholesterol biosynthesis is HMG-CoA reductase. Isolation of a specific inhibitor of this enzyme resulted in the first marketed statin called lovastatin.[6,7] By reducing cholesterol synthesis, statins were shown to up-regulate the LDL receptor. Statins have now become the mainstay therapy for both familial and nonfamilial hypercholesterolemia.

In November 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) released guidelines for treating high blood cholesterol to reduce risk of ASCVD in adults, which represented a paradigm shift in how clinicians had traditionally managed patients.[3] Major changes include identification of statin-benefit groups, removal of specific cholesterol treatment targets, and recommendations against nonstatin therapies in the general population due to lack of data supporting reduced ASCVD. The ACC/AHA guidelines shifted to a focus on statin-benefit groups versus other medical organizations recommending traditional cholesterol targets (eg, LDL goals, percent reduction in LDL) which are highlighted in Table 12–3.[3,8-11] In this chapter, the ACC/AHA guidelines,[3] the National Lipid Association (NLA) recommendations,[8] the 2016 ACC nonstatin expert consensus decision pathway (ECDP),[9] 2017 ACC updated ECDP,[10] and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) guidelines[11] will be reviewed.

LO 2

The ACC/AHA guidelines identify four groups of adult patients targeted for statin treatment (Figure 12–6), including:

- Established clinical ASCVD (secondary prevention)
- Primary prevention with elevation of LDL cholesterol levels 190 mg/dL (4.91 mmol/L) or higher

Table 12–3

US Guidelines for Management of Dyslipidemias

Source	Fasting Lipid Panel Measurement for Risk Assessment	Recommended Lipoprotein Target of Therapy	Treatment Goals
2013 American College of Cardiology/American Heart Association: Blood Cholesterol Guidelines for ASCVD Prevention[3]	Yes Used to evaluate for more severe forms and secondary dyslipidemias and to assess anticipated therapeutic response and adherence to statin therapy	No recommendation	No recommendation
National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia[8] (2014)	Yes	Non-HDL cholesterol and LDL cholesterol Apo B (secondary target)	LDL cholesterol: < 70 mg/dL (1.81 mmol/L) for very high-risk patients < 100 mg/dL (2.59 mmol/L) for high-risk, moderate-risk, and low-risk patients Non-HDL cholesterol: < 100 mg/dL (2.59 mmol/L) for very high-risk patients < 130 mg/dL (3.36 mmol/L) for high-risk, moderate-risk, and low-risk patients Apo B: < 80 mg/dL (0.80 g/L) for very high-risk patients < 90 mg/dL (0.90 g/L) for high-risk, moderate-risk, and low-risk patients

(*Continued*)

Table 12–3

US Guidelines for Management of Dyslipidemias (*Continued*)

Source	Fasting Lipid Panel Measurement for Risk Assessment	Recommended Lipoprotein Target of Therapy	Treatment Goals
2016 American College of Cardiology Expert Consensus Decision Pathway (EDCP) on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2016)[9] and 2017 Update (2017)[10]	Yes	LDL cholesterol and % reduction and non-HDL cholesterol	LDL cholesterol ≥ 50% reduction or < 70 mg/dL (1.81 mmol/L) or non-HDL cholesterol < 100 mg/dL (2.59 mmol/L) for patients > 21 years of age with stable ASCVD without comorbidities on statin ≥ 50% reduction or < 70 mg/dL (1.81 mmol/L) or non-HDL cholesterol < 100 mg/dL (2.59 mmol/L) for patients > 21 years of age with stable ASCVD with comorbidities on statin ≥ 50% reduction or < 70 mg/dL (1.81 mmol/L) or non-HDL cholesterol < 100 mg/dL (2.59 mmol/L) for patients > 21 years of age and baseline LDL cholesterol ≥ 190 mg/dL (4.91 mmol/L) on maximally tolerated statin for secondary prevention ≥ 50% reduction or < 100 mg/dL (2.59 mmol/L) or non-HDL cholesterol < 130 mg/dL (3.36 mmol/L) for patients > 21 years of age and baseline LDL cholesterol ≥ 190 mg/dL (4.91 mmol/L) on maximally tolerated statin for primary prevention ≥ 50% reduction or < 100 mg/dL (2.59 mmol/L) or non-HDL cholesterol < 130 mg/dL (3.36 mmol/L) for patients 40–75 years of age without clinical ASCVD and baseline LDL cholesterol 70–189 mg/dL (1.81–4.89 mmol/L) with diabetes on maximally tolerated statin for primary prevention 30%–49% reduction or < 100 mg/dL (2.59 mmol/L) or non-HDL cholesterol < 130 mg/dL (3.36 mmol/L) for patients 40–75 years of age without clinical ASCVD or diabetes with baseline LDL cholesterol 70–189 mg/dL (1.81–4.89 mmol/L) and ASCVD risk > 7.5% on maximally tolerated statin for primary prevention
American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease (2017)[11]	Yes	Non-HDL cholesterol and LDL cholesterol and Apo B	LDL cholesterol: < 55 mg/dL (1.42 mmol/L) for extreme-risk patients < 70 mg/dL (1.81 mmol/L) for very high-risk patients < 100 mg/dL (2.59 mmol/L) for high-risk and moderate-risk patients < 130 mg/dL (3.36 mmol/L) for low-risk patients Non-HDL cholesterol: < 80 mg/dL (2.07 mmol/L) for extreme-risk patients < 100 mg/dL (2.59 mmol/L) for very high-risk patients < 130 mg/dL (3.36 mmol/L) for high-risk and moderate-risk patients < 160 mg/dL (4.14 mmol/L) for low-risk patients Apo B: < 70 mg/dL (0.70 g/L) for extreme-risk patients < 80 mg/dL (0.80 g/L) for very high-risk patients < 90 mg/dL (0.90 g/L) for high-risk and moderate-risk patients

Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; non-HDL, non–high-density lipoprotein; %, percent.

- Primary prevention with diabetes mellitus (DM), age 40 to 75 years, with LDL cholesterol levels 70 to 189 mg/dL (1.81–4.89 mmol/L)
- Primary prevention without DM, age 40 to 75 years, with an estimated 10-year risk of 7.5% or greater, and LDL cholesterol levels 70 to 189 mg/dL (1.81–4.89 mmol/L)

A new pooled cohort risk estimator was developed to assist with decisions regarding initiation of statin therapy for primary prevention (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/). It should be emphasized that this risk estimator is part of the patient-clinician discussion regarding potential benefit of statin therapy and not the sole determinant

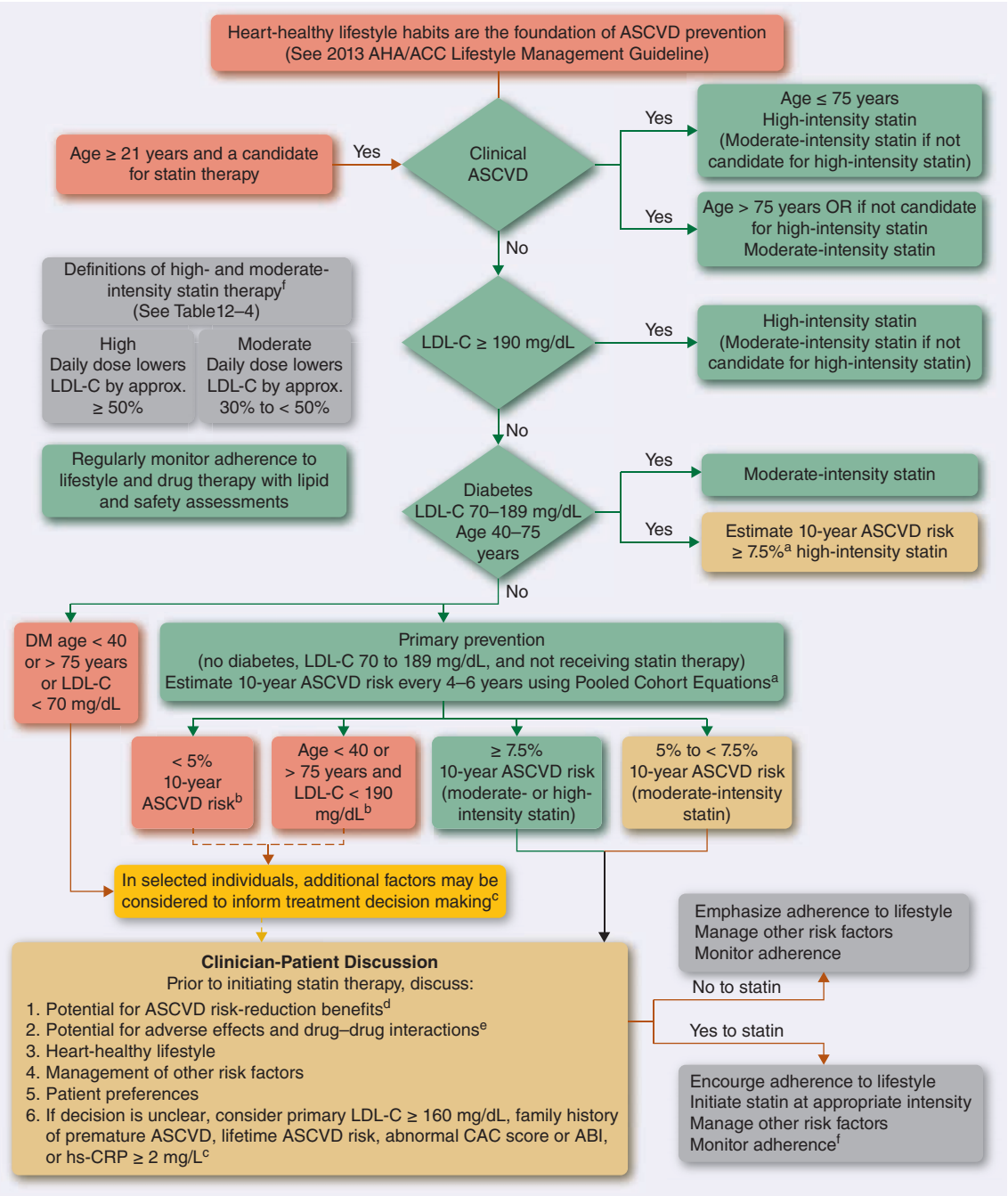

FIGURE 12–6. Summary of statin initiation recommendations for the treatment of blood cholesterol to reduce ASCVD risk in adults. [a]The Pooled Cohort Equation can be used to estimate 10-year ASCVD risk in individuals with or without DM. The estimator within this application should be used to inform decision making in primary prevention patients not on a statin. [b]Consider moderate-intensity statins as more appropriate in low-risk individuals. [c]For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C greater than or equal to 160 mg/dL (4.14 mmol/L) or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset less than 55 years of age in a first-degree male relative or less than 65 years of age in a first-degree female relative, hs-CRP greater than or equal to 2 mg/L, CAC score greater than or equal to 300 Agatston units, or greater than or equal to 75th percentile for age, sex, and ethnicity, ABI less than 0.9, or lifetime risk of ASCVD. [d]Potential ASCVD risk reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative-risk reduction from the intensity of statin initiated (~30% for moderate-intensity statin or ~45% for high-intensity statin). [e]Potential adverse effects. The excess risk of DM is the main consideration in ~0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In randomized controlled trials, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated. [f]Percent reduction in LDL-C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal. (ABI, ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.) The algorithm LDL-C values expressed in mmol/L are 4.91 mmol/L for 190 mg/dL, 4.89 mmol/L for 189 mg/dL, and 1.81 mmol/L for 70 mg/dL. (From Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889–2934, with permission.)

for initiation of therapy. A fasting lipid panel should be used for the initial calculation of the pooled cohort risk estimator. Clinical judgment, which includes risk and benefits, cost, and potential drug–drug interactions, must be exercised. This is especially important since the risk estimator has been shown to overestimate or underestimate risk in some patient populations. If initiation of statin therapy is uncertain based on quantitative risk assessment, additional factors such as LDL cholesterol 160 mg/dL (4.14 mmol/L) or higher, family history of premature ASCVD, high-sensitivity C-reactive protein (hs-CRP) of 2.0 mg/L or higher, coronary artery calcium (CAC) score of 300 Agatston units or higher, ankle brachial index (ABI) less than 0.9, or elevated lifetime ASCVD risk can be considered.

Once the decision to initiate statin therapy is made, the dose intensity is based on the patient's specific statin-benefit group (Figure 12–6). High-intensity statin therapy on average lowers LDL cholesterol by approximately 50% and moderate-intensity statin therapy lowers LDL cholesterol approximately 30% to 49% (see Table 12–4). The ACC/AHA expert panel concluded they could not find evidence for or against titration of drug therapy to specific LDL cholesterol and/or non-HDL cholesterol goals, thus no recommendations were given.[3] A follow-up LDL cholesterol 4 to 12 weeks after initiating therapy is used to assess response (percent LDL cholesterol lowering from baseline) and statin adherence, and not for determining if specific LDL cholesterol goals have been achieved.

In 2014, the NLA issued its recommendation for patient-centered management of dyslipidemia and reaffirmed the importance of setting cholesterol goals for prevention of ASCVD.[8] The NLA emphasized that non-HDL cholesterol is a better primary target for modification than LDL cholesterol, and is now considered a cotarget with LDL cholesterol. KEY CONCEPT The NLA recommendations for "desirable" cholesterol levels are presented in Table 12–5.

Table 12–4

High, Moderate, and Low-Intensity Statin Therapy as Indicated by the ACC/AHA

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL cholesterol, on average, by approximately ≥ 50%	Daily dose lowers LDL cholesterol, on average, by approximately 30% to < 50%	Daily dose lowers LDL cholesterol, on average, by < 30%
Atorvastatin (40[a])–80 mg	**Atorvastatin 10 (*20*) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (*40*) mg	**Rosuvastatin (*5*) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg	**Lovastatin 20 mg**
	Pravastatin 40 (*80*) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg twice daily	
	Pitavastatin 2–4 mg	

[a]Evidence from one RCT only: down-titration if unable to tolerate atorvastatin 80 mg.

Boldface type indicates specific statins and doses that were evaluated in randomized controlled trials (RCTs) by the ACC/AHA guideline committee.

Italic type indicates statins and doses that have been approved by the Food and Drug Administration but were not tested in RCTs reviewed by the ACC/AHA guidelines.

ACC, American College of Cardiology; AHA, American Heart Association; LDL, low-density lipoprotein.

Table 12–5

National Lipid Association Classifications of Cholesterol and Triglyceride Levels in mg/dL (mmol/L)

Lipids	
Non-HDL Cholesterol[a]	
< 130 (3.36)	Desirable
130–159 (3.36–4.11)	Above desirable
160–189 (4.14–4.89)	Borderline high
190–219 (4.91–5.66)	High
≥ 220 (5.69)	Very high
LDL Cholesterol	
< 100 (2.59)	Desirable
100–129 (2.59–3.34)	Above desirable
130–159 (3.36–4.11)	Borderline high
160–189 (4.14–4.89)	High
≥ 190 (4.91)	Very high
HDL Cholesterol	
< 40 (1.03) (men)	Low
< 50 (1.29) (women)	Low
Triglycerides	
< 150 (1.70)	Normal
150–199 (1.70–2.25)	Borderline
200–499 (2.26–5.64)	High
≥ 500 (5.65)	Very high[b]

[a]Non-HDL-C = total cholesterol minus HDL cholesterol.

[b]Severe hypertriglyceridemia is another term used for very high triglycerides in pharmaceutical product labeling.

HDL, high-density lipoprotein; LDL, low-density lipoprotein; non-HDL, non–high-density lipoprotein.

LO 3

KEY CONCEPT The ACC/AHA, NLA, and AACE/ACE guidelines emphasize that lifestyle therapies are an important element of risk reduction efforts in ASCVD prevention, whether or not pharmacotherapy is also used. Therapeutic lifestyle changes (TLC) should be the first approach tried in all patients (Table 12–6), but pharmacotherapy should be instituted concurrently in higher-risk patients. TLC includes dietary restrictions as well as regular exercise and weight reduction if overweight or obese. Additionally, consumption of plant stanols/sterols and dietary fiber should be encouraged as they may reduce LDL cholesterol by 20% to 25%.

Table 12–6

Essential Components of Therapeutic Lifestyle Changes

Component	Recommendation
Dietary cholesterol	< 200 mg/day (5.17 mmol/L)
Saturated fats	Total fat range should be 25%–35% for most cases < 7% of total calories and reduce intake of trans fatty acids
Therapeutic options for LDL-lowering plant stanols/sterols	2 g/day
Increased viscous (soluble) fiber	10–25 g/day
Total calories	Adjust caloric intake to maintain desirable body weight and prevent weight gain
Physical activity	≥ 150 min/week of moderate or higher intensity activity

LDL, low-density lipoprotein.

Table 12–7

American College of Cardiology Expert Consensus Decision Pathway for Nonstatin Therapy to Lower LDL-Cholesterol in the Management of Atherosclerotic Cardiovascular Disease (ASCVD) Risk

Risk Category	Treatment Target	1st Line After Statin	2nd Line After Statin
Primary Prevention			
> 21 years of age and baseline LDL cholesterol ≥ 190 mg/dL (4.91 mmol/L) on maximally tolerated statin	≥ 50% reduction or < 100 mg/dL (2.59 mmol/L) or non-HDL cholesterol < 130 mg/dL (3.36 mmol/L)	Ezetimibe or PCSK9 inhibitor as add-on therapy	BAS as add-on therapy if ezetimibe intolerant and TG < 300 mg/dL (3.39 mmol/L)
40–75 years of age without clinical ASCVD and baseline LDL cholesterol 70–189 mg/dL (1.81–4.89 mmol/L) with DM on maximally tolerated statin	≥ 50% reduction or < 100 mg/dL (2.59 mmol/L) or non-HDL cholesterol < 130 mg/dL (3.36 mmol/L)	Ezetimibe as add-on therapy	BAS as add-on therapy if ezetimibe intolerant and TG < 300 mg/dL (3.39 mmol/L)
40–75 years of age without clinical ASCVD or DM and baseline LDL cholesterol 70–189 mg/dL (1.81–4.89 mmol/L) and an ASCVD risk ≥ 7.5% on maximally tolerated statin	30%–49% reduction or < 100 mg/dL (2.59 mmol/L) or non-HDL cholesterol < 130 mg/dL (3.36 mmol/L)	Ezetimibe as add-on therapy	BAS as add-on therapy if ezetimibe intolerant and TG < 300 mg/dL (3.39 mmol/L)
Secondary Prevention			
> 21 years of age with stable clinical ASCVD without comorbidities on maximally tolerated statin	≥ 50% reduction or < 70 mg/dL (1.81 mmol/L) or non-HDL cholesterol < 100 mg/dL (2.59 mmol/L)	Ezetimibe as add-on therapy	PCSK9 inhibitor as add-on therapy or replacing with PCSK9 inhibitor
> 21 years of age with stable clinical ASCVD with comorbidities on maximally tolerated statin	≥ 50% reduction or < 70 mg/dL (1.81 mmol/L) or non-HDL cholesterol < 100 mg/dL (2.59 mmol/L)	Ezetimibe or PCSK9 inhibitor as add-on therapy	PCSK9 inhibitor as add-on therapy or replacing with PCSK9 inhibitor
> 21 years of age with stable clinical ASCVD and baseline LDL cholesterol ≥ 190 mg/dL (4.91 mmol/L) on maximally tolerated statin	≥ 50% reduction or < 70 mg/dL (1.81 mmol/L) or non-HDL cholesterol < 100 mg/dL (2.59 mmol/L)	Ezetimibe or PCSK9 inhibitor as add-on therapy	PCSK9 inhibitor as add-on therapy or replacing with PCSK9 inhibitor

BAS, bile acid sequestrant; DM, diabetes mellitus; LDL, low-density lipoprotein; non-HDL, non–high-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin 9; TG, triglycerides.

Recommendations for Treatment

▶ *Step 1: Screening and Classification of Initial Lipoprotein Lipid Levels*

Determine lipoprotein profile after fasting for 9 to 12 hours. KEY CONCEPT The NLA and AACE/ACE recommend that all adults older than 20 years are screened at least every 5 years to obtain a lipid profile (see Clinical Presentation and Diagnosis). Children between 2 and 20 years old should be screened for high cholesterol if their parents have premature CHD or if one of their parents has total cholesterol greater than 240 mg/dL (6.21 mmol/L).

▶ *Step 2: Rule Out Secondary Causes of Dyslipidemia*

Certain secondary causes (drugs and diseases) can cause abnormalities in serum lipids and should be evaluated (Table 12–2). Every effort should be made to correct or control underlying diseases such as hypothyroidism and DM. Concurrent medications known to induce lipid abnormalities should be evaluated for discontinuation if alternative medications can be used prior to instituting long-term lipid-modifying therapy.[8,10]

▶ *Step 3: Identify Patients with Very High-Risk Conditions*

LO3 LO4

Individuals with established clinical ASCVD (Table 12–7) or DM with greater or equal to two ASCVD risk factors (Table 12–8) or evidence of atherosclerosis mediated end-organ damage are considered very high risk or extreme risk. NLA, AACE/ACE, and ACC set non-HDL cholesterol and LDL cholesterol goals for very high-risk patients at less than 100 mg/dL (2.59 mmol/L) and less than 70 mg/dL (1.81 mmol/L), respectively.[8-11] The ACC ECDP for nonstatin therapy further set percent LDL cholesterol lowering targets (eg, 50%) in addition to LDL cholesterol and non-HDL cholesterol

Table 12–8

Risk Factors for Atherosclerotic Cardiovascular Disease (ASCVD) According to the National Lipid Association (NLA)[a]

Risk Factor	Definition
Age (years)	Male ≥ 45; female ≥ 55
Family history of premature CHD events[b]	Male first-degree relative at < 55 years Female first-degree relative at < 65 years
Hypertension[c]	SBP ≥ 140 mm Hg DBP ≥ 90 mm Hg
Low HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females
Cigarette smoking	Current

[a]Levels of non-HDL cholesterol and LDL cholesterol are not listed because these risk factors are used to assess risk category and treatment goals for atherogenic lipoprotein cholesterol levels. Diabetes is not listed because it is considered a high- or very high-risk condition for ASCVD risk assessment purposes.

[b]CHD is defined as myocardial infarction, coronary death, or a coronary revascularization procedure.

[c]Note, blood pressure values used by the NLA differ from the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCMA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults.

CHD, coronary heart disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

goals for both primary and secondary prevention patients based on risk levels.[9,10] The 2017 AACE/ACE guidelines set non-HDL cholesterol and LDL cholesterol goals for extreme-risk patients at less than 80 mg/dL (2.07 mmol/L) and less than 55 mg/dL (1.42 mmol/L), respectively.[11] NLA, AACE/ACE, and ACC state pharmacotherapy can be considered when non-HDL cholesterol or LDL cholesterol are equal to or above these targets. For patients with clinical ASCVD or DM, consideration can be given to use of moderate or high-intensity statin therapy, irrespective of baseline cholesterol levels.

▶ *Step 4: Identify Patients with High-Risk Conditions*

LO 3 LO 5 LO 4 LO 5

The ACC ECDP has set criteria for nonstatin therapy for patients with high residual risk after receiving maximum tolerated statin doses based on their statin benefit group and these are described in Table 12–7. The ACC, like the NLA and AACE/ACE, has set non-HDL cholesterol and LDL cholesterol goals for high-risk primary prevention patients at less than 130 mg/dL (3.36 mmol/L) and less than 100 mg/dL (2.59 mmol/L), and at less than 100 mg/dL (2.59 mmol/L) and less than 70 mg/dL (1.81 mmol/L) for secondary prevention patients, respectively.[8-11] Pharmacoltherapy can be considered when the desired LDL-cholesterol lowering is not achieved or LDL or non-HDL cholesterol is equal to or above the targets. If it is not possible to attain desirable LDL and non-HDL cholesterol levels in patients with severe hypercholesterolemia phenotype, a reduction of at least 50% is recommended.[9-11] For FH patients with multiple or poorly controlled other major ASCVD risk factors, clinicians may consider attaining even lower levels of atherogenic cholesterol.[9-11]

▶ *Step 5: Identify Patients with Two or Less ASCVD Risk Factors*

For individuals with two major ASCVD risk factors, quantitative risk scoring should be considered (eg, ASCVD risk calculation) and additional risk indicators (Table 12–9) may be useful for some patients. If quantitative risk score reaches the high-risk threshold, assign patient to high-risk category. If other risk indicators are present, consider assigning to the high-risk category. If no indication is present to assign to high risk, assign to moderate-risk category, with NLA and AACE/ACE goals for non-HDL cholesterol and LDL cholesterol of less than 130 mg/dL (3.36 mmol/L) and less than 100 mg/dL (2.59 mmol/L), respectively. Pharmacotherapy can be considered when non-HDL cholesterol or LDL cholesterol are equal to or above 160 mg/dL (4.14 mmol/L) and 130 mg/dL (3.36 mmol/L), respectively. For individuals with one or no major ASCVD risk factors, the NLA set goals for non-HDL cholesterol and LDL cholesterol level at less than 130 mg/dL (3.36 mmol/L) and less than 100 mg/dL (2.59 mmol/L), respectively. Pharmacotherapy can be considered when non-HDL cholesterol or LDL cholesterol are equal to or above 190 mg/dL (4.91 mmol/L) and 160 mg/dL (4.14 mmol/L), respectively. Consider assigning to a higher risk category based on other known risk indicators, when present.

▶ *Step 6: Treatment of Elevated Triglycerides*

KEY CONCEPT Patients with serum triglycerides exceeding 500 mg/dL (5.65 mmol/L) are at increased risk of pancreatitis, especially when levels exceed 1000 mg/dL (11.3 mmol/L).[8,11] Reducing triglycerides in these individuals becomes the primary target for intervention. Reduction in fats and carbohydrates and abstaining from ethanol should be considered, and secondary causes (Table 12–2) should be assessed. Increase in exercise should be encouraged. Weight loss should also be encouraged if the individual is overweight. When pharmacotherapy is instituted, the goal is to reduce triglycerides to less than 150 mg/dL (1.70 mmol/L). Once triglycerides are

Table 12–9

Risk Indicators (Other Than Major ASCVD Risk Factors) That Might Be Considered for Refinement[a]

Component
1. A severe disturbance in a major ASCVD risk factor, such as multipack per day smoking or strong family history of premature CHD
2. Indicators of subclinical disease, including coronary artery calcium ≥ 300 Agatston units[b] is considered high risk
3. LDL cholesterol ≥ 160 mg/dL (4.14 mmol/L) and/or non-HDL cholesterol ≥ 190 mg/dL (4.91 mmol/L)
4. High-sensitivity C-reactive protein ≥ 2.0 mg/L[c]
5. Lipoprotein (a) ≥ 50 mg/dL (500 mg/L; 125 nmol/L) using an isoform insensitive assay
6. Urine albumin/creatinine ratio ≥ 30 mg/g (3.4 mg/mmol)

[a]The presence of 1 or more of the risk indicators listed may be considered, in conjunction with major ASCVD risk factors, to reclassify an individual into a higher risk category. Except in the case of evidence of subclinical disease defining the presence of ASCVD, reclassification to a higher risk category is a matter of clinical judgment. Doing so will alter the threshold for consideration of pharmacotherapy and/or the treatment goals for atherogenic cholesterol.

[b]Or coronary artery calcium 75th percentile for age, sex, and ethnicity.

[c]Because of high intraindividual variability, multiple high sensitivity C-reactive protein (hs-CRP) values should be obtained before concluding that the level is elevated; hs-CRP should not be tested in those who are ill, have an infection, or are injured. If hs-CRP level is 0.10 mg/L, consider other etiologies such as infection, active arthritis, or concurrent illness.

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL, low-density lipoprotein; non-HDL, non–high-density lipoprotein.

Patient Encounter 1

A 53-year-old Caucasian man with obesity (BMI: 34 kg/m^2) has been referred to you for a follow-up of his cholesterol. He has known hypertension for which he takes losartan 100 mg daily and hydrochlorothiazide 25 mg daily. His blood glucose is 115 mg/dL (6.4 mmol/L). His laboratory test results are within normal limits. His blood pressure today is 138/90 mm Hg with a heart rate of 68 beats/min. He is a nonsmoker. His fasting lipid profile: total cholesterol 240 mg/dL (6.21 mmol/L), triglycerides 200 mg/dL (2.26 mmol/L), HDL cholesterol 38 mg/dL (0.98 mmol/L), non-HDL cholesterol 202 mg/dL (5.22 mmol/L), and LDL cholesterol 162 mg/dL (4.19 mmol/L).

What is your assessment of the patient's cholesterol results?

Should an assessment of his risk factors for ASCVD or an ASCVD risk score be conducted?

Does this patient have clinical ASCVD?

What statin-benefit group does he fit according to ACC/AHA guidelines?

What additional information do you need to evaluate the patient?

Develop a care plan for the patient.

less than 500 mg/dL (5.65 mmol/L) and the risk of pancreatitis is reduced, the primary focus of intervention should once again be on non-HDL and LDL cholesterol. Niacin, fibrates, and long-chain omega-3 fatty acids (OM3FA) are the most effective agents in patients with fasting triglyceride concentrations greater than 1000 mg/dL (11.3 mmol/L).[8,11] For patients with triglycerides 500 to 999 mg/dL (5.65–11.29 mmol/L), a triglyceride-lowering agent or a statin (if no history of pancreatitis) may be reasonable. Individuals with triglycerides between 200 and 499 mg/dL (2.26 and 5.64 mmol/L) have increased triglyceride-rich remnant lipoproteins and small-dense LDL particles, which are considered more atherogenic than large buoyant LDL particles. For patients with high triglycerides between 200 and 499 mg/dL (2.26 and 5.64 mmol/L), statins will generally be first line since they are most effective in reducing non-HDL and LDL-cholesterol levels.

Pharmacotherapy

▶ *Statins (HMG-CoA Reductase Inhibitors)*

KEY CONCEPT Statins are very effective LDL-lowering medications and are proven to reduce the risk of CHD, stroke, and death. Thus, ACC/AHA, NLA, and AACE/ACE consider statins the preferred LDL-lowering medications. Statins are effective in reducing ASCVD and in some cases, mortality. This effectiveness has been demonstrated in both genders, the elderly, patients with DM and hypertension, those with or without preexisting ASCVD, and following an acute coronary syndrome.[12-24] Statins inhibit conversion of HMG-CoA to L-mevalonic acid and subsequently cholesterol. Statins lower LDL cholesterol levels by approximately 21% to 63% (Table 12–10), are moderately effective at reducing triglycerides, and modestly raise HDL cholesterol. Additionally,

Table 12–10

Effects of Lipid-Lowering Drugs on Serum Lipids at FDA-Approved Doses

Lipid-Lowering Drug	LDL Cholesterol	HDL Cholesterol	Triglycerides	Total Cholesterol
Statins				
Atorvastatin	–26% to –60%	+5% to +13%	–17% to –53%	–25% to –45%
Fluvastatin	–22% to –36%	+3% to +11%	–12% to –25%	–16% to –27%
Fluvastatin ER	–33% to –35%	+7% to +11%	–19% to –25%	–25%
Lovastatin	–21% to –42%	+2% to +10%	–6% to –27%	–16% to –34%
Lovastatin ER	–24% to –41%	+9% to +13%	–10% to –25%	–18% to –29%
Pitavastatin	–31% to –45%	+1% to +8%	–13% to –22%	–23% to –31%
Pravastatin	–22% to –34%	+2% to +12%	–15% to –24%	–16% to –25%
Rosuvastatin	–45% to –63%	+8% to +14%	–10% to –35%	–33% to –46%
Simvastatin	–26% to –47%	+8% to +16%	–12% to –34%	–19% to –36%
Cholesterol Absorption Inhibitor				
Ezetimibe	–18%	+1% to +2%	–7% to –9%	–12% to –13%
Bile Acid Sequestrants				
Cholestyramine	–15% to –30%	+3% to +5%	May increase in patients with elevated triglycerides	–10% to –25%
Colesevelam	–15% to –18%	+3% to +5%		–70% to –10%
Colestipol	–15% to –30%	+3% to +5%		–10% to 25%
Nicotinic Acid				
Niacin ER	–5% to –17%	+14% to +26%	–11% to –38%	–3% to –12%
Niacin IR	–5% to –25%	+15% to +39%	–20% to –60%	–3% to –25%
Fibric Acid Derivatives				
Fenofibrate	–31% to +45%	+9% to +23%	–23% to –54%	–9% to –22%
Gemfibrozil	–30% to +30%	+10% to +30%	–20% to –60%	–2% to –16%
Combination Products				
Niacin ER and lovastatin	–30% to –42%	+20% to +30%	–32% to –44%	Not stated
Niacin ER and simvastatin[a]	–12% to –14%	+21% to +29%	–27% to –38%	–9% to –11%
Simvastatin and ezetimibe	–46% to –59%	+8% to +12%	–25% to –26%	–34% to –43%
Omega-3-Fatty Acids				
Lovaza	+45%	+9%	–45%	–10%
Vascepa	–5%	–4%	–27%	–7%
Epanova	+26%	+5%	–31%	–6%
OMTRYG	+20% to +45%	0% to +9%	–25% to –45%	–8% to –10%
Micosomal Transfer Protein Inhibitors				
Lomitapide	–40%	–7%	–45%	–36%
Antisense Oligonucleotide				
Mipomersen	–25%	+15%	–18%	–21%
Proprotein Convertase Subtilisin/ Kexin Type 9 (PCSK9) Inhibitors				
Alirocumab	–48% to –71%			–46% to –59%
Evolocumab	–48% to –71%			–46% to –59%

[a]Percent change relative to simvastatin 20 mg.

ER, extended-release; FDA, Food and Drug Administration; HDL, high-density lipoprotein; IR, immediate-release; LDL, low-density lipoprotein.

statins also inhibit other important by-products in the cholesterol biosynthetic pathway that affect intracellular transport, membrane trafficking, and gene transcription. This may explain some of the cholesterol-independent benefits (so-called pleiotropic effects) of statins such as reducing lipoprotein oxidation, enhancing endothelial synthesis of nitric oxide, and inhibiting **thrombosis**. These pleiotropic effects are thought to contribute to the early benefits of statins on CHD risk, while the decrease in serum lipids accounts for the later benefits.

LO 6

KEY CONCEPT Statins are well tolerated, with less than 4% of patients in clinical trials discontinuing therapy due to adverse side effects (Table 12–11). Elevations in liver function tests (LFTs) and **myopathy**, including **rhabdomyolysis**, are important adverse effects associated with statins. Liver toxicity, defined as LFT elevations greater than three times the upper limit of normal, is reported in less than 2% of patients. Incidence is higher at higher doses, but the progression to liver failure is exceedingly rare. LFTs should be obtained at baseline and as clinically indicated thereafter. Myopathy, defined as muscle weakness not necessarily associated with creatine kinase (CK) elevations, is reported to range from 0% to less than 0.5% for the currently marketed statins at approved doses. Rhabdomyolysis, defined as muscle symptoms with marked elevation in CK at 50 times the upper limit of normal and creatinine elevation usually associated with **myoglobinuria** and brown urine, is very rare.[25] The risks associated with statin-induced myopathy include the following:[25,26]

- Small body frame and frailty
- Multisystem disease (eg, chronic kidney disease, especially due to DM)
- Perioperative periods
- Multiple medications (see next bullet)
- Specific concomitant medications or consumptions (check specific statin package insert for warnings): fibrates (especially gemfibrozil, but other fibrates too), nicotinic acid (rarely), cyclosporine, azole antifungals, macrolide antibiotics, protease inhibitors, nefazodone, verapamil, amiodarone, large quantities of grapefruit juice (usually > 1 quart [about 950 mL] per day), and alcohol abuse (independently predisposes to myopathy).

Table 12–11

Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Statins			
Atorvastatin	10-, 20-, 40-, 80-mg tablets	10–80 mg once daily (at any time of day). Dose adjustment in patients with renal dysfunction is not necessary	Most frequent side effects are constipation, abdominal pain, diarrhea, and nausea. Statins should be discontinued promptly if serum transaminase levels (liver function tests) rise to three times upper limit of normal or if patient develops signs or symptoms of myopathy. Approximate-equivalent doses of HMG-CoA reductase inhibitors are: atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 mg, pitavastatin 2 mg, pravastatin 40 mg, simvastatin 20 mg, and rosuvastatin 5 mg
Fluvastatin	20-, 40-mg capsules; 80-mg extended-release tablets	20–40 mg/day as a single dose (evening) or 40 mg twice daily; 80 mg once daily (evening). Dose adjustments for mild to moderate renal impairment are not necessary	
Lovastatin	10-, 20-, 40-mg tablets	10–80 mg/day as a single dose (with evening meal) or divided twice daily with food. In patients with severe renal insufficiency (creatinine clearance less than 30 mL/min [0.5 mL/s]), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously	
Lovastatin ER	20-, 30-, 60-mg tablets	20–60 mg/day as a single dose. In patients with severe renal insufficiency (creatinine clearance < 30 mL/min [0.5 mL/s]), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously	
Pravastatin	10-, 20-, 40-, 80-mg tablets	10–80 mg/day as a single dose at bedtime. In patients with a history of significant renal or hepatic dysfunction, a starting dose of 10 mg daily is recommended	
Pitavastatin	1-, 2-, 4-mg tablets	1–4 mg/day as a single dose can be taken with or without food, at any time of day. Moderate renal impairment (glomerular filtration rate 30–60 mL/min/1.73 m^2 [0.29–0.58 mL/s/m^2]) and end-stage renal disease on hemodialysis: Starting dose of 1 mg once daily and maximum dose of 2 mg once daily	

(*Continued*)

Table 12–11

Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs (*Continued*)

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Rosuvastatin	5-, 10-, 20-, 40-mg tablets	5–40 mg/day (at any time of day); 40 mg reserved for those who do not achieve LDL cholesterol goal on 20 mg. In patients with history of significant renal dysfunction or Asian, starting dose of 5 mg daily is recommended	
Simvastatin	5-, 10-, 20-, 40-mg tablets	5–40 mg/day as a single dose in the evening, or divided. Recommended starting dose for patients at high risk of CHD is 40 mg/day. In patients with mild to moderate renal insufficiency, dosage adjustment is not necessary. However, caution should be exercised in patients with severe renal insufficiency; such patients should be started at 5 mg/day and be closely monitored. Due to increased risk of myopathy, including rhabdomyolysis, use of the 80 mg dose should be restricted to patients who have been taking simvastatin 80 mg chronically (eg, for 12 months or more) without evidence of muscle toxicity. Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products	
Cholesterol Absorption Inhibitors			
Ezetimibe	10-mg tablets	10 mg once daily. No dosage adjustment is necessary in patients with renal or mild hepatic insufficiency	Overall incidence of adverse events reported with ezetimibe alone was similar to that reported with placebo and generally similar between ezetimibe with a statin and statin alone. The frequency of increased transaminases was slightly higher in patients receiving ezetimibe plus a statin compared with those receiving statin monotherapy (1.3% vs 0.4%)
Bile Acid Sequestrants			
Cholestyramine	4-g packets	4–24 g/day in two or more divided doses	Main side effects are nausea, constipation, bloating, and flatulence, although these may be less with colesevelam. Increasing fluid and dietary fiber intake may relieve constipation and bloating. Impair absorption of fat-soluble vitamins
Colesevelam	625-mg tablets	3750–4375 mg/day as a single dose or divided twice daily, with meals	
	3.75-g oral suspension packet	One packet once a day with meals	
Colestipol	5-g packets	5–30 g/day as a single dose or divided	
	1-g tablets	2–16 g/day as a single dose or divided	
Nicotinic Acid (Prescription Products)			
Niacin ER (Niaspan)	500-, 750-, 1000-mg extended-release tablets	1000–2000 mg once daily at bedtime. Use with caution in patients with renal impairment	Side effects include flushing, itching, gastric distress, headache, hepatotoxicity, hyperglycemia, and hyperuricemia

(*Continued*)

Table 12–11

Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs (*Continued*)

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Niacin IR (Niacor)	500-mg tablets	1–6 g/day in two to three divided doses. Do not exceed 6 g daily	
Fibric Acid Derivatives			
Fenofibrate	54-, 160-mg tablets[a]	54–160 mg/day; the dosage should be minimized in severe renal impairment	Most common side effects are nausea, diarrhea, abdominal pain, and rash. Increased risk of rhabdomyolysis when given with a statin. Fibric acids are associated with gallstones, myositis, and hepatitis
Gemfibrozil	600-mg tablets	1200 mg/day in two doses, 30 minutes before meals; should be avoided in hepatic or severe renal impairment	
Omega-3-Fatty Acids			
Lovaza	1-g capsule containing at least 0.9 g of OM3FA ethyl ester (EPA~0.465 g and DHA ~0.375 g)	4 g/day taken as single 4 g dose (four capsules) or two 2 g doses (two capsules twice daily)	All products are obtained from oil of fish. Should be used with caution in patients with known hypersensitivity to fish and/or shellfish. Side effects include: Side effects of Lovaza/Omtryg include: • Eructation, 4% • Dyspepsia, 3% • Taste perversion, 4% Side effects of Vascepa include: • Arthralgia, 2.3% Side effects of Epanova include: • Diarrhea, 15% • Nausea, 6% • Abdominal pain or discomfort, 5%
Vascepa	1-g capsule containing 1 g of icosapent ethyl	4 g/day taken as 2 g doses (two capsules twice daily)	
Epanova	1-g capsule containing at least 0.85 g OM3FFA (EPA~0.550 g and DHA~0.2 g)	2 or 4 g/day taken as single 2 g dose (2 capsules) or single 4 g dose (four capsules)	
Omtryg	1-g capsule containing at least 0.9 g of OM3FA ethyl ester (EPA ~0.465 g and DHA~0.375 g)	4 g/day taken as single 4 g dose (four capsules) or two 2 g doses (two capsules twice daily)	
Micosomal Transfer Protein Inhibitors			
Lomitapide	5-, 10-, and 20-mg capsules	5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily	Gastrointestinal side effects and elevation in liver enzymes and hepatic fat are common
Antisense Oligonucleotide			
Mipomersen	200 mg subcutaneous injection	200 mg once weekly as a subcutaneous injection	Injection site reactions, hepatic fat, and liver enzyme elevations are common
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors			
Alirocumab	75 mg or 150 mg subcutaneous injection	75–150 mg once every 2 week subcutaneous injection or 300 mg once every month subcutaneous injection	Injection site reactions, nasopharyngitis, influenza, upper respiratory tract infections, urinary tract infection, elevation in liver enzymes
Evolocumab	140 mg or 420 mg subcutaneous injection	140 mg once every 2 week subcutaneous injection or 420 mg once every month subcutaneous injection	Injection site reactions, nasopharyngitis, influenza, upper respiratory tract infections, urinary tract infection, back pain
Combination Products			
Ezetimibe and atorvastatin	10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	Dosage range is 10/10 mg/day through 10/80 mg/day. Recommended usual starting dose is 10/10 or 10/20 mg/day. Recommended starting dose is 10/40 mg/day for patients requiring a > 55% reduction in LDL cholesterol	See previous entries for each drug (ezetimibe and atorvastatin)

(*Continued*)

Table 12–11

Formulation, Dosing, and Common Adverse Effects of Lipid-Lowering Drugs (*Continued*)

Lipid-Lowering Drug	Dosage Forms	Usual Adult Maintenance Dose Range	Adverse Effects
Ezetimibe and simvastatin	10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	Dosage range is 10/10 mg/day through 10/40 mg/day. Recommended usual starting dose is 10/10 or 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive LDL cholesterol reductions. Due to increased risk of myopathy, including rhabdomyolysis, use of the 10/80 mg dose of Vytorin should be restricted to patients who have been taking Vytorin 10/80 mg chronically (eg, for 12 months or more) without evidence of muscle toxicity. Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with Vytorin doses exceeding 10/20 mg/day coadministered with lipid-modifying doses (≥ 1 g/day niacin) of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive Vytorin 10/80 mg coadministered with lipid-modifying doses of niacin-containing products	See previous entries for each drug (ezetimibe and simvastatin)

[a]Dose strengths vary depending on brand.

CHD, coronary heart disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ER, extended release; HMG-CoA, 3-hydroxy-3-methyglutaryl coenzyme A; IR, immediate-release; LDL, low-density lipoprotein; OM3FA, omega-3 fatty acid; OM3FFA, omega-3 free fatty acid.

It is reasonable to check a baseline CK in patients at risk for myopathy. Follow-up CK should only be obtained in patients complaining of muscle pain, weakness, tenderness, or brown urine. Patient assessment for symptoms of myopathy should be done 6 to 12 weeks after starting therapy and at each visit.

Some evidence suggests that statins increase the risk for development of DM. The Food and Drug Administration (FDA) warns of increased blood sugar and glycosylated hemoglobin (HbA_{1c}) levels on statin labels. In addition, the FDA has added to statin labels that cognitive impairment, such as memory loss, forgetfulness and confusion, has been reported by some statin users. It is suggested to look into other causes of cognitive impairment if this occurs while on statins and appears to be reversible, with symptoms disappearing approximately 3 weeks after statin discontinuation. The FDA continues to believe that the cardiovascular benefits of statins outweigh these small increased risks.

With the exception of pravastatin and pitavastatin, the other statins undergo biotransformation by the cytochrome P-450 (CYP) system with lovastatin and simvastatin having the highest risk of drug–drug interactions. Therefore, drugs known to inhibit statin metabolism should be used cautiously or avoided and are highlighted in a recent AHA scientific statement on statin drug interactions.[27] Medications such as cyclosporine and gemfibrozil can inhibit drug transporters in the gut and liver that can increase statin concentrations. The time until maximum effect on lipids for statins is generally 4 to 6 weeks.

► *Cholesterol Absorption Inhibitors*

Ezetimibe blocks biliary and dietary cholesterol as well as phytosterol (plant sterol) absorption by interacting with the NPC1L1 transporter (Figure 12–2).[5] Less cholesterol is delivered to the liver which leads to an upregulation of LDL receptors. This causes a reduction in serum cholesterol and a compensatory increase in cholesterol biosynthesis. Because statins inhibit cholesterol biosynthesis, this compensatory increase by ezetimibe can be blocked when coadministered with a statin.

KEY CONCEPT Ezetimibe reduces LDL cholesterol by an average of 18%. However, larger reductions can be seen in some individuals, presumably due to higher absorption of cholesterol. These individuals appear to have a blunted response to statin therapy. Ezetimibe lowers triglycerides by 7% to 9% and modestly increases HDL cholesterol. (See Table 12–10.)

LO 6 Ezetimibe is contraindicated in patients with active liver disease or unexplained persistent elevations in LFTs. Since statins are the standard of care, a placebo-controlled randomized trial of the effects of ezetimibe monotherapy on CHD morbidity and mortality has never been conducted. Ezetimibe combined with simvastatin was associated with a reduced incidence of ischemic cardiovascular events in low-risk patients with mild to moderate asymptomatic aortic stenosis compared with placebo,[28] as well as reduced incidence of major atherosclerotic events in a wide range of patients with advanced chronic kidney disease.[29] Most recently, ezetimibe combined with simvastatin was shown to further reduce ASCVD events in patients who have suffered a recent myocardial infarction (MI) compared to simvastatin alone.[30] Ezetimibe is primarily used in combination with a statin when adequate reductions in atherogenic cholesterol is not achieved (Table 12–7) or in those patients who are intolerant to statin therapy. The time until maximum effect on lipids for ezetimibe is generally 2 weeks.

Patient Encounter 2, Part 1

A 48-year-old, nonsmoking woman presents to your clinic for a physical examination. She states that she had an MI 1 year ago and she tries to take her medications every day. She has not had her cholesterol evaluated since her MI last year. She reports having chest pain rarely (less than once a month). She has one brother who is 42 years old with hypertension and diabetes but otherwise healthy. Her father had an MI when he was 50 and has elevated cholesterol. The patient is married with two children. She does not smoke and exercises regularly (3 times a week most weeks). She ate breakfast (eggs and bacon) approximately 3 hours ago.

Does this patient have clinical ASCVD?

Can the patient be evaluated today for non-HDL cholesterol?

Should an assessment of her risk factors for ASCVD or an ASCVD risk score be conducted?

What additional information do you need to evaluate the patient?

▶ Bile Acid Sequestrants

Cholestyramine, colestipol, and colesevelam are the oral bile acid-binding resins or sequestrants (BAS) currently available in the United States. Resins are highly charged molecules that bind to bile acids in the gut. The resin–bile acid complex is then excreted in the feces. The loss of bile causes a compensatory conversion of hepatic cholesterol to bile, reducing hepatocellular stores of cholesterol and resulting in an upregulation of LDL receptors which then results in a decrease in serum cholesterol. Resins have been shown to reduce CHD events in patients without CHD.[31]

KEY CONCEPT Resins are moderately effective in lowering LDL cholesterol but do not lower triglycerides. Moreover, in patients with elevated triglycerides, the use of a resin may increase triglycerides. This may be due to a compensatory increase in HMG-CoA reductase activity which results in an increase in secretion of VLDL. The increase in HMG-CoA reductase activity can be blocked with a statin, resulting in enhanced reductions in serum lipids. Resins reduce LDL cholesterol from 15% to 30%, with a modest increase in HDL cholesterol (3%–5%) (Table 12–10). Resins are most often used as adjuncts to statins in patients who require additional lowering of atherogenic cholesterol and are an option to add to statins based on the ACC nonstatin ECDP (Table 12–3).[9] Since these drugs are not absorbed, adverse effects are limited to the gastrointestinal (GI) tract (Table 12–11). About 20% of patients taking cholestyramine or colestipol report constipation and symptoms such as flatulence and bloating. A large number of patients stop therapy because of the GI effects. Resins should be started at the lowest dose and escalated slowly over weeks to months as tolerated until the desired response is obtained. Patients should be instructed to prepare the powder formulations in 6 to 8 ounces (~180–240 mL) of noncarbonated fluids, usually juice (enhances palatability) or water. Fluid intake should be increased to minimize constipation. Colesevelam is better tolerated with fewer GI side effects, although it is more expensive.[32] Colesevelam also has an indication for improvement of glycemic control in type 2 DM. All resins have the potential to prevent absorption of other drugs such as digoxin, warfarin, thyroxine, thiazides, β-blockers, fat-soluble vitamins, and folic acid. Potential drug interactions can be avoided by taking a resin either 1 hour before or 4 hours after these other agents. The time until maximum effect on lipids for resins is generally 2 to 4 weeks.

LO 6

LO 7

▶ Niacin

Niacin (vitamin B_3) has broad applications in the treatment of lipid disorders when used at doses higher than those used as a nutritional supplement. Niacin inhibits FA release from adipose tissue and FA and triglyceride production in liver cells. This results in a reduction in the number of VLDL particles secreted (Figure 12–4), which leads to an overall reduction in LDL cholesterol and a decrease in the number of small dense LDL particles. Niacin also reduces the uptake of HDL-Apo A1 particles and increases uptake of cholesterol esters by the liver, thus improving the efficiency of reverse cholesterol transport between HDL particles and vascular tissue (Figure 12–4). Niacin is indicated for patients with elevated triglycerides, low HDL cholesterol, and elevated LDL cholesterol.[8,11]

Several different niacin formulations are available: immediate-release (IR), sustained-release (SR), and extended-release (ER).[33,34] These formulations differ in terms of dissolution and absorption rates, metabolism, efficacy, and side effects. Limitations of niacin IR and SR are flushing and **hepatotoxicity**, respectively. These differences appear related to the dissolution and absorption rates of niacin formulations and their subsequent metabolism. Niacin IR is available by prescription (Niacor) as well as a dietary supplement, which is not regulated by the FDA.[33] Currently, all SR products are available only as dietary supplements.

Niacin ER (Niaspan) was developed as a once-daily formulation to be taken at bedtime, with the goal of reducing the incidence of flushing without increasing the risk of hepatotoxicity. Niaspan is the only long-acting niacin product approved by the FDA for dyslipidemia.

Niacin use is limited by cutaneous reactions such as flushing and pruritus of the face and body. The use of aspirin or a nonsteroidal anti-inflammatory drug (NSAID) 30 minutes prior to taking niacin can help alleviate these reactions because they are mediated by an increase in prostaglandin D2.[8,11] In addition, taking niacin with food and avoiding hot liquids or alcohol at the time niacin is taken is helpful in minimizing flushing and pruritus. Lastly, slow titration of the niacin dose to minimize and/or prevent flushing (eg, 500 mg/day to 1000 mg/day over 8 weeks).

In general, niacin reduces LDL cholesterol from 5% to 25%, reduces triglycerides by 11% to 60%, and increases HDL cholesterol by 14% to 39% (Table 12–10). Niacin monotherapy has been shown to reduce CHD events and total mortality,[35] as well as the progression of atherosclerosis when combined with a statin.[36] However, a recent trial that tested the effects of adding niacin ER or placebo in patients with CHD optimally treated (LDL cholesterol ~70 mg/dL [1.81 mmol/L]) on a statin was stopped earlier than planned because no apparent benefits by adding niacin ER were found. Moreover, a small and unexplained increase in ischemic stroke in the niacin ER group was seen.[37] Another trial also found no benefit by the addition of niacin ER plus an anti-flush medication (laropiprant).[38] These two trials have resulted in ambiguity in the role of niacin in lipid management. However, niacin is still a useful agent in the management of high triglycerides.

Niacin should be instituted at the lowest dose and gradually titrated to a maximum dose of 2 g daily for ER and SR products and no more than 6 g daily for IR products. FDA-approved niacin products are preferred because of product consistency. Moreover, niacin products labeled as "no flush" do not contain nicotinic acid and therefore have no therapeutic role in the treatment of lipid disorders.[33] The time until maximum effect on lipids for niacins is generally 3 to 5 weeks.

LO 6

LO 6

LO 7

▶ Fibrates

KEY CONCEPT The predominant effects of fibrates are a decrease in triglyceride levels by 20% to 60% and an increase in HDL cholesterol levels by 9% to 30% (Table 12–10). The effect on LDL cholesterol is less predictable. In patients with high triglycerides, however, LDL cholesterol may increase. Fibrates increase the size and reduce the density of LDL particles much like niacin. KEY CONCEPT Fibrates are the most effective triglyceride-lowering drugs and are used primarily in patients with elevated triglycerides and low HDL cholesterol.

Fibrates work by activating peroxisome proliferator-activated receptor-alpha (PPAR-α), a nuclear receptor involved in cellular function. This results in a reduction in triglyceride-rich lipoproteins (VLDL and IDL) and an increase in HDL.

Clinical trials of fibrate therapy in patients with elevated cholesterol and no history of CHD demonstrated a reduction in CHD incidence, although less than the reduction attained with statin therapy.[39] In addition, a large study of men with CHD, low HDL cholesterol, low LDL cholesterol, and elevated triglycerides demonstrated a 24% reduction in risk of death from CHD, nonfatal MI, and stroke with gemfibrozil.[40] Fibrates may be appropriate in prevention of CHD events for patients with established CHD, low HDL cholesterol, and triglycerides below 200 mg/dL (2.26 mmol/L). However, LDL-lowering therapy with statins should be the primary target if non-HDL and LDL cholesterol are elevated. Evidence of a reduction in CHD risk among patients with established CHD has not been demonstrated with fenofibrate.

LO 6 The fibric acid derivatives are generally well tolerated. The most common adverse effects include dyspepsia, abdominal pain, diarrhea, flatulence, rash, muscle pain, and fatigue (Table 12–11). Myopathy and rhabdomyolysis can occur, and the risk appears to increase with renal insufficiency or concurrent statin therapy. If a fibrate is used with a statin, fenofibrate is preferred because it appears to inhibit the glucuronidation of the statins less than gemfibrozil.[41] A CK level should be checked before therapy is started and if symptoms occur. Liver dysfunction has been reported, and LFTs should be monitored. Fibrates increase cholesterol in the bile and have caused gallbladder and bile duct disorders, such as cholelithiasis and cholecystitis. Unlike niacin, these agents do not increase glucose or uric acid levels. Fibrates are contraindicated in patients with gallbladder disease, liver dysfunction, or severe kidney dysfunction. The risk of bleeding is increased in patients taking both a fibrate and warfarin, specifically with gemfibrozil based on a CYP 2C9 interaction which can result in an increase in a patient's international normalized ratio (INR) if adding gemfibrozil to warfarin therapy. Increased INR monitoring is suggested after initiation of gemfibrozil in patients currently taking warfarin. The time until maximum effect on lipids is generally 2 weeks for fenofibrate and 3 to 4 weeks for gemfibrozil.

▶ Long-Chain Omega-3 Fatty Acids (OM3FA)

OM3FA (eicosapentaenoic acid and docosahexaenoic acid), the predominant long-chain FA in the oil of cold-water fish, lower triglycerides by as much as 45% (Table 12–10) when taken in large amounts (2–4 g). Long-chain OM3FA may be useful for patients with high triglycerides despite diet and weight loss, alcohol restriction, and fibrate therapy. This effect may be modulated through reduction in hepatic synthesis and release of VLDL triglycerides, increased β-oxidation of FA, and enhanced triglyceride clearance from triglyceride-rich lipoproteins. Long-chain OM3FA have other cardiac effects such as reduced platelet aggregation and antiarrhythmic properties. The current AHA Scientific Statement on fish consumption, fish oil, OM3FA, and cardiovascular disease recommends an increased intake of OM3FA in the diet.[42]

Prescription-grade long-chain OM3FA ethyl esters and free FA formulations are FDA approved at a dose of 2 to 4 g daily for the treatment of elevated triglycerides (≥ 500 mg/dL [5.65 mmol/L]). Use of high-quality OM3FA free of contaminants such as mercury and organic pollutants should be encouraged when using these agents. Common side effects associated with long-chain OM3FA are dyspepsia and eructation (Table 12–11). LO 6 Patients taking anticoagulant or antiplatelet agents should be monitored more closely when consuming these products because excessive amounts of long-chain OM3FA (eg, > 3 g daily) may lead to bleeding and may increase risk of hemorrhagic stroke.

▶ Microsomal Triglyceride Transport Inhibitors

Lomitapide is an oral inhibitor of microsomal triglyceride transfer protein, thereby inhibiting the normal transfer of triglycerides to Apo B in the lumen of the endoplasmic reticulum and preventing the assembly of Apo B–containing lipoproteins in enterocytes and hepatocytes.[8,11] Lomitapide reduces LDL cholesterol levels on average by 40% (Table 12–10) in homozygous FH patients on maximum tolerated lipid-lowering therapy and LDL apheresis. However, given its mechanism of action, GI side effects and elevation in liver enzymes and hepatic fat are common (Table 12–11). LO 6 Because of the risk of hepatotoxicity, lomitapide is available only through the Risk Evaluation and Mitigation Strategy (REMS) program and is currently FDA approved for the management of patients with homozygous FH. Gastrointestinal side effects are managed by strict adherence to a low-fat diet (< 20% of total calories from fat) and gradual dose escalation based on acceptable safety and tolerability. Lomitapide is primarily metabolized by CYP 3A4. Lomitapide interacts with numerous agents such as strong and moderate CYP 3A4 inhibitors and 3A4 inducers. Lomitapide is classified as pregnancy category X.

▶ Antisense Oligonucleotide Inhibitor of Apo B-100 Synthesis

Mipomersen is a once-weekly subcutaneous injectable antisense inhibitor of Apo B synthesis. When given in combination with maximum tolerated doses of lipid-lowering therapy, it can reduce LDL cholesterol by an additional 25% in homozygous FH patients (Table 12–10).[8,11] Injection site reactions, flu-like symptoms, hepatic fat, and liver enzyme elevations are common (Table 12–11). Because of the risk of hepatotoxicity similar to lomitapide, mipomersen is available only through a REMS program. Mipomersen is not a substrate for CYP metabolism and is metabolized by endonucleases and exonucleases. Therefore, LO 6 mipomersen has minimal clinically relevant drug–drug interactions. Mipomersen is pregnancy category B.

▶ Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

Alirocumab and evolocumab are subcutaneous injectable human monoclonal antibodies that bind to PCSK9. PCSK9 binds to the LDL receptors on hepatocyte surfaces to promote low-density lipoprotein receptor (LDLR) degradation. LDLR is the primary receptor that clears circulating LDL; therefore, the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL. By inhibiting the binding of PCSK9 to LDLR, these agents increase the number of LDLRs available to clear LDL, thereby lowering LDL levels. In clinical trials, these agents have produced an additional

48% to 71% decrease in LDL levels when used in combination with statin therapy, compared with statin monotherapy. Both medications are FDA approved for heterozygous FH or ASCVD as an adjunct to diet and maximally tolerated statin therapy, when additional LDL lowering is required.[9,10] Evolocumab is also indicated as an adjunct in homozygous FH.[9,10] Recently, the results of the CV outcomes study for evolocumab and bococizumab (not currently FDA approved) were published.[43,44] The evolocumab CV outcome study demonstrated a reduction in the primary CV composite endpoint on top of statin therapy and was a primary driver for the updated ACC ECDP for nonstatin therapy presented in Table 12–7. Alirocumab's CV outcome trial demonstrated a reduction in major adverse cardiovascular events in post-acute coronary syndrome patients who were taking maximally tolerated statins compared to placebo.[45,46]

Combination Pharmacotherapy

A large proportion of the US population remains at a high risk for future CV events despite treatment with statin therapy. Reasons for high residual risk include inadequate starting doses, lack of dose escalation, and high baseline risk warranting lower treatment targets.[47] In addition, if lack of response is seen, patient adherence and adverse events should be assessed. Moreover, patients with concomitant elevations in triglycerides may need combination drug therapy to reach their non-HDL cholesterol goal. KEY CONCEPT Combination drug therapy is an effective means to achieve greater reductions in non-HDL and LDL cholesterol (statin plus ezetimibe or PCSK9 inhibitor) as well as lowering serum triglycerides (statin plus long-chain OM3FA or fibrate).

▶ *Combination Therapy for Elevated LDL Cholesterol*

LO 3 LO 5

For patients who do not achieve their non-HDL and LDL cholesterol goals with statin monotherapy and lifestyle modifications, including those unable to tolerate high doses due to adverse effects, combination therapy may be appropriate. The ACC ECDP for nonstatin therapy highlighted in Table 12–7 describes the first-line and second-line add-on therapies to statins for patients for both primary and secondary prevention of ASCVD. First-line add-on therapies include ezetimibe or PCSK9 inhibitors. Second-line add-on therapies include BAS. Ezetimibe, PCSK9 inhibitors, and BAS combine effectively with statins to augment further cholesterol reduction, with the largest LDL cholesterol and non-HDL cholesterol reductions seen with PCSK9 inhibitors combined with statins. Adverse events are similar to those of each product taken separately. The time until maximum effect on lipids for this combination is generally 2 to 6 weeks.

Some patients, in particular those with genetic forms of hypercholesterolemia such as FH (Table 12–1), require three or more drugs to manage their disorder. It is recommended that patients with FH obtain a minimum of greater than or equal to 50% reduction in LDL cholesterol.[8,11]

▶ *Combination Therapy for Elevated Cholesterol and Triglyceridemia with or Without Low HDL Cholesterol*

Fibrates are the most effective triglyceride-lowering agents and also raise HDL cholesterol levels. Combination therapy with a fibrate, particularly gemfibrozil, and a statin has been found to increase the risk for myopathy. Therefore, more frequent monitoring, thorough patient education, and consideration of factors that increase risk as reviewed previously should be considered.

KEY CONCEPT The evidence of reducing non-HDL and LDL cholesterol while substantially raising HDL cholesterol (statin plus niacin or fibrate) to reduce the risk of CHD related events to a greater degree than statin monotherapy remains in question. A recent trial found that the combination of fenofibrate and simvastatin did not reduce the overall rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke, as compared with simvastatin alone. However, in a prespecified subgroup analysis, incremental benefits of adding a fenofibrate to simvastatin therapy were noted in patients with triglycerides greater than or equal to 204 mg/dL (2.31 mmol/L) and HDL cholesterol less than or equal to 34 mg/dL (0.88 mmol/L).[48] Combining niacin with a statin augments the non-HDL and LDL cholesterol-lowering potential of niacin while enhancing both the HDL cholesterol-raising effects and triglyceride-lowering effects of the statin. A statin combined with niacin appears to offer greater benefits for reducing atherosclerosis progression compared with a statin

Patient Encounter 2, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: ST elevation MI 1 year ago with two drug eluting stents placed (one in left anterior descending artery and one in circumflex)

FH: Father and mother both alive. Father had MI at age 50. Brother has hypertension and type 2 DM

SH: Works for the post office as a letter sorter and exercises 3 times a week (rides bike 8–10 miles each time she exercises). Drinks alcohol (1–2 beers most nights)

Meds: Multivitamin once daily; lisinopril 20 mg once daily, metoprolol succinate 100 mg once daily, aspirin 81 mg daily, clopidogrel 75 mg daily, amlodipine 10 mg daily, simvastatin 20 mg daily

ROS: No chest pain, shortness of breath, or dizziness today in clinic

PE:

VS: BP 138/78 mm Hg, pulse 64 beats/min, RR 16 breaths/min, T 98.6°F (37°C), waist circumference 35 in (89 cm)

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Abd: Soft, nontender, nondistended; positive for bowel sounds, no hepatosplenomegaly or abdominal aortic aneurysm

Exts: ABI 1.0

Neck: No carotid and basilar bruits

EENT: Within normal limits

Labs: Total cholesterol 205 mg/dL (5.30 mmol/L), triglycerides 220 mg/dL (2.48 mmol/L), HDL cholesterol 40 mg/dL (1.03 mmol/L), non-HDL cholesterol 165 mg/dL (4.27 mmol/L), LDL cholesterol 121 mg/dL (3.14 mmol/L), and glucose 110 mg/dL (6.1 mmol/L), all other labs within normal limits

Given this additional information, what is your assessment of the patient's ASCVD risk?

Identify your treatment goals for the patient based on the ACC/AHA guidelines.

What nonpharmacologic and pharmacologic alternatives are available for the patient?

Should her children be screened for high cholesterol and why?

Develop a care plan for the patient.

alone;[33] however, the incremental benefits on reducing CHD events remain in question.[40] Similar to fenofibrate, a subset of patients in both the highest triglyceride and lowest HDL cholesterol tertiles showed a trend toward benefit with addition of ER niacin. Formulations combining ER niacin and lovastatin (Advicor) and ER niacin and simvastatin (Simcor) are available, and are indicated for treatment of primary hypercholesterolemia and mixed dyslipidemia. The time until maximum effect on lipids for this combination is generally 3 to 6 weeks.

Compared with monotherapy, combination therapy may reduce patient adherence through increased side effects and increased costs. When used appropriately and with proper precautions, however, combination therapy is effective in normalizing lipid abnormalities, particularly in patients who cannot tolerate adequate doses of statin therapy for more severe forms of dyslipidemia.

OUTCOME EVALUATION

LO 6 LO 7

- The successful outcome in cholesterol management is to reduce cholesterol and triglycerides in an effort to alter the natural course of atherosclerosis and decrease future cardiovascular events and pancreatitis.
- Use an adequate trial of TLC in all patients, but institute pharmacotherapy concurrently in higher-risk patients.
- For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk because of their ability to substantially reduce non-HDL and LDL cholesterol, ability to reduce morbidity and mortality from atherosclerotic disease, convenient once-daily dosing, availability of inexpensive generics, and low risk of side effects.

Patient Care Process

Collect Information:

- Obtain fasting cholesterol profile.
- Obtain vital signs and physical examination findings.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.
- Obtain history of lipid-lowering therapy use (current and past).
- Obtain a family history for premature heart disease.
- Obtain a smoking history.
- Obtain a medical history for other comorbidities that may increase ASCVD risk.
- Obtain history of current diet and exercise regimen/pattern.

Assess the Information:

- Assess any abnormal lipid levels (Table 12–5).
- Assess lifestyle factors including diet and exercise habits.
- Assess if patient fits any of the four ACC/AHA statin benefit groups (Figure 12–6).
- Assess major risk factors for ASCVD (Table 12–8). Assign patient to risk category based on assessment and risk scoring as previously described (eg, Figure 12–6 and Tables 12–7 and 12–9).
- Assess if taking any medications that may contribute to abnormal lipid levels (Table 12–2).
- Assess concomitant diseases that may contribute to abnormal lipid levels (Table 12–2).
- Assess treatments for cholesterol the patient has used in the past (if any). If already receiving pharmacotherapy for dyslipidemia, assess efficacy, safety, and adherence. Are there any significant drug interactions?

Develop a Care Plan:

- Determine treatment goal for percent LDL cholesterol lowering, non-HDL cholesterol, and LDL cholesterol based on risk category (Table 12–7).
- Discuss importance of family screening if patient has FH.
- Select TLCs and educate patient on importance of TLCs and regular physical activity (Table 12–6).
- Consider starting pharmacotherapy in patients based on their risk category for ASCVD (eg, statin benefit groups in Figure 12–6). Consider potential disease and drug interactions that may affect choice or intensity of pharmacotherapy (Table 12–11).
- For patients with ASCVD or DM, consideration should be given to use of moderate or high-intensity statin therapy (Table 12–4), irrespective of baseline cholesterol levels.
- Determine patient's prescription coverage.

Implement the Care Plan:

LO 7

- Provide patient education and address concerns associated with ASCVD, hyperlipidemia, drug therapy, and therapy adherence.
- Educate patient on TLC interventions (eg, exercise, diet modifications).
- Start pharmacotherapy concordant with statin benefit group or overall ASCVD risk in collaboration with health care team.
- Develop a follow-up plan for the patient to assess efficacy and safety.

LO 7

- Stress the importance of medication adherence to the patient.
- Address any patient concerns about dyslipidemia and its management.

Follow-up: Monitor and Evaluate:

- Follow-up at regular intervals to assess cholesterol levels for attaining goals for dyslipidemia and monitoring of side effects (Table 12–11).
- Review medication adherence.
- Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status.
- For patients with FH, if it is not possible to attain desirable cholesterol levels, a reduction of at least 50% is recommended.
- Intensify TLC for those patients above cholesterol targets.
- Titrate therapy or add additional drug as needed.

- Use an individualized patient monitoring plan in an effort to promote medication safety, minimize side effects, maintain treatment adherence, and achieve lipid goals.
- Lipid goals should be assessed by determing if the patient has achieved their target LDL cholesterol reduction based on their statin benefit group (eg, clinical ASCVD patient on a high-intensity statin should achieve at least a 50% reduction in LDL cholesterol; if baseline LDL cholesterol values not available to calculate percent reduction then achieving an LDL cholesterol of less than 70 mg/dL [1.81 mmol/L] or a non-HDL cholesterol of less than 100 mg/dL [2.59 mmol/L] are additional targets).

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Abbreviations Introduced in This Chapter

AACE	American Association of Clinical Endocrinologists
ABI	Ankle brachial index
ACC	American College of Cardiology
ACE	American College of Endocrinology
AHA	American Heart Association
Apo	Apolipoprotein
ASCVD	Atherosclerotic cardiovascular disease
BAS	Bile acid sequestrant
C	Cholesterol
CAC	Coronary artery calcium
CETP	Cholesterol ester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
CVD	Cardiovascular disease
CV	Cardiovascular
CYP	Cytochrome P-450
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DM	Diabetes mellitus
ECDP	Expert Consensus Decision Pathway
EPA	Eicosapentaenoic acid
ER	Extended-release
FA	Fatty acid
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GI	Gastrointestinal
HbA_{1c}	Glycosylated hemoglobin
HDL	High-density lipoprotein
HL	Hepatic lipase
HMG-CoA	3-hydroxy-3-methyglutaryl coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IDL	Intermediate-density lipoprotein
INR	International normalized ratio
IR	Immediate-release
LDL	Low-density lipoprotein
LDLR	Low-density lipoprotein receptor
LFT	Liver function test
LPL	Lipoprotein lipase
LRP	LDL-related protein
MI	Myocardial infarction
NLA	National Lipid Association
NPC1L1	Niemann-Pick C1 Like 1
NSAID	Nonsteroidal anti-inflammatory drug
OM3FA	Omega-3 fatty acid
OM3FFA	Omega-3 free fatty acid
PPAR-α	Peroxisome proliferator-activated receptor-alpha
PCSK9	Proprotein convertase subtilisin/kexin 9
REMS	Risk evaluation and mitigation strategy
SBP	Systolic blood pressure
SR	Sustained-release
SR-BI	Scavenger receptors
TG	Triglycerides
TLC	Therapeutic lifestyle changes
VLDL	Very low-density lipoprotein

REFERENCES

1. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. Arch Intern Med. 1993;153:1065–1073.
2. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146–e603.
3. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63 (25 Pt B):2889–2934.
4. Genest J. Lipoprotein disorders and cardiovascular risk. J Inherit Metab Dis. 2003;26:267–287.
5. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001;345:1583–1592.
6. Endo A. The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res. 1992;33(11):1569–1582.
7. Brown MS, Faust JR, Goldstein JL, Kaneko I, et al. Induction of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity in human fibroblasts incubated with compactin (ML-236B), a competitive inhibitor of the reductase. J Biol Chem. 1978; 253(4):1121–1128.
8. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1—executive summary. J Clin Lipidol. 2014; 8(5):473–488.
9. Lloyd-Jones DM, Morris PB, Ballantyne CM et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2016;68:92–125.
10. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2017; in press. Available from: https://doi.org/10.1016/j.jacc.2017.07.745
11. Jellinger PS, Handelsman Y, Rosenbilt PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for the management of dyslipidemia and prevention of atherosclerosis. Endocr Pract. 2017;23(suppl 2): 1–87.
12. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3):133–140.
13. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195–2207.
14. Shepherd J, Cobbe SM, Ford I, et al., for The West of Scotland Coronary Prevention Study Group. Prevention of coronary heart

disease with pravastatin in men with hypercholesterolemia. N Engl J Med. 1995;333:1301–1307.
15. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361:1149–1158.
16. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemia, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288:2998–3007.
17. Calhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364:685–696.
18. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–1389.
19. Sacks FM, Pfeffer MA, Moye LA, et al., for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335:1001–1009.
20. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet. 2002;360(9326):7–22.
21. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;399(19):1349–1357.
22. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid-lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350:1495–1504.
23. LaRosa JC, Grundy SM, Waters DD, et al. Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–1435.
24. Downs JR, Clearfield M, Weis S, et al., for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. JAMA. 1998;270:1615–1622.
25. Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipidol. 2014;8(3 suppl):S58–S71.
26. Banach M, Rizzo M, Toth PP, et al. Statin intolerance—an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci. 2015;11(1):1–23.
27. Wiggins BS, Saseen JJ, Page RL 2nd, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2016;134(21):e468–e495.
28. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med. 2008;359:1343–1356.
29. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784): 2181–2192.
30. Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.
31. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984;251:365–374.
32. Daiichi Sankyo, Inc. Welchol [prescribing information]. Parsippany, NJ: Author. 2014.
33. Meyers CD, Carr MC, Park S, et al. Varying cost and free nicotinic acid content in over-the-counter niacin preparations for dyslipidemia. Ann Intern Med. 2003;139:996–1002.
34. McKenney JM, Proctor JD, Harris S, et al. A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients. JAMA. 1994;271:672–677.
35. Canner PL, Berge GK, Wender NK, et al. Fifteen-year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol. 1986;18:1245–1255.
36. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial biology for the investigation of the treatment effects of reducing cholesterol (ARBITER) 2. A double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation. 2004;110:3512–3517.
37. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365(24):2255–2267.
38. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014; 371(3):203–212.
39. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317:1237–1245.
40. Robins SJ, Collins D, Wittes JT, et al., for the VA-HIT Study Group. Veterans Affairs High-Density Lipoprotein Intervention Trial. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA. 2001;285(12):1585–1591.
41. Prueksaritanont T, Zhao JJ, Ma B, et al. Mechanistic studies on metabolic interactions between gemfibrozil and statins. J Pharmacol Exp Ther. 2002;301(3):1042–1051.
42. Kris-Etherton PM, Harris WS, Appel LJ, for the Nutrition Committee: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002;106:2747–2757.
43. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713–1722.
44. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. N Engl J Med. 2017;376(16):1527–1539.
45. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J. 2014; 168(5):682–689.
46. ODYSSEY outcomes: results suggest use of PCSK9 inhibitor reduces CV events, LDL-C in ACS patients. American College of Cardiology. Available from: http://www.acc.org/latest-in-cardiology/articles/2018/03/05/15/53/sat-9am-odyssey-outcomes-cv-outcomes-with-alirocumab-after-acs-acc-2018. Accessed April 20, 2018.
47. Pearson TA, Laurora I, Chu H, et al. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med. 2000;160:459–467.
48. The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563–1574.

13 Hypovolemic Shock

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LEARNING OBJECTIVES

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

1. List the most common etiologies of decreased intravascular volume in hypovolemic shock patients.
2. Describe the major hemodynamic and metabolic abnormalities that occur in patients with hypovolemic shock.
3. Describe the clinical presentation including signs, symptoms, and laboratory test measurements for the typical hypovolemic shock patient.
4. Prepare a treatment plan with clearly defined outcome criteria for a hypovolemic shock patient that includes both fluid management and pharmacologic therapy.
5. Compare and contrast relative advantages and disadvantages of crystalloids, colloids, and blood products in the treatment of hypovolemic shock.
6. Outline the elements of damage control resuscitation in traumatic hemorrhagic shock patients.
7. Formulate a stepwise monitoring strategy for a hypovolemic shock patient.

INTRODUCTION

The primary function of the circulatory system is to supply oxygen and vital metabolic compounds to cells throughout the body, as well as removal of metabolic waste products. Circulatory shock is a life-threatening condition whereby this principal function is compromised resulting in inadequate cellular oxygen utilization.[1,2] When circulatory shock is caused by a severe loss of blood volume or body water, it is called hypovolemic shock. KEY CONCEPT By definition, hypovolemic shock occurs as a consequence of inadequate intravascular volume to meet the oxygen and metabolic needs of the body. Rapid and effective restoration of circulatory homeostasis using fluids, pharmacologic agents, and/or blood products is imperative to prevent complications of untreated shock and ultimately death.

ETIOLOGY AND EPIDEMIOLOGY

Practitioners must have a good understanding of cardiovascular physiology to diagnose, treat, and monitor circulatory problems in critically ill patients. The interrelationships among the major hemodynamic variables are depicted in Figure 13–1.[3] These variables include mean arterial pressure (MAP), cardiac output (CO), systemic vascular resistance (SVR), heart rate (HR), stroke volume (SV), left ventricular size, afterload, myocardial contractility, and preload. Although an oversimplification, Figure 13–1 is beneficial in conceptualizing where the major abnormalities occur in patients with circulatory shock as well as predicting the body's compensatory responses.

Hypovolemic shock is caused by a loss of intravascular volume either by hemorrhage or fluid loss (eg, dehydration). There is a profound deficit in preload, defined as the volume in the left ventricle at the end of diastole. Decreased preload results in subsequent decreases in SV, CO, and eventually, MAP. As such, restoration of preload becomes an overarching goal in the management of hypovolemic shock.

The prognosis of shock patients depends on several variables, including severity, duration, underlying etiology, preexisting organ dysfunction, and reversibility.[4] Data are not readily available on the incidence of hypovolemic shock, although hypovolemia due to hemorrhage is a major factor in 40% to 50% of trauma deaths annually.[5]

PATHOPHYSIOLOGY

The total amount of water in a typical 70-kg (154-lb) adult is approximately 42 L (Figure 13–2). About 28 of the 42 L are inside the cells of the body (intracellular fluid); the remaining 14 L are in the extracellular fluid space (fluid outside of cells, ie, interstitial fluid and plasma). Circulating blood volume for a normal adult is roughly 5 L (70 mL/kg) and is composed of 2 L of red blood cell fluid (intracellular) and 3 L of plasma (extracellular).

KEY CONCEPT Regardless of etiology, the most distinctive clinical manifestations of hypovolemic shock are arterial hypotension, clinical signs of hypoperfusion, and metabolic acidosis.[2] Metabolic acidosis is a consequence of an accumulation of lactic acid resulting from tissue hypoxia and anaerobic metabolism. If the decrease in MAP is severe and protracted, such hypotension will inevitably lead to severe hypoperfusion and organ dysfunction. Diminished intravascular volume can result from severe external or internal bleeding, profound fluid losses from gastrointestinal (GI) sources such as diarrhea or vomiting, or urinary losses such as diuretic use, diabetic ketoacidosis, or diabetes insipidus (Table 13–1).[1] Other sources of intravascular fluid loss can occur through damaged skin, as seen with burns, or via capillary leak into the interstitial space or peritoneal cavity, as seen with edema or ascites. This latter phenomenon

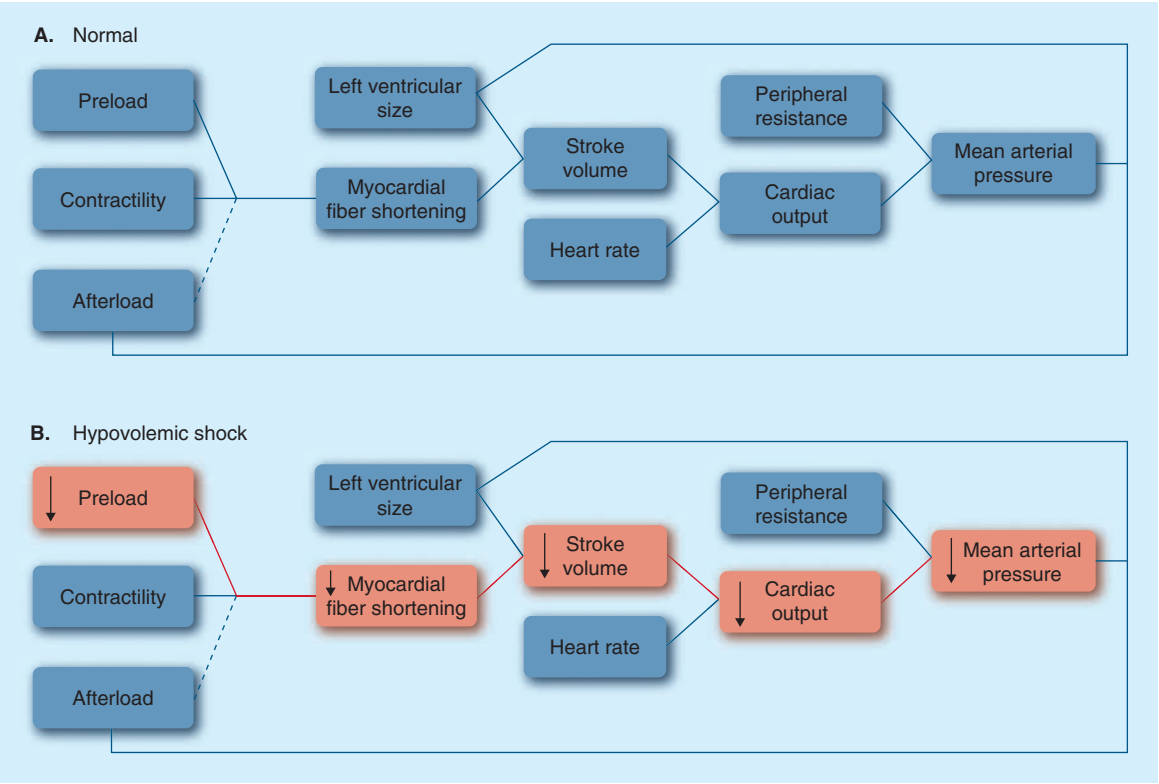

FIGURE 13–1. Hemodynamic relationships among key cardiovascular parameters (**A**). Solid lines represent a direct relationship; the broken line represents an inverse relationship. In (**B**), the alterations typically observed in hypovolemic shock are highlighted with arrows depicting the likely direction of the alteration. (Panel A from Braunwald E. Regulation of the circulation. I. N Engl J Med. 1974;290:1124–1129, with permission.)

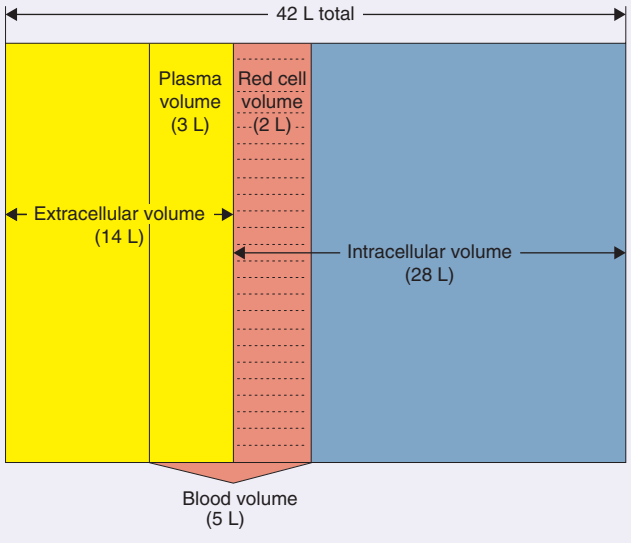

FIGURE 13–2. Distribution of body fluids showing the extracellular fluid volume, intracellular body fluid volume, and total body fluids in a 70-kg (154-lb) adult. Extracellular volume (ECV; yellow section of figure) comprises 14 L of total body fluid (42 L). Plasma volume makes up approximately 3 L of the 14 L of ECV. Intracellular volume (blue section of figure) accounts for the remaining 28 L of total body fluids, with roughly 2 L located within the red blood cells. Blood volume (~5 L) is also depicted and made up of primarily red blood cells and plasma (red section of figure). (From Guyton AC, Hall JE. Textbook of Medical Physiology, 8th ed. Philadelphia, PA: Saunders; 1991:275, with permission.)

is often referred to as third spacing because fluid accumulates in the interstitial space disproportionately to the intracellular and extracellular fluid spaces. Regional ischemia may also develop as blood flow is naturally shunted from organs such as the GI tract or the kidneys to more immediately vital organs such as the heart and brain.

Hypovolemic shock symptoms begin to occur with decreases in intravascular volume in excess of 750 to 1500 mL (about 1.5–3 pints) or 15% to 30% of the circulating blood volume (20–40 mL/kg in pediatric patients).[6] Decreases in preload result in decreases in SV. Initially, CO may be partially maintained by compensatory tachycardia. Similarly, reflex increases in SVR and myocardial contractility may diminish arterial hypotension. Regardless, rapid losses (eg, minutes) undoubtedly have more profound effects than losses over a longer period (eg, hours). This neurohumoral response to hypovolemia is mediated by the sympathetic nervous

Table 13–1

Major Hypovolemic Shock Etiologies[1,2]

I. Hemorrhagic
- Trauma
- Gastrointestinal bleeding
- Abdominal aortic aneurysm

II. Nonhemorrhagic (dehydration)
- Vomiting
- Diarrhea
- Third spacing
- Burns
- Fistulae

system in an attempt to preserve perfusion to vital organs such as the heart and brain. Two major end points of this response are to conserve water to maximize intravascular volume and to improve tissue perfusion by increasing MAP and CO (oxygen delivery). The body attempts to maximize its fluid status by decreasing water and sodium excretion through release of antidiuretic hormone (ADH), aldosterone, and cortisol. MAP is maintained by peripheral vasoconstriction mediated by catecholamine release and the renin-angiotensin system.[1] CO is augmented by catecholamine release and fluid retention.[1,7] Unfortunately, the increased sympathetic drive may become detrimental as tissue ischemia occurs with inconsistent microcirculatory flow.[1] Regardless, when intravascular volume losses exceed 1500 mL (about 3 pints), the compensatory mechanisms are inadequate, typically resulting in a fall in CO and MAP; acute losses greater than 2000 mL (about 4 pints) are life threatening (35 mL/kg in pediatric patients).[8] The decrease in CO results in a diminished delivery of oxygen to tissues within the body and activation of an acute inflammatory response.[1,5] Oxygen delivery can be further compromised by inadequate blood hemoglobin levels due to hemorrhage and/or diminished hemoglobin saturation due to impaired ventilation. Decreased delivery of oxygen and other vital nutrients results in diminished production of the energy substrate, adenosine triphosphate (ATP). Lactic acid is then produced as a by-product of anaerobic metabolism within tissues throughout the body.[7] Lactic acidosis is a key indicator that inadequate tissue perfusion has occurred.[7]

KEY CONCEPT Protracted tissue hypoxia sets in motion a downward spiral of events leading to organ dysfunction and eventual failure if untreated. Table 13–2 describes the effects of shock on the body's major organs. Relative failure of more than one organ is referred to as the multiple organ dysfunction syndrome (MODS). Involvement of the heart is particularly devastating considering the central role it plays in oxygen delivery and the potential for myocardial dysfunction to perpetuate the shock state. Preexisting organ dysfunction and buildup of inflammatory mediators can also exacerbate the effects of hypovolemic shock to the point of irreversibility.[5] For example, acute or chronic heart failure can lead to pulmonary edema, further aggravating gas exchange in the lungs and ultimately tissue hypoxia. Only about one-third of early-onset MODS is quickly reversible (within 48 hours) with proper fluid resuscitation. Thus it is imperative that hypovolemic shock be treated quickly to avoid MODS.[9]

Table 13–2

Hypovolemic Shock Manifestations on Major Organs

Heart
- Myocardial ischemia
- Dysrhythmias

Brain
- Restlessness, confusion, obtundation
- Global cerebral ischemia

Liver
- Release of liver enzymes
- Biliary stasis

Lungs
- Pulmonary edema
- Acute respiratory distress syndrome (ARDS)

Kidneys
- Oliguria
- Decreased glomerular filtration
- Acute kidney injury

Gastrointestinal tract
- Stress-related mucosal disease
- Bacterial translocation

Hematologic
- Thrombocytopenia
- Coagulopathies

LO 3

Clinical Presentation and Diagnosis

General

Patients will be in acute distress, although symptoms and signs will vary depending on the severity of the hypovolemia and whether the etiology is hemorrhagic versus nonhemorrhagic.

Symptoms

- Thirst
- Weakness
- Light-headedness

Signs

- Hypotension, arterial systolic blood pressure (SBP) less than 90 mm Hg or fall in SBP greater than 40 mm Hg
- Tachycardia
- Tachypnea
- Hypothermia
- Oliguria
- Dark, yellow-colored urine
- Skin color: pale to ashen; may be cyanotic in severe cases
- Skin temperature: cool to cold
- Mental status: confusion to coma
- Pulmonary artery (PA) catheter measurements: decreased CO, decreased SV, increased SVR, low pulmonary artery occlusion pressure (PAOP)
- Organ dysfunction (see Table 13–2)

Laboratory Tests

- Increased serum lactate
- Decreased arterial pH
- Decreased hemoglobin/hematocrit (hemorrhagic hypovolemic shock)
- Hypernatremia
- Elevated serum creatinine (SCr)
- Elevated blood urea nitrogen
- Hyperglycemia

TREATMENT

Desired Outcomes

KEY CONCEPT The major goals in treating hypovolemic shock are to restore effective circulating blood volume, as well as manage its underlying cause. In achieving this goal, the downward spiral of events that can perpetuate severe or protracted hypovolemic shock is interrupted. This is accomplished through the delivery of adequate oxygen and metabolic substrates such as glucose and electrolytes to the tissues throughout the body that will

optimally bring about a restoration of organ function and return to homeostasis. Evidence of the latter is a return to the patient's baseline vital signs, relative normalization of laboratory test results, and alleviation of other signs and symptoms of hypovolemic shock previously discussed. Concurrent supportive therapies are also warranted to avoid exacerbation of organ dysfunction associated with the hypovolemic shock event.

General Approach to Therapy

LO 4 Securing an adequate airway and ventilation is imperative in hypovolemic shock patients consistent with the "VIP Rule" of resuscitation: Ventilate (oxygen administration), Infuse (fluid resuscitation), and Pump (administration of a vasoactive agent).[2] Any compromise in ventilation only accentuates the tissue hypoxia occurring secondary to inadequate perfusion. Thus, early sedation, endotracheal intubation, and mechanical ventilation typically occur at this stage of resuscitation (Figure 13–3). Intravenous (IV) access is also essential for administration of fluids and medications, and is facilitated through the placement of peripheral IV lines or catheterization with central venous lines if rapid or large volumes of resuscitative fluids are indicated. Placement of an arterial catheter is advantageous to allow for accurate and continual monitoring of MAP, as well as arterial blood gas (ABG) sampling. A bladder catheter should be inserted for ongoing monitoring of urine output. Baseline laboratory tests that should be obtained immediately include complete blood cell count with differential, serum chemistry profile, liver enzymes, prothrombin and partial thromboplastin times, and serum lactate. A urinalysis and an ABG should also be obtained, and ongoing electrocardiogram (ECG) monitoring should be performed. In addition to restoring circulating blood volume, it is necessary to prevent further losses from the vascular space. This is especially true with hemorrhagic hypovolemic shock where identifying the bleeding site and achievement of hemostasis are critical in the successful resuscitation of the patient. This frequently involves surgical treatment of hemorrhages.

Upon stabilization, placement of a PA catheter may be indicated based on the need for more extensive cardiovascular monitoring than is available from noninvasive measurements such as vital signs, cardiac rhythm, and urine output.[10,11] Key measured parameters obtained from a PA catheter are the PAOP, which is a measure of left ventricular preload, and CO. From the CO values and simultaneous measurement of HR and MAP, one can calculate the left ventricular SV and SVR.[11] Placement of a PA catheter should be reserved for patients at high risk of death due to the severity of shock or preexisting medical conditions such as heart failure.[12] An alternative to the PA catheter is placement of a central venous catheter that typically resides in the superior vena cava to monitor central venous pressure (CVP). Central venous catheters are less expensive, can be more readily placed, and have been associated with comparable survival and fewer complications than PA catheters in select critically ill patient subsets (eg, acute lung injury).[13] Thus, movement has been away from the routine use of PA catheters.

▶ *Fluid Therapy*

The use of fluids is the cornerstone of managing hypovolemic shock.[1,2] KEY CONCEPT Three major therapeutic options are available to clinicians for restoring circulating blood volume: crystalloids (electrolyte-based solutions), colloids (large molecular weight solutions), and blood products.[14] Blood products are used only in instances involving hemorrhage (or severe preexisting anemia), thus leaving crystalloids and colloids as the mainstay of therapy in all types of hypovolemic shock, along with adjunctive vasopressor support. The aggressiveness of fluid resuscitation (rate and volume) is driven by the severity of the hypovolemic shock and the underlying cause. Warming of all fluids to 37°C (98.6°F) prior to administration is an important consideration to prevent hypothermia, arrhythmias, and coagulopathy because these complications will have a negative impact on the success of the resuscitation effort.[15]

Crystalloids Conventional crystalloid solutions are fluids with (a) electrolyte composition that approximates plasma known as balanced solutions (eg, lactated Ringer's solution [LR] or Plasma-Lyte), or (b) a total calculated osmolality similar to that of plasma (280–295 mOsm/kg [mmol/kg]), such as 0.9% sodium chloride (also known as normal saline [NS] or 0.9% NaCl) (Table 13–3).[14,16] Thus, conventional crystalloids distribute in normal proportions throughout the extracellular fluid space upon administration. In other words, expansion of the intravascular space only increases by roughly 200 to 250 mL for every liter of isotonic crystalloid fluid administered.[5] Hypertonic crystalloid solutions such as 3% NaCl or 7.5% NaCl have osmolalities substantially higher than plasma. The effect observed with these fluids is a relatively larger volume expansion of the intravascular space. By comparison with conventional crystalloids, administration of 250 mL of 7.5% sodium chloride results in an intravascular space increase of 500 mL.[5] This increase is a result of the fluid administered as well as osmotic drawing of intracellular fluid into the intravascular and interstitial spaces. This occurs because the hypertonic saline increases the osmolality of the intravascular and interstitial fluid compared with the intracellular fluid. Hypertonic saline also has the potential for decreasing the inflammatory response.[1] Despite these theoretical advantages, data are lacking demonstrating superiority of hypertonic crystalloid solutions compared with isotonic solutions.[17,18] Crystalloids are generally advocated as the initial resuscitation fluid in hypovolemic shock because of their availability, low cost, and equivalent outcomes compared with colloids.[10] A reasonable initial volume of an isotonic crystalloid (0.9% NaCl, LR, or Plasma-Lyte) in adult patients is 1000 to 2000 mL administered over the first hour of therapy.[6] Ongoing external or internal bleeding requires more aggressive fluid resuscitation. KEY CONCEPT In the absence of ongoing blood loss, administration of 2000 to 4000 mL of isotonic crystalloid normally reestablishes baseline vital signs in adult hypovolemic shock patients.[19]

LO 5

Patient Encounter Part 1

A 27-year-old man is admitted to the trauma center with a severely mangled right arm from a heavy equipment accident at work. He has extensive soft tissue damage, an open humerus fracture, and is actively bleeding. The first responders report heavy blood loss at the scene and in transit. The patient is in obvious pain and is only partially oriented. He is agitated so much that he is interfering with the trauma team's ability to assess and care for him. His initial blood pressure (BP) is 77/45 mm Hg.

Is this patient in shock? If so, what type of shock does the patient have and what is the cause?

Describe ways that the patient can be stabilized for a full assessment.

Describe the first nonpharmacologic steps in treating the patient.

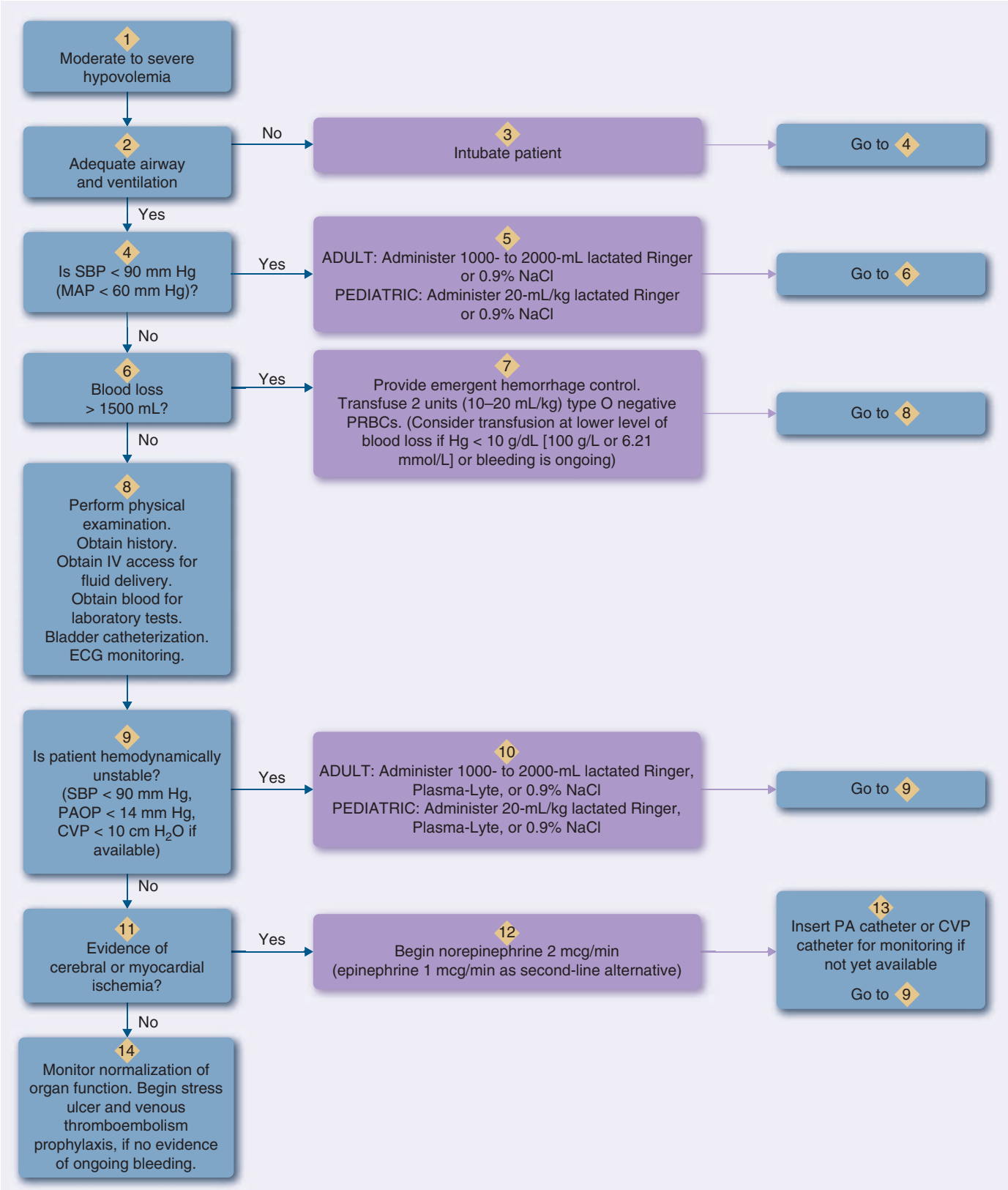

FIGURE 13–3. Treatment algorithm for the management of moderate to severe hypovolemia (balanced solution: lactated Ringer's solution, Plasma-Lyte). (CVP, central venous pressure; ECG, electrocardiogram; Hg, hemoglobin; IV, intravenous; MAP, mean arterial pressure; NaCl, sodium chloride or normal saline; PA, pulmonary artery; PAOP, pulmonary artery occlusion pressure; PRBCs, packed red blood cells; SBP, systolic blood pressure.) Hemoglobin concentration of 10 g/dL is equivalent to 100 g/L or 6.21 mmol/L.

Table 13–3

Composition of Common Resuscitation Fluids[14,16]

Fluid	Na (mEq/L)[a]	Cl (mEq/L)[a]	K (mEq/L)[a]	Mg (mEq/L)[b]	Ca (mEq/L)[b]	Lactate (mEq/L)[a]	Other	pH	Osmolality (mOsm/kg)[c]
0.9% NaCl	154	154						5.0	308
3% NaCl	513	513						5.0	1027
7.5% NaCl	1283	1283						5.0	2567
Lactated Ringer	130	109	4		2.7	28		6.5	273
Plasma-Lyte A	140	98	5	3			27 mEq/L (27 mmol/L) Acetate	7.4	294
Plasma-Lyte 148	140	98	5	3			27 mEq/L (27 mmol/L) Acetate	5.5	294
Hetastarch (Hextend)	143	124	3	0.9	5	28	Hetastarch 6 g/dL (60 g/L)	5.9	307
Hetastarch (Hespan)	154	154					Hetastarch 6 g/dL (60 g/L)	5.5	310
Pentastarch	154	154					Pentastarch 10 g/dL (100 g/L)	5.0	326
5% Albumin	130–160	130–160					Albumin 5 g/dL (50 g/L)	6.9	
25% Albumin	130–160	130–160					Albumin 25 g/dL (250 g/L)	6.9	
5% PPF	130–160	130–160	0.25				Plasma proteins 5 g/dL (50 g/L) (88% albumin)	7.0	
Dextran 40	154	154					Dextran 10 g/dL (100 g/L) (avg molecular weight 40 kDa)		
Dextran 70	154	154					Dextran 6 g/dL (60 g/L) (avg molecular weight 70 kDa)	5.5	308
Dextran 75	154	154					Dextran 6 g/dL (60 g/L) (avg molecular weight 75 kDa)	5.5	308

[a]For these values, mEq/L = mmol/L (eg, 154 mEq/L Na = 154 mmol/L).

[b]For these values, mEq/L × 0.5 = mmol/L (eg, 0.9 mEq/L Mg = 0.45 mmol/L Mg).

[c]For this value, mOsm/kg = mmol/kg (eg, 308 mOsm/kg = 308 mmol/kg).

avg, average; Ca, calcium; Cl, chloride; K, potassium; kDa, kilodalton; Mg, magnesium; Na, sodium; NaCl, sodium chloride or normal saline; PPF, plasma protein fraction.

Selected populations, such as burn patients, may require more aggressive fluid resuscitation.[20] In hemorrhagic shock patients, approximately three to four times the shed blood volume of isotonic crystalloids is needed for effective resuscitation.[20] Nevertheless, individualization of therapy is critical with well-defined endpoints to avoid excessive administration of crystalloids based on studies in trauma patients.[21]

Side effects from crystalloids primarily involve fluid overload and electrolyte disturbances of sodium, potassium, and chloride.[1] Dilution of coagulation factors can also occur resulting in a dilutional coagulopathy.[5] Two clinically significant differences between balanced solutions and NS is that the former contains potassium and has a lower sodium content (130 vs 154 mEq/L [mmol/L]). Therefore, balanced crystalloid solutions have a greater potential than NS to cause hyponatremia and/or hyperkalemia. Alternatively, NS can cause hypernatremia, hypokalemia, metabolic acidosis, and hyperchloremia. This latter adverse event is particularly concerning as a potential risk factor for acute kidney injury in critically ill patients.[22] Thus, based on their buffering capacity, lower chloride content, and respective side-effect profiles, balanced crystalloid solutions are deemed, in theory, to be the superior resuscitative fluid compared with NS by some authorities.[23,24] However, improvements in outcome have not been consistently documented with balanced crystalloid solutions nor a clear association of NS that contains a higher chloride content with acute kidney injury.[22,25] Therefore, currently there is no consensus in selecting a balanced crystalloid solution over NS.

Colloids Understanding the effects of colloid administration on circulating blood volume necessitates a review of those physiological forces that determine fluid movement between capillaries and the interstitial space throughout the circulation (Figure 13–4).[5,26] Relative hydrostatic pressure between the capillary lumen and the interstitial space is one of the major determinants of net fluid flow in or out of the circulation. The other major determinant is the relative colloid osmotic pressure between the two spaces (ie, oncotic pressure). Administration of exogenous colloids results in an increase in the intravascular colloid osmotic pressure. The effects of colloids on intravascular volume are a consequence of their relatively large molecular size (> 30 kilodaltons [kDa]), limiting their passage across the capillary membrane in large amounts. Alternately stated, colloids can be conceptualized as "sponges" drawing fluid into the intravascular space from the interstitial space. In the case of isooncotic colloids (5% albumin, 6% hetastarch, and dextran products), initial expansion of the intravascular space is essentially 65% to 75% of the volume of colloid administered, accounting for some "leakage" of the colloid from the intravascular space.[5]

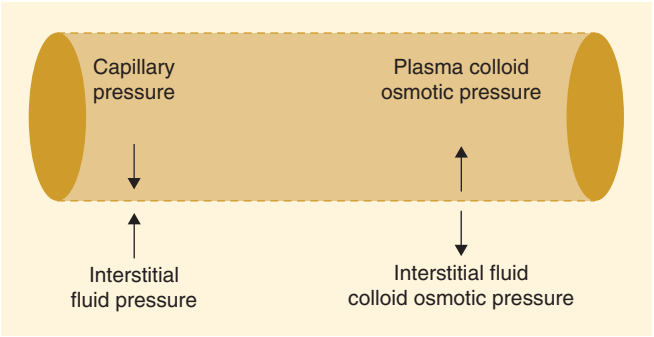

FIGURE 13–4. Operative forces at the capillary membrane tend to move fluid either outward or inward through the capillary membrane. In hypovolemic shock, one therapeutic strategy is the administration of colloids that can sustain and/or draw fluid from the interstitial space by increasing the plasma colloid osmotic pressure. (From Guyton AC, Hall JE. Textbook of Medical Physiology, 8th ed. Philadelphia, PA: Saunders; 1991:174, with permission.)

KEY CONCEPT Thus, in contrast to isotonic crystalloid solutions that distribute throughout the extracellular fluid space, the volume of isooncotic colloids administered remains relatively confined to the intravascular space. In the case of hyperoncotic solutions such as 25% albumin, fluid is pulled from the interstitial space into the vasculature, resulting in an increase in the intravascular volume that is much greater than the original volume of the 25% albumin that was administered. Although theoretically attractive, hyperoncotic solutions should not be used for hypovolemic shock because the expansion of the intravascular space is at the expense of depletion of the interstitial space. Exogenous colloids available in the United States include 5% albumin, 25% albumin, 5% plasma protein fraction (PPF), 6% hetastarch, 10% pentastarch, 10% dextran 40, 6% dextran 70, and 6% dextran 75 (see Table 13–3). The first three products are derived from pooled human plasma. Hetastarch and pentastarch are semisynthetic hydroxyethyl starches derived from amylopectin. The dextran products are semisynthetic glucose polymers that vary in terms of the average molecular weight of the polymers. Superiority of one colloid solution over another in terms of efficacy has not been clearly established.[27,28] Nonetheless, data suggests that albumin appears advantageous in septic patients while it should be avoided in patients with traumatic brain injury.[14]

For years within the critical care literature, a controversy known as the "colloid versus crystalloid debate" raged over the relative merits of these two types of resuscitation fluids. Largely in response to a major trial that demonstrated no difference in mortality between patients receiving saline versus albumin,[29] the Food and Drug Administration (FDA) issued a notice to health care providers declaring albumin safe for use in most critically ill patients.[30] However, based on previous data, there does not appear to be a clear-cut overall advantage relative to mortality for either crystalloids or colloids in these patient groups.[30] This was confirmed in a large study known as the CRISTAL (Colloids Versus Crystalloids for the Resuscitation of the Critically Ill) Randomized Trial published in 2013.[31] Thus, most clinicians today prefer using crystalloids based on their availability and inexpensive cost compared with colloids.[20,28] However, in addition to these factors, a shift in this debate has recently taken place focused on adverse events.

LO 5

Generally, the major adverse effects associated with colloids are fluid overload, dilutional coagulopathy, and anaphylactoid/anaphylactic reactions.[32] Because of direct effects on the coagulation system with the hydroxyethyl starch and dextran products, they should be avoided in hemorrhagic shock patients. Further, hetastarch has been associated with an increased risk of acute kidney injury in several recent clinical trials. As such, hydroxyethyl starch products are no longer recommended.[28] Despite these general limitations, there is a paradigm shift in a subset of hypovolemic shock patients, ie, traumatic hemorrhagic shock to minimize crystalloids, increase the use of blood products and plasma, as well as accepting lower MAP values (permissive hypotension). Collectively, this approach is referred to as damage control resuscitation (DCR).[33]

LO 6

▶ *Blood Products*

KEY CONCEPT Blood products are indicated in hypovolemic shock patients who have sustained blood losses from hemorrhage exceeding 1500 mL. This, in fact, is the only setting in which freshly procured whole blood is administered. In virtually all other settings, blood products are given as the individual components of whole blood units, such as packed red blood cells (PRBCs), fresh-frozen plasma (FFP), platelets, cryoprecipitate, and prothrombin complex concentrates (PCC).[34] This includes ongoing resuscitation of hemorrhagic shock when PRBCs can be transfused to increase oxygen-carrying capacity in concert with crystalloid solutions to increase blood volume. In patients with documented coagulopathies, FFP for global replacement of lost or diluted clotting factors, or platelets for patients with severe thrombocytopenia (< 20–50 × 10^3/mm^3 [20–50 × 10^9/L]) should be administered.[35,36] Data suggests that increasing the ratio of FFP to PRBC units may be associated with improved mortality and a reduction in the number of PRBC transfusions in patients requiring multiple transfusions.[37,38] Use of **viscoelastic testing** may also be a valuable tool for assessing coagulation defects and guiding FFP and PCC administration, especially emergently.[39] Type O negative blood or "universal donor blood" is given in emergent cases of hemorrhagic shock. Thereafter, blood that has been typed and cross-matched with the recipient's blood is given.

LO 5

The traditional threshold for PRBC transfusion in hypovolemic shock has been a serum hemoglobin of less than 10 g/dL (100 g/L [6.21 mmol/L]) and hematocrit (Hct) less than 30% (0.30). However, for critically ill patients who have received appropriate fluid resuscitation and have no signs of ongoing bleeding, a more restrictive transfusion threshold of 7 g/dL (70 g/L [4.34 mmol/L]) appears to be safe.[40] Traditional risks from allogeneic blood product administration include hemolytic and nonhemolytic transfusion reactions and transmission of blood-borne infections in contaminated blood. Recent large studies have also shown that transfusions are associated with increased infection and higher mortality, possibly because of adverse immune and inflammatory effects.[34,41] Increased thromboembolic events and mortality have been documented for patients receiving PRBCs stored longer than 28 days.[42] Thus administration of blood products should be restricted whenever possible and used as early as possible following donation.

▶ *Pharmacologic Therapy*

Vasopressor is the term used to describe any pharmacologic agent that can induce arterial vasoconstriction through stimulation of the α_1-adrenergic receptors or V_1 receptor. KEY CONCEPT Although replenishment of intravascular volume is undoubtedly the

Patient Encounter Part 2

PMH: Unable to assess initially

Meds: Unable to assess initially

SH: Social alcohol use

FH: Unable to assess initially

PE:

VS: BP 77/45 mm Hg, P 130 beats/min, RR 24 breaths/min, T 36.0°C (96.8°F), Ht 5'10" (178 cm), Wt 85 kg (187 lb), urine output: none since bladder catheterization 10 minutes ago

Neuro: Was in pain and agitated upon entering the trauma center. Now calmer but disoriented after one-time doses of hydromorphone and midazolam

Cardiovascular: Heart sounds and ECG normal except for tachycardia

Pulmonary: Normal breath sounds

Abd: WNL

Extremities: Right arm with open fracture, soft tissue damage, and moderate bleeding

Pertinent labs: pH 7.20, $PaCO_2$ 34 mm Hg (4.5 kPa), PaO_2 70 mm Hg (9.3 kPa), Na 133 mEq/L (mmol/L), Cl 98 mEq/L (mmol/L), HCO_3 16 mEq/L (mmol/L), K 5.2 mEq/L (mmol/L), Mg 2.8 mg/dL (1.15 mmol/L), lactate 6.0 mEq/L (mmol/L), SCr 1.5 mg/dL (133 µmol/L), Hct 28% (0.28)

What signs and symptoms of hypovolemic shock are present in this patient?

What laboratory abnormalities related to hypovolemic shock are present in this patient and why?

Describe treatment goals for the patient in the next hour.

Develop a pharmacologic and fluid therapy plan for initial therapy. Defend your selections compared to alternative agents.

Discuss the role in therapy for blood products, sodium bicarbonate, and hemostatic agents in the patient at this time.

Describe treatment goals for the patient in the next 24 hours.

cornerstone of hypovolemic shock therapy, use of vasopressors may be warranted as a temporary measure in patients with profound hypotension or evidence of organ dysfunction in the early stages of shock.[2,10] Vasopressors are typically used concurrently with fluid administration after the latter has not resulted in adequate restoration of MAP and/or tissue perfusion.[43] Table 13–4 lists those vasopressors recommended for use in the management of hypovolemic shock.[1] Although vasopressor therapy may improve the hemodynamic profile in shock patients, data are lacking that they improve mortality.[44] Furthermore, a study found that early use of vasopressors (ie, phenylephrine, norepinephrine, dopamine, vasopressin) in the resuscitation of patients with hemorrhagic shock may actually be associated with increased mortality.[45] Regardless, data suggest that if vasopressors are used, norepinephrine is preferable to dopamine secondary to increased incidence of arrhythmias associated with the latter agent in the treatment of shock patients.[46,47] Thus norepinephrine should be considered the first-line vasopressor therapy for these patients.[2,44] Epinephrine should be considered as a second-line vasopressor in patients with shock because of its association with tachyarrhythmias, impaired abdominal organ (splanchnic) circulation, and hypoglycemia.[2,43] In cases involving concurrent heart failure, an inotropic agent such as dobutamine may be needed, in addition to the use of a vasopressor.[2]

Vasopressors are almost exclusively administered as continuous infusions because of their very short duration of action and the need for close titration of their dose-related effects. Starting doses should be at the lower end of the dosing range followed by rapid titration upward if needed to maintain adequate MAP. Monitoring of end-organ function such as adequate urine output should also be used to monitor therapy. Once MAP is restored, vasopressors should be weaned and discontinued as soon as possible to avoid any untoward events.[2] The most significant systemic adverse events associated with vasopressors are excessive vasoconstriction

Table 13–4

Vasopressor Drugs

		Adrenergic Effects			
Drug	**Usual IV Dose**	**α**	**β_1**	**Dopaminergic**	**Potential to Cause Arrhythmias**
Dopamine	10–20 mcg/kg/min[a]	+++	++	+++	+++
Norepinephrine	0.5–80 mcg/min	+++	++	0	++
Epinephrine	1–200 mcg/min	++	+++	0	+++
Phenylephrine	0.5–9 mcg/kg/min	+++	0	0	0

[a]Lower dosages of dopamine may not produce desired α_1-adrenergic (vasopressor) effects.

+ = Low

++ = Moderate

+++ = High

IV, intravenous.

Patient Encounter Part 3

One hour after the initial fluid bolus, the patient's vital signs are BP 82/54 mm Hg, P 125 beats/min, RR 21 breaths/min, urine output 10 mL in the past hour. Pertinent new labs: lactate 4.5 mEq/L (mmol/L). He is weak and confused.

Assess the patient's condition compared to one hour ago.

Develop a plan for additional therapy, if any, that you recommend at this time.

Outline a plan for monitoring the patient over the next 24 hours.

What cultural beliefs, norms, or values should be considered when treating patients with hemorrhagic shock?

resulting in decreased organ perfusion and potential to induce arrhythmias (see Table 13–4). Central venous catheters should be used to minimize the risk of local tissue necrosis that can occur with extravasation of peripheral IV catheters.

▶ *Hemostatic Agents*

Several systemic pharmacologic agents have been used historically in patients with severe bleeding including the procoagulant, recombinant activated factor VII. Off-label use of this latter drug has fallen into disfavor due to uncertain efficacy, safety concerns, and high acquisition cost. In recent years, the greatest interest has shifted instead to the use of the antifibrinolytic drug, tranexamic acid. A recent study of tranexamic acid in trauma patients with or at risk of significant bleeding demonstrated a decrease in mortality compared with placebo.[48] As such, a recent European guideline recommends the use of tranexamic acid within 3 hours of injury (1 gram IV over 10 minutes then 1 gram over 8 hours) as an adjunctive agent in the management of bleeding trauma patients as well as spurring additional research including possible prehospital use.[35]

▶ *Supportive Care Measures*

Lactic acidosis, which typically accompanies hypovolemic shock as a consequence of tissue hypoxia, is best treated by reversal of the underlying cause. Administration of alkalizing agents such as sodium bicarbonate has not been demonstrated to have any beneficial effects and may actually worsen intracellular acidosis.[49] Noteworthy, however, the latter precautionary statement is based on limited retrospective data in a variety of patients with lactic acidosis. Because GI ischemia is a common complication of hypovolemic shock, prevention of stress-related mucosal disease should be instituted as soon as the patient is stabilized. The most common agents used for stress ulcer prophylaxis are the histamine$_2$-receptor antagonists and proton pump inhibitors. Prevention of thromboembolic events is another secondary consideration in hypovolemic shock patients. This can be accomplished with the use of external devices such as sequential compression devices and/or antithrombotic therapy such as the low-molecular-weight heparin products or unfractionated heparin. Sequential compression devices are preferred in any hypovolemic shock patient at risk of ongoing bleeding.

Patient Care Process

LO 7

Collect Information:

- Conduct medical history to determine the cause of shock to guide pharmacologic and nonpharmacologic therapy.
- Obtain pertinent laboratory tests (electrolytes, complete blood count [CBC], coagulation tests, ABG, serum lactate, liver function tests) to help determine shock severity and organ dysfunction.

Assess the Information:

- Assess airway/ventilation status to determine the need for supplemental oxygen/mechanical ventilation.
- Assess vital signs and urine output at least every 15 minutes (continuously if possible) to determine shock severity.
- Determine adequacy of current blood product therapy (if applicable).
- Determine adequacy of current vasopressor/inotropic therapy (if applicable).

Develop a Care Plan:

- Assure venous access to deliver fluid resuscitation.
- Determine fluid to be used including rate of administration.
- Determine if blood products are needed and dose. It should be noted that some religious denominations (eg, Jehovah's witnesses) object to transfusions of blood products including whole blood, PRBCs, and FFP, although certain products (eg, platelets, clotting factors, albumin) may be acceptable depending on the individual patient's choice. Cultural/religious preferences should be assessed and considered.
- Ascertain need for continued vasopressor therapy.
- Consider using tranexamic acid in bleeding trauma patients.

Implement the Care Plan:

- Start aggressive crystalloid IV fluid therapy if SBP is less than 90 mm Hg (MAP < 60 mm Hg).
- If required (see Figure 13–3), transfuse PRBCs and provide emergent control of ongoing hemorrhaging.
- Begin vasopressor therapy if there is evidence of cerebral or myocardial ischemia.
- Use the resulting data to optimize therapy if a PA catheter is placed.
- Avoid electrolyte disturbances and adverse drug events.

Follow-up: Monitor and Evaluate:

- Determine if appropriate treatment goals for the first hour and first 24 hours of therapy have been met (see Outcome Evaluation).
- Determine if the underlying cause of hypovolemic shock has been addressed (eg, control of bleeding or GI fluid losses).
- Ascertain if supportive care measures such as prophylaxis for stress ulcers and venous thromboembolism are indicated.

OUTCOME EVALUATION

KEY CONCEPT Successful treatment of hypovolemic shock is measured by the restoration of MAP to baseline values and reversal of associated organ dysfunction. The likelihood of a successful fluid resuscitation is directly related to the expediency of treatment. Therapy goals include:

- Arterial SBP greater than 90 mm Hg (MAP > 60–75 mm Hg) within 1 hour.
- Organ dysfunction reversal evident by increased urine output to greater than 0.5 mL/kg/hour (1.0 mL/kg/hour in pediatrics), return of mental status to baseline, and normalization of skin color and temperature over the first 24 hours.
- HR should begin to decrease reciprocally to increases in the intravascular volume within minutes to hours.
- Normalization of laboratory measurements expected within hours to days following fluid resuscitation. Specifically, normalization of base deficit and serum lactate is recommended within 24 hours and may be associated with decreased mortality.[50]
- Achievement of PAOP to a goal pressure of 14 to 18 mm Hg occurs (alternatively, CVP 8–12 mm Hg).

Abbreviations Introduced in This Chapter

ABG	Arterial blood gas
ADH	Antidiuretic hormone
ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
BP	Blood pressure
Ca	Calcium
CBC	Complete blood count
Cl	Chloride
CO	Cardiac output
CRISTAL	Colloids Versus Crystalloids for the Resuscitation of the Critically Ill trial
CVP	Central venous pressure
DCR	Damage control resuscitation
ECG	Electrocardiogram
FDA	Food and Drug Administration
FFP	Fresh-frozen plasma
GI	Gastrointestinal
Hct	Hematocrit
HR	Heart rate
IV	Intravenous
K	Potassium
kDa	Kilodalton
LR	Lactated Ringer
MAP	Mean arterial pressure
Mg	Magnesium
MODS	Multiple organ dysfunction syndrome
Na	Sodium
NaCl	Sodium chloride
NS	Normal saline
PA	Pulmonary artery
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PAOP	Pulmonary artery occlusion pressure
PCC	Prothrombin complex concentrate
PPF	Plasma protein fraction
PRBCs	Packed red blood cells
SBP	Systolic blood pressure
SCr	Serum creatinine
SV	Stroke volume
SVR	Systemic vascular resistance
VIP	Ventilate, infuse, pump

REFERENCES

1. Todd RS, Turner KL, Moore FA. Shock: General. In: Gabrielli A, Lyon JA, Yu M, eds. Civetta, Taylor, & Kirby's Critical Care, 4th ed. Philadelphia, PA: Wolters Kluwer Lippincott Williams & Wilkins; 2009:813–834.
2. Vincent JL, De Backer D. Circulatory shock. New Eng J Med. 2013;369:1726–1734.
3. Braunwald E. Regulation of the circulation. I. New Eng J Med. 1974;290:1124–1129.
4. Vallet B, Wiel E, Lebuffe G. Resuscitation from circulatory shock. In: Fink MP, Abraham E, Vincent JL, Kochanek PM, eds. Textbook of Critical Care, 5th ed. Philadelphia: Elsevier Saunders; 2005:905–910.
5. Puyana JC. Resuscitation of hypovolemic shock. In: Fink MP, Abraham E, Vincent JL, Kochanek PM, eds. Textbook of Critical Care, 5th ed. Philadelphia: Elsevier Saunders; 2006:1933–1943.
6. Cinat ME, Hoyt DB. Hemorrhagic shock. In: Gabrielli A, Lyon JA, Yu M, eds. Civetta, Taylor, & Kirby's Critical Care. Philadelphia, PA: Wolters Kluwer Lippincott Williams & Wilkins; 2009:893–923.
7. Jones AE, Kline JA. Shock. In: Marx JA, Hockberger RS, Walls RM, eds. Rosen's Emergency Medicine: Concepts and Clinical Practice, 6th ed. Philadelphia: Mosby Elsevier; 2006:41–56.
8. Harbrecht BG, Alarcon LH, Peitzman AB. Management of shock. In: Moore EE, Feliciano DV, Mattox KL, eds. Trauma, 5th ed. New York: McGraw-Hill; 2004:201–226.
9. Ciesla DJ, Moore EE, Johnson JL, et al. Multiple organ dysfunction during resuscitation is not postinjury multiple organ failure. Arch Surg. 2004;139:590–594.
10. Moore FA, McKinley BA, Moore EE. The next generation in shock resuscitation. Lancet. 2004;363:1988–1996.
11. Rhodes A, Grounds RM, Bennett ED. Hemodynamic monitoring. In: Fink MP, Abraham E, Vincent JL, Kochanek PM, eds. Textbook of Critical Care, 5th ed. Philadelphia: Elsevier Saunders; 2005:735–739.
12. Practice guidelines for pulmonary artery catheterization: an updated report by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization. Anesthesiology. 2003;99:988–1014.
13. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wheeler AP, Bernard GR, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. New Eng J Med. 2006;354:2213–2224.
14. Myburgh JA, Mythen MG. Resuscitation fluids. New Eng J Med. 2013;369:1243–1251.
15. Hoffman GL. Blood and blood components. In: Marx JA, Hockberger RS, Walls RM, eds. Rosen's Emergency Medicine Concepts and Clinical Practice, 6th ed. Philadelphia: Mosby Elsevier; 2006:56–61.
16. Zaloga GP, Kirby RR, Bernards WC, Layon AJ. Fluids and electrolytes. In: Civetta JM, Taylor RW, Kirby RR, eds. Critical Care, 3rd ed. New York: Lippincott-Raven; 1997:413–441.
17. Bunn F, Roberts I, Tasker R, Akpa E. Hypertonic versus near isotonic crystalloid for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2004:CD002045.
18. Patanwala AE, Amini A, Erstad BL. Use of hypertonic saline injection in trauma. Am J Health-Syst Pharm. 2010;67:1920–1928.

19. Mullins RJ. Management of shock. In: Mattox KL, Feliciano DV, Moore EE, eds. Trauma, 4th ed. New York: McGraw-Hill; 2000:195–232.
20. Shafi S, Kauder DR. Fluid resuscitation and blood replacement in patients with polytrauma. Clin Orthop Relat Res. 2004;(422):37–42.
21. Wang CH, Hsieh WH, Chou HC, et al. Liberal versus restricted fluid resuscitation strategies in trauma patients: a systematic review and meta-analysis of randomized controlled trials and observational studies. Crit Care Med. 2014;42:954–961.
22. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. Br J Surg. 2015;102:24–36.
23. Todd SR, Malinoski D, Muller PJ, Schreiber MA. Lactated Ringer's is superior to normal saline in the resuscitation of uncontrolled hemorrhagic shock. J Trauma. 2007;62:636–639.
24. Zampieri FG, Ranzani OT, Azevedo LC, Martins ID, Kellum JA, Liborio AB. Lactated ringer is associated with reduced mortality and less acute kidney injury in critically ill patients: a retrospective cohort analysis. Crit Care Med. 2016;44:2163–2170.
25. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the SPLIT randomized clinical trial. JAMA. 2015;314:1701–1710.
26. Guyton AC, Hall JE. Textbook of Medical Physiology, 10th ed. Philadelphia: Saunders; 2000.
27. Bunn F, Trivedi D, Ashraf S. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev. 2011:CD001319.
28. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013;2:CD000567.
29. Finfer S, Bellomo R, Boyce N, French J, Myburgh J. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. New Eng J Med. 2004;350:2247–2256.
30. Safety of albumin administration in critically ill patients. Rockville, MD: U.S. Food and Drug Administration; 2005 May 16, 2005.
31. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310:1809–1817.
32. Barron ME, Wilkes MM, Navickis RJ. A systematic review of the comparative safety of colloids. Arch Surg. 2004;139:552–563.
33. Chang R, Holcomb JB. Optimal fluid therapy for traumatic hemorrhagic shock. Crit Care Clin. 2017;33:15–36.
34. Boucher BA, Hannon TJ. Blood management: a primer for clinicians. Pharmacotherapy. 2007;27:1394–1411.
35. Kelley DM. Hypovolemic shock: an overview. Crit Care Nurs Q. 2005;28:2–19.
36. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care. 2013;17:R76.
37. Maegele M, Lefering R, Paffrath T, et al. Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft fur Unfallchirurgie. Vox sanguinis. 2008;95:112–119.
38. Wafaisade A, Maegele M, Lefering R, et al. High plasma to red blood cell ratios are associated with lower mortality rates in patients receiving multiple transfusion (4≤red blood cell units<10) during acute trauma resuscitation. J Trauma. 2011;70:81–88; discussion 88–89.
39. Inaba K, Rizoli S, Veigas PV, et al. 2014 Consensus conference on viscoelastic test-based transfusion guidelines for early trauma resuscitation: report of the panel. J Trauma Acute Care Surg. 2015;78:1220–1229.
40. Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med. 2009;37:3124–3157.
41. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA. 2014;311:1317–1326.
42. Spinella PC, Carroll CL, Staff I, et al. Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. Crit Care. 2009;13:R151.
43. Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Resp Crit Care Med. 2011;183:847–855.
44. Havel C, Arrich J, Losert H, Gamper G, Mullner M, Herkner H. Vasopressors for hypotensive shock. Cochrane Database Syst Rev. 2011:CD003709.
45. Sperry JL, Minei JP, Frankel HL, et al. Early use of vasopressors after injury: caution before constriction. J Trauma. 2008;64: 9–14.
46. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. New Eng J Med. 2010;362:779–789.
47. Patel GP, Grahe JS, Sperry M, et al. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. Shock. 2010;33:375–380.
48. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376:23–32.
49. Kim HJ, Son YK, An WS. Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: a retrospective analysis. PloS One. 2013;8:e65283.
50. Tisherman SA, Barie P, Bokhari F, et al. Clinical practice guideline: endpoints of resuscitation. J Trauma. 2004;57:898–912.

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14 Asthma

Lori Wilken and Amanda Eades

LEARNING OBJECTIVES

LO

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

1. Describe the pathophysiology and clinical presentation of acute and chronic asthma.
2. List the treatment goals for asthma.
3. Identify environmental factors associated with worsening asthma control.
4. Select inhaled drug delivery devices based upon patient characteristics.
5. List the steps to use a metered-dose inhaler correctly.
6. Recommend an asthma medication regimen for an adult patient based on symptoms.
7. Describe the purpose of an individualized asthma action plan.

INTRODUCTION

KEY CONCEPT Asthma is a complex disorder and has been defined as "a heterogeneous disease, usually characterized by chronic airway inflammation."[1] Airflow limitation results in wheezing, breathlessness, chest tightness, and coughing, particularly at night or early in the morning.[1] Severity of chronic asthma ranges from mild intermittent symptoms to a severe and disabling disease. Despite variability in the severity of chronic asthma, all patients with asthma are at risk of acute severe disease. International guidelines emphasize the importance of treating underlying airway inflammation to control asthma and reducing asthma-associated risks.[1–3]

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Asthma is the most prevalent chronic disease of childhood, and it causes significant morbidity and mortality in both adults and children. About 235 million adults and children worldwide have asthma.[4] In the United States, asthma affects 8.3% of adults (20.4 million) and 8.3% of children (6.1 million).[5] Asthma is the primary diagnosis for 6.3 million physician office visits, 2 million emergency department visits, and 3651 deaths annually.[5]

Asthma is also a significant economic burden in the United States, with costs totaling nearly $60 billion annually.[6] Prescription medications are the single largest direct medical expenditure and account for 71% of direct medical costs.[6]

Asthma results from a complex interaction of genetic and environmental factors. There appears to be an inherited component because the presence of asthma in a parent is a strong risk factor for developing asthma in a child. This risk increases when a family history of **atopy** is also present. The presence of atopy is a strong prognostic factor for continued asthma as an adult.

Environmental exposure also appears to be an important etiologic factor. Although asthma occurs early in life for most patients, those with occupational asthma develop the disease later upon exposure to specific allergens in the workplace. Exposure to secondhand smoke after birth increases the risk of childhood asthma.[7] Adult-onset asthma may be related to atopy, nasal polyps, aspirin sensitivity, occupational exposure, or recurrence of childhood asthma.

PATHOPHYSIOLOGY

LO 1

KEY CONCEPT Asthma is characterized by airway narrowing and inflammation primarily in medium-sized bronchi. A key feature of the pathophysiology is airway hyperresponsiveness, which is exaggerated narrowing of the airways in response to a trigger or allergen such as cold air, strong odors, pollen, or dust. Airway narrowing results from contraction of airway smooth muscle, increased mucus secretion, airway edema, and remodeling.[1]

Airway inflammation is initiated by an inhaled allergen or trigger such as dust, pollen, or animal dander inducing a type 2 T-helper $CD4^+$ (T_H2) response. This leads to B-cell production of antigen-specific immunoglobulin E (IgE), pro-inflammatory cytokines (eg, interleukin-5), and chemokines that recruit and activate eosinophils, neutrophils, and alveolar macrophages.[2] Further exposure to the antigen results in cross-linking of cell-bound IgE in mast cells and basophils, causing release of preformed inflammatory mediators such as histamine, cysteinyl leukotrienes, and prostaglandin D_2.[1]

Activation and degranulation of mast cells and basophils result in an early-phase response involving acute bronchoconstriction that lasts approximately 1 hour after allergen exposure. In the late-phase response, activated airway cells release inflammatory cytokines and chemokines, thereby recruiting more inflammatory cells into the lungs. The late-phase response occurs 4 to 6 hours after the initial allergen challenge and results in less intense bronchoconstriction as well as increased airway hyperresponsiveness and airway inflammation.[2]

CLINICAL PRESENTATION AND DIAGNOSIS

See accompanying box for the clinical presentation and diagnosis of asthma. Diagnosis is based on a detailed medical history, physical examination of the upper respiratory tract and skin, and spirometry. The clinician determines if episodic symptoms of airflow obstruction are present, whether airflow obstruction

is at least partially reversible, and that alternative diagnoses are excluded.[1–3] Spirometry is required for diagnosing asthma in patients older than 5 years because the medical history and physical examination are not reliable for characterizing the status of lung impairment or excluding other diagnoses.[1–3] Methacholine bronchoprovocation test is used to clinically evaluate airway hyperresponsiveness.

▶ *Chronic Asthma*

KEY CONCEPT In chronic asthma, initial classification of asthma severity is based on current disease impairment and future risk. The term *impairment* refers to the frequency and severity of symptoms, use of short-acting β_2-agonists (SABA) for quick relief of symptoms, pulmonary function, and impact on normal activity and quality of life. *Risk* refers to the potential for future severe exacerbations and asthma-related death, progressive loss of lung function (adults) or reduced lung growth (children), and the occurrence of drug-related adverse effects.[2]

▶ *Acute Asthma*

In acute asthma, symptoms of wheezing, coughing, and shortness of breath increase. Most exacerbations can be treated at home, while some mandate hospitalization. The severity of the asthma exacerbation does not depend upon the classification of the patient's chronic asthma. Patients with intermittent asthma can have life-threatening acute exacerbations.

Clinical Presentation and Diagnosis of Asthma

LO 1

General Findings

- Asthma presentation ranges from normal pulmonary function with symptoms only during acute exacerbations to significantly decreased pulmonary function with continuous symptoms of daily coughing, wheezing, and shortness of breath.
- Acute asthma can present rapidly (within 3–6 hours), but deterioration more commonly occurs over a longer period, even days or weeks. Acute asthma can be life threatening.
- Family history, social history, precipitating factors, history of exacerbations, and development of symptoms are important components of an asthma diagnosis.

LO 1

Symptoms

- Patients usually complain of wheezing, shortness of breath, coughing (usually worse at night), and chest tightness.
- Patients may be anxious and agitated. In acute severe asthma, patients may be unable to communicate in complete sentences.
- Mental status changes (eg, confusion, irritability, agitation) may indicate impending respiratory failure.
- The presence of precipitating factors (eg, smoke, mold, or viral illness) worsens symptoms.
- Symptoms usually have a pattern (eg, worse at night, seasonal symptoms).

LO 1

Signs

- Vital signs may reflect tachypnea, tachycardia, and hypoxemia.
- On inspection, there may be hyperexpansion of the thorax and use of accessory muscles.
- Auscultation of the lungs may detect end-expiratory wheezes in mild exacerbations or wheezing throughout inspiration and expiration in severe exacerbations.
- Bradycardia and absence of wheezing may indicate impending respiratory failure.
- In acute asthma, patients may present with pulsus paradoxus, diaphoresis, and cyanosis.

Laboratory Tests

- Spirometry may demonstrate airway limitation and excessive airway variability. Airway limitation is demonstrated by a decrease in the FEV_1/FVC (forced expiratory volume in the first second/forced vital capacity) less than 80% (0.80) and a decrease in the FEV_1 to less than 80% of the predicted value. Excessive airway variability is seen with: (a) a positive bronchodilator test, (b) positive bronchial or exercise challenge tests, (c) excessive variability in twice-daily peak expiratory flow (PEF) measurements, and (d) significant increases in FEV_1 after four weeks of an anti-inflammatory medication. Significant lung function improvement in adults is defined as an increase in greater than 200 mL and 12% in the FEV_1 from baseline. For children, lung function improvement is an increase in the FEV_1 greater than 12% of the predicted value. Spirometry may be normal if the patient is not symptomatic.
- A complete blood count with differential may show an elevated eosinophil count.
- Elevated serum immunoglobulin E (IgE) levels may be present.
- Immunoassays are serologic tests used to detect allergies in patients that may have sensitivities to molds, dust mites, pollen, and other triggers that worsen asthma control. The test is an interaction between antigens, in the form of a protein from the trigger and the patient's antigen-specific antibody. The test is used when skin testing is not available or cannot be used because it is a less sensitive test than skin testing.

Other Diagnostic Tests

- Full pulmonary function tests should be performed at baseline in patients 5 years or older to rule out other disorders.
- Arterial blood gases (to evaluate PCO_2) should be obtained for patients in severe distress, suspected hypoventilation, or when PEF or FEV_1 is at least 30% less than the percent predicted after initial treatment.
- Pulse oximetry is performed at each visit to assess for hypoxemia.
- Methacholine challenge test or bronchoprovocation may be performed if the diagnosis of asthma is questionable.
- Fraction of exhaled nitric oxide (FeNO) changes from baseline may indicate inflammation or a response to an inhaled corticosteroid (ICS). A normal value in adults is less than 25 parts per billion (ppb).

TREATMENT

Desired Outcomes

LO 2

The goals of treatment for asthma are directed at maintaining long-term control using the least amount of medications and minimizing adverse effects.[1,2] Treatment goals are to: (a) prevent chronic and troublesome symptoms, (b) require infrequent use (2 or fewer days/week) of SABA for quick relief of symptoms, (c) maintain normal or near-normal pulmonary function, (d) maintain normal activity levels, (e) meet patients' and families' expectations of satisfaction with asthma care, (f) prevent exacerbations of asthma and the need for emergency department visits or hospitalizations, (g) prevent progressive loss of lung function, and (h) provide optimal medications with minimal or no adverse effects.

Nonpharmacologic Therapy

Incorporating nonpharmacologic care and education is important for patients with asthma. Patient education begins at the time of diagnosis and meets the individual patient's needs. Components of education involve asthma trigger avoidance, proper administration of inhaled medications, and asthma self-management (Table 14–1).

Table 14–1

Nonpharmacologic Interventions to Improve Symptom Control in Patients with Asthma

LO 3

Tobacco use
- Strongly encourage smokers to quit
- Advise parents/caregivers of children with asthma to not smoke and not allow smoking in rooms or cars that children use
- Assess smokers/ex-smokers for COPD or overlapping features of asthma and COPD

Physical activity
- Encourage regular physical activity for its general health benefits
- If exercise-induced bronchospasm, use a SABA 5–30 minutes prior to physical activity
- Encourage stretching and warm-up exercises prior to physical activity

LO 3

Occupational exposures
- Ask patients with adult-onset asthma about work history and other exposures
- Record when work-related exposures and symptoms occur, when bronchodilator is needed, and peak airflow at work vs. home
- Use respiratory protective devices such as air-purifying masks to help protect against noxious occupational inhalants
- Identify and eliminate occupational sensitizers and remove sensitized patients from further exposure

Medications
- Ask about asthma before prescribing NSAIDs and advise patients to stop NSAIDs if asthma worsens after use
- If β-blockers are indicated, choose cardioselective agents (eg, atenolol). Asthma is not an absolute contraindication to β-blocker use, but consider the risk vs. benefit

LO 3

Indoor allergens
- Animal dander: Remove carpet from bedroom if possible; keep pets out of bedroom; consider removal of pets from the home
- Mold: Consider reducing indoor humidity to 30%–50%; dehumidify basements; fix water leaks and eliminate water sources associated with mold growth
- Dust mites: Encase mattress and pillows in allergen-impermeable covers; wash sheets and blankets in hot water weekly (> 130°F [54.4°C])
- Cockroaches: Do not leave food or garbage exposed; use poison bait or traps to control insects

Diet
- Encourage a diet high in fruits and vegetables for its general health benefits
- Avoid foods for which there is a confirmed allergy
- Encourage weight reduction if overweight or obese
- Avoid foods containing sulfites if they cause symptoms (eg, beer, wine, shrimp, dried fruit, processed potatoes)

Vaccinations
- Administer yearly influenza vaccine to patients with moderate-to-severe asthma[9]
- Follow CDC recommendations for administering the pneumococcal vaccine[10]

Emotional stress
- Identify goals and strategies (eg, relaxation, breathing exercises) to deal with emotional stress if it worsens asthma

LO 3

Weather conditions
- Avoid strenuous outdoor activities during unfavorable weather conditions
- Cover the nose and mouth with a scarf on cold or windy days

Outdoor allergens
- When pollen counts are high, remain indoors and keep windows and doors closed
- If time is spent outdoors, shower afterward to remove allergens on the skin
- Avoid being outdoors in areas of high pollution

CDC, Centers for Disease Control and Prevention; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; SABA, short acting β_2 agonist.

Data obtained from Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention, 2017 (www.ginasthma.org) and National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 August. (https://www.ncbi.nlm.nih.gov/books/NBK7232/).

Patient Encounter Part 1

HPI: A 49-year-old man presents to the clinic with a chronic cough. He is frustrated that he can't sleep at night because of coughing. The cough is dry with clear sputum. He uses albuterol every night and multiple times a day. He is still able to work and feels better during the day. He has tried numerous medications and feels like nothing works. He took fluticasone propionate/salmeterol HFA once daily for 8 days and felt no relief. He now uses fluticasone propionate/salmeterol HFA intermittently. He has had oral prednisone bursts twice in the past 3 months with relief of his symptoms. He demonstrates use of an MDI using two consecutive puffs of his inhaler. He does rinse his mouth after use. He has tried using ranitidine and omeprazole in the past with no improvement in his nighttime cough. He tried using nasal corticosteroids for his allergies and sinuses with no relief.

PMH:

- Moderate, persistent asthma diagnosed during childhood; has never been hospitalized or intubated. Three prednisone bursts in the past year. Upper respiratory infections trigger worsening asthma symptoms. He has symptoms during all seasons, but winter is the worst. He is able to take NSAIDs without worsening his asthma.
- Allergic rhinitis
- Chronic sinusitis
- Nasal polyps

Family History: He has a cousin and an aunt with asthma.

Social History: He never smoked, and there are no smokers in the home; uses ETOH socially, 1–2 beers on special occasions. He has a dog that is allowed in the bedroom. He works as a patient transporter in a local hospital. His home has wood flooring with HVAC in the bedroom. There is some mold from flooding this past summer.

Allergies: Pollen, ragweed, trees, grass, roaches, dust mites, dogs and cats. No known medication allergies.

What symptoms are consistent with asthma?

What other common diseases can cause a cough?

Why is it important to ask about prednisone and albuterol use?

What nonpharmacologic interventions may help improve the patient's asthma control?

Pharmacologic Therapy

Treatment of chronic asthma involves avoidance of triggers known to precipitate or worsen asthma and use of long-term control and quick-relief medications. Long-term control medications include ICS, inhaled long-acting β_2-agonists (LABAs), oral leukotriene receptor antagonists (LTRAs), inhaled long-acting muscarinic antagonists (LAMA), and biologic agents. Quick-relief medications include SABAs, short-acting muscarinic antagonists (SAMAs), and short bursts of systemic corticosteroids.

▶ *Drug Delivery Devices*

LO 4

KEY CONCEPT Direct airway administration of asthma medications through inhalation is the most efficient route and minimizes systemic adverse effects. Inhaled asthma medications are available in metered-dose inhalers (MDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulized solutions. Selection of the appropriate inhalation device depends on patient characteristics and medication availability (Table 14–2).

Poor inhaler technique results in increased oropharyngeal deposition of the drug, leading to decreased efficacy and increased adverse effects. Table 14–2 describes the steps for appropriate use of MDIs. Because MDIs are challenging to use correctly, use of valved-holding-chambers (VHCs) or spacers is recommended with the MDI to decrease the need for coordination of actuation with inhalation, decrease oropharyngeal deposition, and increase pulmonary drug delivery.[11,12]

▶ *β_2-Adrenergic Agonists*

β_2-Agonists relax airway smooth muscle by directly stimulating β_2-adrenergic receptors in the airway.[13] They also increase mucociliary clearance and stabilize mast cell membranes. Inhaled β_2-agonists are classified as either short-acting (SABA) or long-acting (LABA) based on duration of action. Oral β_2-agonists have increased adverse effects and are not recommended for asthma treatment.

The early-phase response to antigen in an asthma exacerbation is blocked by pretreatment with inhaled SABAs. The SABAs have a faster onset of action in acute asthma than muscarinic antagonists. Adverse effects of β_2-agonists include tachycardia, tremor, and hypokalemia, which are usually not troublesome with inhaled dosage forms.

Short-Acting Inhaled β_2-Agonists KEY CONCEPT Inhaled SABAs are the most effective agents for reversing acute airway obstruction caused by bronchoconstriction and are the drugs of choice for treating acute asthma and symptoms of chronic asthma as well as preventing exercise-induced bronchospasm.[1] Inhaled SABAs have an onset of action of less than 5 minutes and a duration of action of 4 to 6 hours. Using an MDI with a VHC or spacer has faster medication delivery and is as effective as administration by nebulization.

Albuterol (known as salbutamol outside the United States), the most commonly used inhaled SABA, is available as an MDI and solution for nebulization. Levalbuterol, the pure R-enantiomer of albuterol (and referred to as R-salbutamol outside the United States), is available as an MDI and solution for nebulization. Levalbuterol has similar efficacy to albuterol and is purported to have fewer side effects; however, clinical trials have not demonstrated this benefit.[14]

For both the albuterol and levalbuterol MDI, the typical dose is two inhalations every 4 hours as needed for asthma symptoms. During an asthma exacerbation, the usual SABA doses are increased to four inhalations every 4 hours until symptoms resolve. Scheduled chronic daily dosing of SABAs is not recommended for two reasons. First, the need to use an inhaled SABA is one key indicator of uncontrolled asthma. Therefore, patients are educated to record SABA use. Second, scheduled SABA use decreases the duration of bronchodilation provided by the SABA.

Long-Acting Inhaled β_2-Agonists LABAs provide 12 to 24 hours of bronchodilation after a single dose. Because of the long

LO 4 LO 5

Table 14–2

Age Recommendations and Proper Use of Inhalation Devices

Device Type	Recommended Age	Proper Use	Common Mistakes
Metered-dose inhaler (MDI)	≥ 5 years of age	1. Shake the inhaler well before use 2. Remove the cap 3. Exhale away from the inhaler 4. Tilt your head back slightly and place the mouthpiece into the mouth with lips sealed tightly around the inhaler 5. Press down on the inhaler to release medication as you start to breathe in slowly. Breathe in for a full breath (3–5 seconds) 6. Hold your breath for as long as possible, up to 10 seconds to allow the medicine to reach deeply into your lungs 7. If directed to take a second puff, wait 1 minute, then repeat steps 1–6	• Actuating 2 puffs at the same time • Actuating the inhaler, waiting and then inhaling • Exhaling immediately after inhalation
MDI plus valved-holding chamber (VHC)	If < 4 years old, use VHC with mask; If ≥ 4 years of age, use VHC alone	1. Shake the inhaler well before use 2. Remove the cap from inhaler and from the spacer, if it has one 3. Put the inhaler into the spacer 4. Breathe out, away from the spacer 5. Bring the spacer to your mouth, put the mouthpiece between your teeth, and close your lips around it 6. Press the top of your inhaler once 7. Breathe in slowly until you have taken a full breath. If you hear a whistle sound, you are breathing in too fast 8. Hold your breath for about 10 seconds, then breath out Use a spacer with mask for children under 5 years old, or for those unable to hold their breath. If a mask is used, take 6 normal breaths instead of one long breath.	• Inhaling too quickly and making the VHC whistle
Soft mist inhaler (SMI)	Respimat 6 years of age and older	1. Assemble and prime the device 2. Twist the base 3. Open the mouthpiece 4. Exhale away from the inhaler 5. Place the mouth on the mouthpiece and avoid covering the ventilation holes 6. Actuate the inhaler and inhale a slow steady breath 7. Hold your breath for 10 seconds 8. Exhale 9. Repeat steps 2–8 one time for complete dose	• Covering the ventilation holes with the mouth • Actuating the inhaler, waiting and then inhaling • Exhaling immediately after inhaling
Nebulizer	Any age, preferably infants or elderly	1. Add medication to the medication cup 2. Assemble the tubing to the air compressor 3. Assemble tubing to the medication cup 4. Assemble mouthpiece to the medication cup 5. Plug in air compressor and turn the nebulizer on 6. Place mouth on the mouthpiece and breathe in and out slow and steadily into the mouthpiece	• Using a mask unnecessarily • Not cleaning the mouthpiece and medication cup • Not replacing the tubing
Dry powder inhaler (DPI)	Diskus ≥ 4 years old Ellipta ≥ 12 years old Flexhaler ≥ 6 years old Respiclick ≥ 4 years old Twisthaler ≥ 4 years old	1. Open the inhaler 2. Exhale away from the inhaler 3. Place mouth on the mouthpiece 4. Inhale a quick, steady breath 5. Hold breath for 10 seconds or as long as comfortable 6. Exhale away from the inhaler	• Shaking the device • Exhaling into the inhaler • Inhaling too slowly

Table 14–3

Usual Doses of Long-Term Control Medications in Asthma

Medication	Dosage Form	Ages 0–11 Years	Adults and Children > 12 Years
Inhaled Corticosteroids (see Table 14–4)			
Long-Acting β_2-Agonists			
Salmeterol	DPI 50 mcg/blister	Ages 0–3 years: N/A Ages 4–11 years: One inhalation every 12 hours	One inhalation every 12 hours
Formoterol	DPI 12 mcg/capsule	Ages 0–4 years: N/A Ages 5–11 years: Inhalation of one capsule every 12 hours	Inhalation of one capsule every 12 hours
Long Acting Muscarinic Agents			
Tiotropium	SMI 1.25 mcg/actuation	Ages 0–5: N/A Ages 6–11: Two inhalation of 1.25 mcg once daily	Two inhalations of 1.25 mcg once daily
Leukotriene Modifiers			
Montelukast	4 mg or 5 mg chewable tablets 4 mg granule packets 10 mg tablet	Ages 1–5 years: 4 mg at bedtime Ages 6–11 years: 5 mg at bedtime	Ages 12–14 years: 5 mg at bedtime Ages 15 and older: 10 mg at bedtime
Zafirlukast	10 or 20 mg tablets	Ages 0–4 years: N/A Ages 5–11 years: 10 mg twice daily	20 mg tablet twice daily
Zileuton	600 mg extended-release tablet 600 mg immediate-release tablet	N/A: only approved for those 12 years of age and older	Extended-release tablets: 1200 mg twice daily after morning and evening meals Immediate-release tablets: 600 mg four times daily
Anti-IgE Monoclonal Antibody			
Omalizumab	SC injection, 150 mg/1.2 mL after reconstitution with 1.4 mL sterile water for injection	Ages 0–5: N/A Ages 6–11: 75–375 mg SC every 2–4 weeks, depending on body weight and pretreatment serum IgE level; see dosing chart[b]	150–375 mg SC every 2–4 weeks, depending on body weight and pretreatment serum IgE level; see dosing chart[b]
Anti-Interleukin-5 Receptor Monoclonal Antibodies			
Mepolizumab	SC injection, 100 mg/mL after reconstitution with 1.2 mL sterile water for injection	N/A	100 mg SC once every 4 weeks
Reslizumab	IV solution, 100 mg/10mL vial	N/A	3 mg/kg IV infusion over 20–50 minutes every 4 weeks
Benralizumab	SC injection, 30 mg/mL prefilled syringe	N/A	30 mg SC every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter

[a]Dosages are provided for products that have been approved by the US FDA or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

[b]https://www.xolair.com/pdf/dosingTables092916.pdf.

DPI, dry powder inhaler; IgE, immunoglobulin E; IV, intravenous; N/A, safety and efficacy not established; SC, subcutaneous; SMI, soft mist inhaler.

duration of bronchodilation, these agents are useful for patients experiencing nocturnal symptoms.

LABAs are indicated for chronic treatment of asthma as add-on therapy for patients not controlled on low to medium doses of ICS (see Table 14–3 for dosing). Adding a LABA is at least as effective in improving symptoms and decreasing asthma exacerbations as doubling the dose of an ICS or adding an LTRA to ICS.[3,15] Adding a LABA to ICS therapy also reduces the amount of ICS necessary for asthma control.[3]

LABAs should not be used as monotherapy for chronic asthma. There may be an increased risk of severe asthma exacerbations and asthma-related deaths when LABAs are used alone.[16] Labeling for all drugs containing LABAs includes a black box warning against their use without an ICS. The risk of increased severe asthma exacerbations does not appear to be increased in adults receiving both a LABA and ICS.[17]

Salmeterol is dosed twice daily and is available as a single-ingredient product and as a fixed-ratio combination product containing an ICS. Formoterol and vilanterol are available only in combination with inhaled corticosteroids (Table 14–4). Combination products may increase adherence because of the need for fewer inhalers and inhalations. Indacaterol, olodaterol, and arformoterol are LABAs approved only for COPD.

► *Corticosteroids*

Corticosteroids are the most potent anti-inflammatory agents available for asthma treatment and are available in inhaled, oral, and injectable dosage forms. They decrease airway inflammation, attenuate airway hyperresponsiveness, and minimize mucus production and secretion. Corticosteroids also improve the response to β_2-agonists.

Inhaled Corticosteroids KEY CONCEPT ICS are the preferred therapy for all forms of persistent asthma in all age groups.[1,2] ICS are more effective than LTRA in improving lung function and preventing emergency department visits and hospitalizations

Table 14–4

Estimated Comparative Daily Dosages for Combined Inhaled Corticosteroid and Long-Acting β_2-Agonist Products for Asthma

	Ages 0–11 Years			Ages 12 and Older		
Medication	**Low Dose**	**Medium Dose**	**High Dose**	**Low Dose**	**Medium Dose**	**High Dose**
Fluticasone/salmeterol Diskus DPI 100/50 mcg, 250/50 mcg, 500/50 mcg	100/50 mcg, 1 inhalation twice daily[a,b]	100/50 mcg, 1 inhalation twice daily[a,b]	100/50 mcg, 1 inhalation twice daily[a,b]	100/50 mcg, 1 inhalation twice daily	250/50 mcg, 1 inhalation twice daily	500/50 mcg, 1 inhalation twice daily
Fluticasone/salmeterol Respiclick DPI 55/14 mcg, 113/14 mcg, 232/14 mcg	N/A	N/A	N/A	55/14 mcg, 1 inhalation twice daily	113/14 mcg, 1 inhalation twice daily	232/14 mcg, 1 inhalation twice daily
Fluticasone/salmeterol HFA 45/21 mcg, 115/21 mcg, 230/21 mcg	N/A	N/A	N/A	45/21 mcg, 2 inhalations twice daily	115/21 mcg, 2 inhalations twice daily	230/21 mcg, 2 inhalations twice daily
Budesonide/formoterol HFA 80/4.5 mcg, 160/4.5 mcg	80/4.5 mcg, 2 inhalations twice daily[c, d]	80/4.5 mcg, 2 inhalations twice daily[c, d]	80/4.5 mcg, 2 inhalations twice daily[c, d]	80/4.5 mcg, 1 inhalation twice daily	160/4.5 mcg, 1 inhalation twice daily	160/4.5 mcg, 2 inhalations twice daily
Mometasone/formoterol MDI 100/5 mcg, 200/5 mcg	N/A	N/A	N/A	100/5 mcg, 1 inhalation twice daily	200/5 mcg, 1 inhalation twice daily	200/5 mcg, 2 inhalations twice daily
Fluticasone furoate/vilanterol DPI 100/25 mcg, 200/25 mcg	N/A	N/A	N/A	100/25 mcg, 1 inhalation daily[e]	100/25 mcg, 1 inhalation daily[e]	200/25 mcg, 1 inhalation daily[e]

[a]N/A in children 0–4 years of age.

[b]Doses based on clinical trials. Maximum of fluticasone/salmeterol 100/50 mcg, 1 inhalation twice daily is approved in children ages 4–11 years without specification of low, medium, or high dosage.

[c]Not FDA approved in children < 6 years of age.

[d]Maximum budesonide/formoterol 80/4.5 mcg, 2 inhalations twice daily is approved in children 6–11 years of age without specification of low, medium, or high dosage.

[e]FDA approved for adults 18 years and older.

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; N/A, safety and efficacy not established.

due to asthma exacerbations.[1,2] The primary advantage of using ICS compared with systemic corticosteroids is the targeted drug delivery to the lungs, which decreases the risk of systemic adverse effects. Product selection is based on preference for dosage form, delivery device, and cost.

All ICS are equally effective if given in equipotent doses (Table 14–5).[18] ICS have a flat dose-response curve; doubling the dose has a limited additional effect on asthma control.[19] Cigarette smoking decreases the response to ICS, and smokers require higher doses of ICS than nonsmokers.[20] Although some beneficial effect is seen within 12 hours of administration of an ICS, 2 weeks of therapy is necessary to see significant clinical effects. Longer treatment may be necessary to realize the full effects on airway inflammation.

For most delivery devices, the majority of the drug is deposited in the mouth and throat and swallowed. Local adverse effects of ICS include oral candidiasis, cough, and dysphonia. The incidence of local adverse effects can be reduced by using an MDI with a VHC and by having the patient rinse the mouth with water and expectorate after using the ICS. Decreasing the dose reduces the incidence of hoarseness.

Systemic absorption occurs via the pulmonary and oral routes. Systemic adverse effects include adrenal suppression, decreased bone mineral density, skin thinning, cataracts, and easy bruising, and occur more frequently with higher ICS doses.[2] Linear growth velocity is reduced by less than half a centimeter per year and height after 1 year of treatment is decreased by less than 1 cm

Patient Encounter Part 2

Home Medications:

- Albuterol MDI 2 puffs every 6 hours as needed for coughing. Last filled 2 weeks ago.
- Albuterol 2.5 mg solution for inhalation every 6 hours as needed for wheezing. Last filled 2 weeks ago.
- Cetirizine 10 mg PO daily for allergies. Last filled 3 months ago, #30.
- Fluticasone-salmeterol HFA 115/21 mcg, 2 inhalations twice daily to prevent asthma symptoms. Rinse after use. Last filled 2 months ago, #120 inhalations.
- Montelukast 10 mg PO once daily for allergies and to prevent asthma symptoms. Last filled 3 months ago, #30.
- Sodium chloride OTC nasal rinse (Sinus Rinse Kit nasal powder for reconstitution): Use as directed at bedtime for sinuses.

Vaccinations: He gets the influenza vaccine yearly.

What is the patient doing incorrectly with his MDI? What is he doing correctly?

Using motivational interviewing techniques, discuss adherence with medications.

Table 14–5

Estimated Comparative Daily Dosages for Inhaled Corticosteroids for Asthma

	Ages 0–11 Years			Ages 12 and Older		
Medication	**Low Dose**	**Medium Dose**	**High Dose**	**Low Dose**	**Medium Dose**	**High Dose**
Beclomethasone HFA 40 or 80 mcg/puff	80–160 mcg/day in 2 divided doses[a]	160–320 mcg/day in 2 divided doses[a]	> 320 mcg/day in 2 divided doses[a]	80–240 mcg/day in 2 divided doses	240–480 mcg/day in 2 divided doses	> 480 mcg/day in 2 divided doses
Budesonide DPI 90 or 180 mcg/puff	180–400 mcg/day in 2 divided doses[a]	400–800 mcg/day in 2 divided doses[a]	> 800 mcg/day in 2 divided doses[a]	180–600 mcg/day in 2 divided doses	600–1200 mcg/day in 2 divided doses	> 1200 mcg/day in 2 divided doses
Budesonide inhalation suspension for nebulization 0.25 mg/2 mL, 0.5 mg/2 mL, 1 mg/2 mL	Ages 0–4: 0.25–0.5 mg once daily or divided twice daily; Ages 5–11: 0.5 mg once daily or divided twice daily	Ages 0–4: 0.5–1 mg once daily or divided twice daily; Ages 5–11: 1 mg once daily or divided twice daily	Ages 0–4: > 1 mg once daily or divided twice daily; Ages 5–11: 2 mg once daily or divided twice daily	N/A	N/A	N/A
Ciclesonide HFA 80, 160 mcg/puff	N/A	N/A	N/A	160–320 mcg/day in 2 divided doses	160–640 mcg/day in 2 divided doses	320–640 mcg/day in 2 divided doses
Flunisolide HFA 80 mcg/puff	160 mcg/day in 2 divided doses[a]	320 mcg/day in 2 divided doses[a]	≥ 640 mcg/day in 2 divided doses[a]	320 mcg/day in 2 divided doses	320–640 mcg/day in 2 divided doses	> 640 mcg/day in 2 divided doses
Fluticasone furoate DPI 100 or 200 mcg/puff	N/A	N/A	N/A	100 mcg once daily	200 mcg once daily	200 mcg once daily
Fluticasone propionate Respiclick® DPI 55, 113, or 232 mcg/puff	N/A	N/A	N/A	55 mcg twice daily	113 mcg twice daily	232 mcg twice daily
Fluticasone propionate Diskus® DPI 50, 100, or 250 mcg/puff	100–200 mcg/day in 2 divided doses[a]	200–400 mcg/day in 2 divided doses[a]	> 400 mcg/day in 2 divided doses[a]	100–300 mcg/day in 2 divided doses	300–500 mcg/day in 2 divided doses	> 500 mcg/day in 2 divided doses
Fluticasone propionate HFA 44, 110, or 220 mcg/puff	88–176 mcg/day in 2 divided doses	176–352 mcg/day in 2 divided doses	> 352 mcg/day in 2 divided doses	88–264 mcg/day in 2 divide doses	264–440 mcg/day in 2 divided doses	> 440 mcg/day in 2 divided doses
Mometasone DPI 110, 220 mcg/puff	110 mcg once daily[b]	220–440 mcg once daily or in 2 divided doses[b]	> 440 mcg/day[b]	220 mcg once daily	440 mcg once daily or in 2 divided doses	> 440 mcg/day

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; N/A, safety and efficacy not established.

in children treated with low and medium dose ICS.[21,22] Risk of pneumonia is also increased significantly with ICS use. [23]

A significant drug interaction causing Cushing syndrome and adrenal insufficiency occurs when potent inhibitors of CYP3A4 (ritonavir, itraconazole, ketoconazole) are administered with high doses of ICS.[18]

Poor adherence to ICS treatment is common and contributes to uncontrolled asthma.[24] The slow onset of action and concerns about side effects are major deterrents to using these highly effective medications.

Considerable variability in response to ICS exists, with up to 40% of patients not responding to ICS. This lack of response may be related to functional glucocorticoid-induced transcript 1 gene (*GLCCI1*) variant in some patients with asthma.[25]

Systemic Corticosteroids Prednisone, prednisolone, and methylprednisolone are the cornerstone of treatment for acute asthma not responding to a SABA (see Table 14–6 for recommended doses).[1,2] The onset of action for systemic corticosteroids is 4 to 12 hours. For this reason, systemic corticosteroids are started early in the course of acute exacerbations. The oral route is preferred in acute asthma; there is no evidence that intravenous corticosteroid administration is more effective. Therapy with systemic corticosteroids is continued until the PEF is 70% or more of the personal best measurement and asthma symptoms are resolved. The duration of therapy usually ranges from 3 to 10 days. Tapering the corticosteroid dose in patients receiving short bursts (up to 10 days) is usually not necessary because any adrenal suppression is transient and rapidly reversible.[2]

Because of serious potential adverse effects, systemic corticosteroids are avoided as long-term controller medication for asthma, if possible. If systemic therapy is necessary, once-daily or every-other-day therapy is used with repeated attempts to decrease the dose or discontinue the drug.

Table 14–6

Usual Dosages for Quick-Relief Medications for Asthma in Home Setting[a,b]

Medications	Dosage Form	Children 0–11 Years	Adults and Children 12 Years of Age and Older
Inhaled SABA			
Albuterol HFA	MDI (inhalation suspension) 90 mcg/inhalation, 200 inhalations/canister	0–3 years: N/A 4–11 years: 1–2 puffs every 4–6 hours as needed	2 puffs every 4–6 hours as needed
Albuterol	DPI (inhalation powder) 90 mcg/inhalation, 200 inhalations/canister	0–3 years: N/A 4–11 years: 1–2 puffs every 4–6 hours as needed	2 puffs every 4–6 hours as needed
Albuterol	Nebulizer solution 0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, 5 mg/mL (0.5%)	0–4 years: 0.63–2.5 mg every 4–6 hours as needed 5–11 years: 1.25–5 mg every 4–8 hours as needed	2.5 mg every 6–8 hours as needed
Levalbuterol HFA	MDI (inhalation suspension) 45 mcg/puff, 200 puffs/canister	0–3 years: N/A 4–11 years: 1–2 puffs every 4–6 hours as needed	2 puffs every 4–6 hours as needed
Levalbuterol	Nebulizer solution 0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/0.5 mL, 1.25 mg/3 mL	0–4 years: 0.31–1.25 mg every 4–6 hours as needed 5–11 years: 0.31–0.63 mg every 8 hours as needed	0.63 mg every 6–8 hours as needed; may titrate to 1.25 mg every 8 hours if inadequate response
Systemic Corticosteroids			
Methylprednisolone	2, 4, 8, 16, 32 mg oral tablets	1–2 mg/kg/day by mouth in 2 divided doses (maximum 60 mg/day) for 3–10 days	40–60 mg/day by mouth as single or two divided doses for 3–10 days
Prednisolone	5 mg oral tablets; 5 mg/5 mL and 15 mg/5 mL oral liquid	1–2 mg/kg/day by mouth in 2 divided doses (maximum 60 mg/day) for 3–10 days	40–60 mg/day by mouth as single or two divided doses for 3–10 days
Prednisone	1, 2.5, 5, 10, 20, 50 mg oral tablets; 5 mg/mL and 5 mg/5 mL oral liquid	1–2 mg/kg/day by mouth in 2 divided doses (maximum 60 mg/day) for 3–10 days	40–60 mg/day by mouth as single or two divided doses for 3–10 days

[a]Dosages are provided for products that have been approved by the US FDA or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.

[b]Doses are increased in the hospital/emergency department setting.

DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; N/A; safety and efficacy not established; SABA, short-acting β_2-agonist.

▶ *Muscarinic Antagonists*

Muscarinic antagonists inhibit the effects of acetylcholine on muscarinic receptors in the airways and protect against cholinergic-mediated bronchoconstriction. The bronchodilator effects of the SAMAs are not as pronounced as SABAs in asthma.[1,2]

Ipratropium bromide is available as an MDI and solution for nebulization. Its onset of action is approximately 15 minutes, and the duration of action is 4 to 8 hours. The addition of ipratropium bromide to SABAs during a moderate to severe asthma exacerbation improves pulmonary function and decreases hospitalization rates in both adult and pediatric patients.[26] A SABA combined with ipratropium to increase bronchodilation is only indicated in the emergency department setting.

Tiotropium bromide is an inhaled LAMA available as a soft-mist inhaler for asthma. It has an onset of action of approximately 30 minutes and duration longer than 24 hours. Tiotropium is used as a long-term controller medication in patients with uncontrolled asthma already taking an ICS or an ICS and LABA combination.[27,28] Tiotropium decreases severe exacerbations, improves lung function, and is steroid sparing. Because of its safety and efficacy profile, tiotropium is the preferred LAMA for chronic asthma treatment. Aclidinium, glycopyrrolate, and umeclidinium are LAMAs approved only for COPD.

Muscarinic-antagonists may cause bothersome adverse effects such as blurred vision, dry mouth, and urinary retention. Increased cardiovascular events have been reported for ipratropium but not tiotropium.[29,30]

▶ *Leukotriene Receptor Antagonists*

The LTRAs are anti-inflammatory medications that either inhibit 5-lipoxygenase (zileuton) or competitively antagonize the effects of leukotriene D_4 (montelukast, zafirlukast). These agents improve FEV_1 and decrease asthma symptoms, SABA use, and asthma exacerbations. Although these agents offer the convenience of oral administration, they are significantly less effective than low ICS doses.[2,31] Combining an LTRA with an ICS is not as effective as an ICS plus a LABA but is considered steroid-sparing.[1,2] LTRAs are beneficial for asthma patients with allergic rhinitis, aspirin sensitivity, or exercise-induced bronchospasm.

Montelukast is generally well tolerated with minimal need for monitoring and few drug interactions. Zileuton and zafirlukast are less commonly used because of the risk of hepatotoxicity. Zileuton use requires liver function monitoring prior to use, monthly for 3 months, every 3 months for the first year of use, and periodically thereafter. Zileuton and zafirlukast are metabolized through the CYP 2C9 hepatic pathway and have significant drug interactions. All three agents have reports of neuropsychiatric events, such as sleep disorders, aggressive behavior, and suicidal thoughts.

▶ *Biologic Agents*

About 10% of patients have severe asthma requiring frequent, if not daily, oral corticosteroids and high doses of inhaled corticosteroids. Biologic agents target specific inflammatory sites and allow patients to reduce corticosteroid use.

Anti-IgE Monoclonal Antibody Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that inhibits binding of IgE to receptors on mast cells and basophils, resulting in inhibition of inflammatory mediator release and attenuation of the early- and late-phase allergic response. Omalizumab is indicated for treatment of patients with moderate to severe persistent asthma whose asthma is not controlled by ICS and who have a positive skin test or in vitro reactivity to aeroallergens. Omalizumab significantly decreases ICS use, reduces the number and length of exacerbations, and increases asthma-related quality of life.[32]

Omalizumab is given as a subcutaneous injection every 2 to 4 weeks in the office or clinic. The initial dose is based on the patient's weight and baseline total serum IgE concentration. See Table 14–3 for dosing recommendations. Subsequent IgE levels are not monitored.

The most common adverse effects are injection site reactions and include bruising, redness, pain, stinging, itching, and burning. Anaphylactic reactions are rare but may occur at any time after medication administration. Monitoring the patient for an anaphylactic reaction for 2 hours after medication administration is recommended for the first 3 months; thereafter, monitoring time can be reduced to 30 minutes.[33] It is also important to issue a prescription for and provide patient education on the use of subcutaneous epinephrine for an anaphylactic reaction from omalizumab. Omalizumab has been associated with an increased risk of cardiovascular and cerebrovascular events (eg, myocardial infarction, transient ischemic attack, venous thrombosis) and perhaps cancer, but the magnitude of the increased risk is unclear.[34]

Anti-Interleukin-5 (IL-5) Receptor Monoclonal Antibodies Mepolizumab, reslizumab, and benralizumab are monoclonal antibodies that block the cytokine interleukin-5 (IL-5). IL-5 triggers the cascade of inflammation by activating eosinophils. By blocking eosinophils in patients with eosinophilic asthma, mepolizumab and benralizumab have significantly decreased asthma exacerbations and decreased the dose or need for oral corticosteroids.[35,36] Mepolizumab and benralizumab are both subcutaneous injections that need to be administered in a clinic setting because of the potential for anaphylactic reactions. Reslizumab has not shown the same clinical benefits as mepolizmab or benralizumab and is an intravenous infusion administered every 4 weeks in an infusion center.[37] See Table 14-3 for dosing. Common side effects include nasopharyngitis, headache, formation of positive anti-drug antibodies, and worsening asthma or upper respiratory tract infections. Because of the potential for anaphylactic reactions, consideration should be given to providing patients with epinephrine auto-injectors along with education. Long-term side effects of the anti-IL-5 receptor monoclonal antibodies, including opportunistic and parasitic infections, are unknown. Patients who have had or have an active helminth infection should avoid anti-IL-5 antibodies. Because of the immunosuppressive effects and case reports of anti-IL-5 receptor monoclonal antibody medications causing herpes zoster infections, the varicella vaccine and the recombinant zoster vaccine (Shingrix), if indicated, should be considered prior to initiation of treatment with an anti-IL-5 antibody. This drug class is not approved for children younger than age 12 or in patients who are pregnant or breastfeeding. All of these medications are very expensive, so identifying appropriate patients is important.

▶ *Macrolides*

Recent evidence indicates that azithromycin 500 mg orally three times weekly for 48 weeks decreases asthma exacerbations and improves quality of life for adults with asthma not controlled with an ICS and LABA.[38] Potential benefits result from anti-inflammatory and not antimicrobial properties. Screening for hearing impairment, cardiovascular arrhythmias, and drug interactions is recommended prior to initiating treatment.

Treatment of Chronic Asthma

KEY CONCEPT The intensity of pharmacotherapy for chronic asthma is based on disease severity for initial therapy and level of control for subsequent therapies. The least amount of medications necessary to meet the therapeutic goals is used.[2]

The first step in asthma management is evaluating the patient's asthma control and risk for future exacerbations (Tables 14–7 and 14-8). Pharmacologic treatment is initiated based on the recommendations for stepwise therapy (Table 14-9). Treatment

Table 14–7

Assessment of Asthma Control in Adults, Adolescents, and Children

Adults, Adolescents, and Children 6–11 Years		Children ≤ 5 Years	
Asthma Symptoms	**Level of Symptom Control**	**Asthma Symptoms**	**Level of Symptom Control**
In the past 4 weeks, has the patient had: • Daytime asthma symptoms more than twice per week • Nighttime awakening due to asthma • Reliever needed for symptoms more than twice per week • Activity limitation due to asthma	If yes to none of these = well controlled If yes to 1–2 of these = partly controlled If yes to 3–4 of these = uncontrolled	In the past 4 weeks, has the child had: • Daytime asthma symptoms for more than a few minutes, more than once a week • Nighttime awakening or nighttime coughing due to asthma • Reliever medication needed more than once per week • Activity limitation due to asthma	If yes to none of these = well controlled If yes to 1–2 of these = partly controlled If yes to 3–4 of these = uncontrolled

- If asthma is not well controlled, assess inhaler technique, adherence to therapies, and environmental controls before considering adjustment of therapy.
- Consider stepping up therapy if uncontrolled symptoms or recent exacerbations or high risk for exacerbations (see Table 14–8). Refer to Table 14–10 for stepwise approach to control asthma symptoms.
- Consider stepping down therapy if symptoms controlled for 3 months + low risk for exacerbations.

Data obtained from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. www.ginasthma.org.

Table 14–8

Risk Factors for Asthma Exacerbation

- Uncontrolled asthma symptoms
- Frequent use of SABA (mortality increased if more than 1 × 200-dose canister used per month)
- Inadequate ICS therapy (not prescribed, poor adherence, poor technique)
- Low FEV_1 (especially if < 60% predicted)
- Major psychological or socioeconomic problems
- Exposures: smoking, allergen exposure if sensitized
- Comorbidities: Obesity, rhinosinusitis, confirmed food allergy
- Sputum or blood eosinophilia; elevated FeNO (in adults with allergic asthma)
- Pregnancy
- History of intubation or treatment in ICU for asthma
- 1 or more severe exacerbations in the past 12 months

FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; ICU, intensive care unit; SABA, short-acting β_2-agonist.

Table 14–9

LO 6

GINA Recommendations for Initial Controller Treatment in Adults and Adolescents

Symptom Presentation	Preferred Option (Evidence Level)
• Asthma symptoms or need for SABA < 2×/month; no waking due to asthma in the past month; no risk factors for exacerbations; no exacerbations in the past year	No controller medication (D)
• Infrequent asthma symptoms, but patient has ≥ 1 risk factor for exacerbation	Low dose ICS (D)
• Asthma symptoms or need for SABA between twice a month and twice a week, or patient wakes due to asthma once or more a month	Low dose ICS (B)
• Asthma symptoms or need for SABA more than twice a week	Low dose ICS[a] (A)
• Troublesome asthma symptoms most days, or waking due to asthma once a week or more	Medium/high dose ICS (A) or low-dose ICS + LABA[b] (A)
• Severely uncontrolled asthma or patient presents with an acute exacerbation	Short course of OCS + high-dose ICS (A) or moderate-dose ICS/LABA[b] (D)

[a]Less effective option is LTRA.

[b]Not recommended for initial controller treatment in children 6–11 years.

Levels of evidence: A = randomized controlled trials (RCTs) and meta-analyses, rich body of data; B = RCTs and meta-analyses, limited body of data; C = nonrandomized trials, observational studies; D = panel consensus judgment.

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist, LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2-agonist.

Data from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. www.ginasthma.org.

recommendations involve two categories based on patient age: children 5 years of age and younger, and individuals 6 years of age and older. Therapeutic plans must be individualized.

▶ *Intermittent Asthma*

Patients with intermittent asthma only need SABAs. This asthma classification includes patients with exercise-induced bronchospasm (EIB), seasonal asthma, or asthma symptoms associated with infrequent trigger exposure. Patients pretreat with a SABA prior to exposure to a known trigger, such as exercise.

Exercise is one of the most common precipitants of asthma symptoms. Shortness of breath, wheezing, or chest tightness usually occur during or shortly after vigorous exercise, peak 5 to 10 minutes after stopping the activity, and resolve within 20 to 30 minutes. Warming up prior to exercise and covering the mouth and nose with a scarf or mask during cold weather may prevent exercise-induced asthma (Table 14–1). Pretreatment with a SABA 5 to 20 minutes prior to exercise is the treatment of choice and will protect against bronchospasm for 2 to 3 hours. Regular treatment with an ICS or LTRA is recommended if SABA treatment is needed daily for exercise and not working effectively.[39]

▶ *Persistent Chronic Asthma*

Patients with persistent chronic asthma require daily long-term control therapy. ICS are the long-term control medication of choice at all levels of severity (mild, moderate, and severe) and in all age groups.[2] SABAs are prescribed for all patients with asthma for use on an as-needed basis.

After initiating therapy, patients are monitored within 2 to 6 weeks to ensure that asthma control has been achieved. Before increasing therapy, the patient's inhaler technique and adherence to therapy are evaluated. Medication intensification is based on individualized response to therapy (Table 14–10).

Patients with controlled asthma are monitored at 1- to 6-month intervals to ensure that control is maintained. A gradual step-down in long-term controller therapy is attempted once control has been maintained for at least 3 months. Controversy exists about how best to taper long-term controller medication. The ICS dose can be decreased before removing the LABA, or the LABA can be discontinued while maintaining the same ICS dose.[2,40] Clinical trials are ongoing to resolve this issue.

Treatment of Acute Asthma

KEY CONCEPT In acute asthma, early and appropriate intensification of therapy is important to resolve the exacerbation and prevent relapse and future severe airflow obstruction. Early and aggressive treatment is necessary for quick resolution.[41]

The optimal treatment of acute asthma depends on the severity of the exacerbation. The patient's condition usually deteriorates over several hours, days, or weeks. Table 14–11 contains guidance for treating an asthma exacerbation.

Based on the initial response to SABA therapy, the severity of the exacerbation is assessed, and treatment is appropriately intensified. Patients deteriorating quickly or not responding to quick-relief medications should go to the emergency department for assessment and treatment of the exacerbation. Patients responding to therapy in the emergency department with a sustained response to a SABA are discharged home. Patients are discharged with a SABA, a 3- to 10-day course of oral corticosteroid, an ICS, and perhaps other appropriate long-term controller medications.

Table 14–10

GINA Stepwise Approach to Control Symptoms and Minimize Future Risk

Adolescents and Adults

Step	Preferred Controller Option	Other Controller Options
1	No controller As-needed SABA	May consider low-dose ICS if at risk for exacerbations
2	Low-dose ICS	LTRA
3	Low-dose ICS + LABA	Medium-dose ICS (preferred over addition of LABA for patients ages 6–11) High-dose ICS Low-dose ICS + LTRA
4	Medium/high dose ICS/LABA	Add tiotropium if history of exacerbations (not for children < 12 years old) High dose ICS + LTRA
5	Refer to specialist for consideration of add-on treatment such as tiotropium, anti-IgE, anti-IL5	Add low-dose OCS

Children Ages 5 Years and Younger

Step	Preferred Controller Option	Other Controller Options
1	No controller As-needed SABA	
2	Low dose ICS	LTRA Intermittent ICS
3	Moderate-dose ICS	Low-dose ICS + LTRA
4	Continue controller and refer to asthma specialist	Add LTRA Increase ICS frequency Add intermittent ICS

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2 agonist.

Data from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. www.ginasthma.org.

Patients who do not respond adequately to intensive therapy in the emergency department within 3 to 4 hours are admitted to the hospital. During hospitalization, oxygen, continuous nebulization of SABA, systemic corticosteroids, and alternative treatments such as magnesium and heliox may be used to treat the exacerbation.

Patients with oxygen saturation less than 90% (0.90; < 95% [0.95] in children, pregnant women, and patients with coexisting heart disease) receive oxygen with the dose adjusted to keep oxygen saturation above this level. Administration of low oxygen concentrations (< 30% [0.30] of the fraction of inspired oxygen or FiO_2) by nasal cannula or facemask is usually sufficient to reverse hypoxemia in most patients.

Asthma Self-Management

LO 7

Self-management plans give patients the freedom to adjust therapy based on personal assessment of disease control using predetermined written instructions from the physician. Written asthma action plans, a part of standard care, initiate early treatment of worsening asthma to potentially prevent hospitalizations and death.

The plan includes instructions on daily management and how to recognize and handle worsening asthma.[2] Asthma control is assessed by evaluating symptoms of worsening asthma and/or monitoring PEF. Early signs of deterioration include increasing nocturnal symptoms, increasing use of inhaled SABAs, or symptoms that do not respond to increased use of inhaled SABAs. Providing patients with a prescription for oral corticosteroids to use on an as-needed basis for the initiation of an asthma exacerbation is part of asthma self-management.

Measurement of PEF is considered for patients with moderate to severe persistent asthma, poor perception of worsening asthma or airflow obstruction, and those with an unexplained response to environmental or occupational exposures.[2] PEF measurements are not necessary for a patient to receive an asthma action plan. The plan can be based upon symptoms only. PEF is measured daily in the morning upon waking or when asthma symptoms worsen. For PEF-based action plans, the patient's personal best PEF is established over a 2- to 3-week period when the patient is receiving optimal treatment.[2] Subsequent PEF measurements are evaluated in relation to their variability from the patient's best PEF measurement. PEF measurements in the range of 80% to 100% of personal best (green zone) indicate that current therapy is acceptable. A PEF in the range of 50% to 79% of personal best (yellow zone) indicates an impending exacerbation, and therapy is intensified with SABA therapy, possibly oral corticosteroids, and a call to the physician. A PEF less than 50% (red zone) signals a medical alert; patients use their SABA immediately, take oral corticosteroids, and go to the emergency department.

Special Populations

▶ *Pregnancy*

Approximately 4% to 8% of pregnant women are affected by asthma with about one-third experiencing worsening asthma during pregnancy.[42] It is safer for pregnant women to have asthma treated with medications than to experience worsening asthma. Uncontrolled asthma is a greater risk to the fetus than asthma medication use. Consequently, asthma exacerbations should be managed aggressively with pharmacotherapy. The stepwise approach to asthma therapy in pregnancy is similar to that for the general population.

Budesonide has the most safety data in humans and is the preferred ICS. However, there are no data indicating that other ICS present increased risk to the mother or fetus. Albuterol is the drug of choice for treating asthma symptoms and exacerbations in pregnancy.

Table 14–11

Assessment and Treatment of Asthma Exacerbations in the Urgent or Emergency Care Setting

	Signs and Symptoms		
Severity	**> 5 Years of Age**	**Children ≤ 5 Years of Age**	**Clinical Course**
Mild to Moderate	Talks in sentences Prefers sitting to lying Not agitated Respiratory rate increased Accessory muscles not used Pulse rate 100–120 bpm O_2 saturation (on air) 90%–95% (0.90–0.95) PEF > 50% predicted or personal best	Talks in sentences Breathless Wheezing may be present May be agitated Pulse rate < 100 bpm if mild Pulse rate < 200 bpm (0–3yrs) or ≤ 180 bpm (4–5 yrs) if moderate O_2 saturation ≥ 92% (0.92)	• SABA by nebulizer or MDI + spacer • Ipratropium bromide may decrease need for hospitalization and improve FEV_1 compared to SABA alone • Systemic corticosteroid × 5–7 days for adult; 3–5 days for children • Oxygen (if needed); target saturation 93%–95% (0.93–0.95) for adults; 94%–98% (0.94–0.98) for children; > 95% (0.95) during pregnancy • Epinephrine indicated only if exacerbation is associated with anaphylaxis and angioedema
Severe	Talks in words, not sentences Sits hunched forward Respiratory rate > 30/min Accessory muscles in use Pulse rate > 120 bpm O_2 saturation (on air) < 90% (0.90) PEF < 50% predicted or personal best	Talks in words, not sentences Pulse rate > 200 bpm (0–3 yrs) or > 180 bpm (4–5 yrs) O_2 saturation < 92% (0.92) Marked subcostal and/or sub-glottic retractions	• Requires ED visit and likely hospitalization; immediate transfer to hospital is indicated if child ≤ 5 years of age • Give inhaled SABA + ipratropium bromide in ED setting; no benefit from adding ipratropium to SABA once hospitalized • Oxygen to maintain saturation 93–95% (0.93–0.95) for adults; 94%–98% (0.94–0.98) for children; > 95% (0.95) during pregnancy • Oral or IV systemic corticosteroids; oral preferred if possible • Consider IV magnesium[a] • Epinephrine indicated only if exacerbation is associated with anaphylaxis and angioedema
Subset: Life Threatening	Too dyspneic to speak Drowsiness Confusion Silent chest Central cyanosis Pulse rate > 200 bpm PEF < 25% predicted or personal best	Unable to speak or drink Central cyanosis Silent chest Confusion	• Transfer to ICU • While waiting, start SABA + ipratropium bromide, IV corticosteroids, and O_2 to maintain saturation 93%–95% (0.93–0.95) for adults; 94%–98% (0.94–0.98) for children; > 95% (0.95) during pregnancy • Prepare patient for intubation • Consider IV magnesium[a] • Epinephrine indicated only if exacerbation is associated with anaphylaxis and angioedema

[a]Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations; however, it reduces hospital admissions in some patients, including adults with FEV_1 < 25%–30% predicted at presentation; adults and children who fail to respond to initial treatment and have persistent hypoxemia; and children whose FEV_1 fails to reach 60% predicted after 1 hour of care. The role of magnesium sulfate is not established for children ages 5 years and younger but may be considered as an adjuvant to standard treatment in children 2 years or age and older with severe asthma.

bpm, beats per minute; ED, emergency department; FEV_1, forced expiratory volume in first second; ICU, intensive care unit; MDI, metered-dose inhaler; O_2, oxygen; PEF, peak expiratory flow; SABA, short acting β_2-agonist.

Data obtained from Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2017. Available from: www.ginasthma.org

▶ *Young Children*

Although asthma is the most common disease in children, its diagnosis and monitoring are challenging. Treatment in children 0 to 4 years of age is extrapolated from studies completed in adults and older children. Albuterol and ICS are the treatments of choice in this group. However, use of montelukast is common because it is available in an oral, chewable formulation and is not a corticosteroid. Route of delivery is an important issue. Nebulization treatment is commonly used, and MDI with VHC is becoming more popular due to its decreased time of administration compared with nebulization. Budesonide is the only corticosteroid available in nebulization form and is approved for use in this age group. If young patients are not controlled on as-needed SABA, they should be stepped up to low-dose ICS. LTRA are alternatives to ICS. If the patient continues to be uncontrolled on low-dose ICS, the ICS may be increased to medium dose or an LTRA may be added to the low-dose ICS.[1]

OUTCOME EVALUATION

Chronic Asthma

- Assess onset, duration, and timing of subjective symptoms such as wheezing, shortness of breath, chest tightness, cough, nocturnal awakenings, and activity level. Use validated questionnaires (such as the Asthma Control Test, Asthma Therapy Assessment Questionnaire, or Asthma Control Questionnaire) to objectively document control.
- Monitor the use of SABAs. Using a SABA more than twice a week in intermittent asthma may indicate the need to

Patient Encounter Part 3

ROS:

General: + fever and chills 2 days ago, now resolved. No night sweats

ENT: + allergic rhinitis, + nasal congestion, + postnasal drip, occasional mouth breathing, no sleep apnea

Respiratory: + asthma, + cough; no shortness of breath or wheezing

CV: No chest pain, palpitations, or history of coronary artery disease

Endocrine: No cold/heat intolerance or fatigue; no history of diabetes or thyroid disease

Heme: No easy bruising or bleeding

GI: No nausea, vomiting, diarrhea, or acid reflux

MS: No joint swelling or arthritis; some muscle aches/pains over the weekend; flu-like symptoms 2 days ago

GU: No dysuria

Derm: No hives, eczema, angioedema, or rash

Neuro: No dizziness, tingling, or numbness

PE:

VS: Temp 36.3°C, BP 158/84, Pulse 90, RR 20, SaO_2 98% (0.98), Ht 170 cm, Wt 79 kg, BMI 27.3 kg/m^2

Gen: NAD

Eyes: PERRL, EOMI

HEENT: OP clear, septal spur with deviation to the left noted, TMs clear

Lungs: CTA bilaterally, + slight wheezing at both bases

CV: RRR no m/r/g

Abd: Soft, NT/ND

Skin: No rash/hives, + hyper-pigmented cheeks

Neuro/Psych: Grossly normal, normal affect

Asthma Control Test: 8 out of 25 (goal above 20), very poorly controlled; 3 months prior to today's visit ACT: 15

PEFR: 350 L/min best. Not done in clinic today. Does not check at home.

FeNO: Today 55 ppb (< 25 ppb "normal"); FeNO at last visit 50 ppb

Review of RAST testing: + ragweed, trees, grass, roaches, dust mites, dogs, and cats

Spirometry from 1 month ago:

	Measured	% Predicted
FVC (L)	3.87	112.73
FEV_1 (L)	2.51	89.09
FEV_1/FVC (%)	64.8 (0.648)	
TLC (L)	5.93	92.47
DLCO (mL/min/mm Hg)	29.31	143.09

Summary: Reduced FEV_1/FVC. The FVC and FEV_1 are normal. There is a response to inhaled bronchodilator. The FRC, TLC, and diffusing capacity are normal.

Labs: Na 141 mEq/L (mmol/L) , K 3.6 mEq/L (mmol/L), Cl 104 mEq/L (mmol/L), CO_2 30 mEq/L (mmol/L), anion gap 7, Ca 9.3 mg/dL (2.33 mmol/L), Scr 0.92 mg/dL (81 µmol/L), estimated GFR 106 mL/min/1.73 m^2, IgE 90 IU/mL (kIU/L)

WBC 9.6 × 10^9/L, Hgb 15.4 g/dL (154 g/L; 9.56 mmol/L), Hct 43.9% (0.439) , MCV 83.9 µm^3 (fL), MCH 29.5 pg/cell, MCHC 35.1 g/dL (351 g/L), RDW 14.2% (0.142), Plt 216 ×10^9/L; absolute eosinophil count 0.9 × 10^9/L (high)

Aspergillus antibody: none detected

What risk factors does the patient have for an asthma exacerbation?

How do the above laboratory and procedures help to assess the patient's asthma?

What therapeutic alternative regimens are available for this patient?

Provide this patient with an asthma action plan.

Recommend monitoring and follow-up for this patient.

initiate long-term control therapy. Use of more than one canister per month indicates the need to step up long-term control therapy.

- Determine the frequency of patient exacerbations. Frequent exacerbations, unscheduled clinic visits, emergency department visits, and hospitalizations due to asthma may indicate the need to reassess the patient's asthma regimen and environment.
- Measure lung function using office spirometry yearly or after therapeutic changes have been made in patients older than 5 years.
- Identify environmental factors triggering asthma exacerbations and provide trigger avoidance recommendations.
- Perform medication reconciliation to identify discrepancies in medications prescribed and used by the patient and to determine drug and disease state interactions.
- Assess the patient's inhaler technique at every visit and always ensure proper technique before stepping up therapy.
- Determine adherence to long-term controller medications. Assess the patient's understanding of the indication for long-term controller medication and identify adverse events, cost issues, and need for refills.
- Review and update the patient's asthma action plan and provide the patient with a written copy of the plan.
- Update the patient's immunization status and provide an annual influenza vaccination.

Acute Asthma

In addition to the outcomes measured for chronic asthma, acute asthma monitoring also includes the following:

- Measure PEF and assess asthma symptoms. The goal PEF measurement is 70% of the patient's personal best peak flow after the first three doses of an inhaled SABA and

Patient Care Process: Chronic Asthma

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review previous full pulmonary function tests, RAST, CBC, IgE levels, and chemistry panel.
- Assess patient's peak flow measurement (if applicable).
- Collect current asthma control using validated questionnaire (eg, ACT or c-ACT) results.
- Document current height, weight, blood pressure, heart rate, and pulse oximetry.
- Auscultate the lungs for wheezing. Examine ears, eyes, nose, and throat. Look in the mouth for signs of oral candidiasis if on ICS.
- Identify asthma attacks since the last visit, including emergency room visits or hospitalizations or use of oral corticosteroid bursts.
- Ask about tobacco use and exposure to secondhand smoke (tobacco or marijuana).
- Ask the patient to demonstrate his/her inhaler use. Ask when the inhaler is used, how many times in the past week the inhaler was used, and when the inhaler was refilled.
- Identify the number of missed days of school or work because of asthma.
- Ask about patient (or caregiver) goals and satisfaction with asthma control.
- Collect diet and exercise information and use of SABA before exercise.
- Identify comorbid conditions that may affect asthma control including gastroesophageal reflux disease (GERD), allergic rhinitis, sleep apnea, anxiety, and depression.

Assess the Information:

- Evaluate medication side effects (rapid heart rate, jitteriness, bad taste, cough, dysphonia, lack of efficacy).
- Verify medication adherence. Examine the patient's inhaler for the number of doses remaining. Call the dispensing pharmacy to determine fill history of inhalers.
- Determine whether the patient is taking any medications (including prescription, OTC, or supplements) that may cause cough or worsen asthma control.
- Determine if patient's asthma medications are appropriate based on spirometry results, exacerbation history, and current asthma control (see Table 14–7 for assessing control).
- Identify changes in home, work, or school environment that may contribute to worsening asthma symptoms.
- Assess for worsening in comorbid conditions that may contribute to worsening asthma symptoms.
- Identify factors that may be affecting medication adherence including side effects, cost issues, formulary issues, and unclear understanding of purpose of inhalers.
- Assess inhaler technique. Identify if patient has any barriers that inhibit them from using their inhaler correctly.
- Determine if the patient needs the influenza or pneumococcal vaccines.
- Assess the patient's readiness to stop using tobacco or marijuana.

Develop a Care Plan:

- Document the patient's specific goals for asthma control, including no missed school/work, no hospitalizations or emergency department visits, no need for oral corticosteroids, increased ability to exercise on a daily basis, ACT above 20 or peak flow reading at least 80% of the patient's personal best measurement.
- If the patient is not controlled, before adding medications or increasing dosing, make sure the patient is using the current inhalers correctly and is willing to use the inhaler.
- If asthma is not controlled and patient is adherent to their asthma medications and using them correctly, consider a step up in therapy (Table 14–10.)
- Identify patient preference, ability to pay, and insurance coverage for MDI, DPI, SMI, or nebulization.
- If the patient is controlled and has been on the current regimen for 3 months or longer, consider discontinuing or lowering the dose of controller medications.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report adverse effects that may occur.
- Review patient's technique with new inhalers. Use pictures and videos of inhalers. (http://use-inhalers.com/)
- Treat oral candidiasis if present. Discuss rinsing and spitting after ICS use and possibly the need for a spacer to decrease side effects.
- Provide an updated medication list with indication and use of each inhaler device.
- Provide an updated asthma action plan with medication changes.
- Review environmental asthma triggers and avoidance plans.
- Administer and update vaccinations.
- Discuss diet and exercise (using SABA prior to exercise if needed).
- Refill all asthma-related medications, including medications to treat allergic rhinitis and GERD.

Follow-up: Monitor and Evaluate:

- Schedule follow-up physician visits depending on asthma control (2 weeks–6 months).
- Check spirometry yearly.
- Review inhaler technique and use at every visit.
- Update asthma action plan yearly or with each medication change.
- Monitor ACT quarterly.
- Monitor medication refill history.
- Evaluate asthma-related hospitalizations, emergency department visits, and oral corticosteroid use.

improved asthma symptoms. Spirometry is not usually conducted in the emergency department.

- Check respiratory rate and measure oxygenation using pulse oximetry and provide oxygen via nasal cannula if needed. The goal oxygen saturation is greater than 90% (0.90) in adults and greater than 95% (0.95) in children, pregnant women, and patients with coexisting cardiovascular disease.
- Obtain a PCO_2 measurement via arterial blood gases in patients with severe asthma exacerbations. An increased PCO_2 indicates the potential for respiratory failure.
- Monitor serum potassium for hypokalemia upon admission and periodically throughout the admission in patients receiving high dose or continuous nebulization of SABA.

Abbreviations Introduced in This Chapter

CYP	Cytochrome P-450 isoenzyme
DPI	Dry powder inhaler
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HFA	Hydrofluoroalkane
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
LABA	Long-acting β_2-agonist
MDI	Metered-dose inhaler
NHLBI	National Heart, Lung, and Blood Institute
NSAID	Nonsteroidal anti-inflammatory drug
PCO_2	Partial arterial pressure of carbon dioxide
PEF	Peak expiratory flow
ppb	Parts per billion
SABA	Short-acting β_2-agonist
SMI	Soft mist inhaler
TH2	Type 2 T-helper $CD4^+$ cell

REFERENCES

1. Global strategy for asthma management and prevention 2017 (update). Available from: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed August 27, 2017.
2. NHLBI National Asthma Education and Prevention Program, Expert Panel Report-3. Guidelines for the diagnosis and management of asthma. NIH Publication No. 07-4051. Bethesda, MD: U.S. Department of Health and Human Services, 2007. Available from: http://www.ncbi.nlm.nih.gov/books/NBK7232/. Accessed September 1, 2017.
3. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343–373.
4. Asthma fact sheet No. 307. April 2017. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs307/en/index.html. Accessed September 1, 2017.
5. Fast Stats: Asthma 2016. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/nchs/fastats/asthma.htm. Accessed June 6, 2018.
6. Barnett SBL, Nurmagambetov TA. Control of asthma in the United States: 2002–2007. J Allergy Clin Immunol. 2011;127:145–152.
7. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. Available from: http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf. Accessed November 2, 2014.
8. Lung disease including asthma and adult vaccination. Centers for Disease Control and Prevention. Available from: vaccination. http://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/lung-disease.html. Accessed August 27, 2017.
9. Flu and people with asthma. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/flu/asthma/. Accessed August 27, 2017.
10. Pneumococcal vaccination. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/pneumococcal/vaccination.html#ppsv23. Accessed August 27, 2017.
11. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. Chest. 2005;127:335–371.
12. Rubin BK. Pediatric aerosol therapy: new devices and new drugs. Respir Care. 2011;56(9):1411–1421.
13. Proskocil BJ, Fryer AD. β_2-agonist and anticholinergic drugs in the treatment of lung disease. Proc Am Thorac Soc. 2005;2:305–310.
14. Kelly HW. Levalbuterol for asthma: A better treatment? Curr Allergy Asthma Rep. 2007;7:310–314.
15. Lemanske RF, Mauger DT, Sorkness CA. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med. 2010;362:975–985.
16. Nelson HS, Weiss ST, Bleeker ER, et al. and the Smart Study Group. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129:15–26.
17. Stempel DA, Raphiou IH, Kral KM, Yeakey AM, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. N Engl J Med. 2016;374(19):1822–1830.
18. Kelly HW. Comparison of inhaled corticosteroids: an update. Ann Pharmacother. 2009;43:519–527.
19. Kelly HW. Inhaled corticosteroid dosing: doubling for nothing? J Allergy Clin Immunol. 2011;128:278–281.
20. Tomlinson JEM, McMahon AD, Chaudhuri R, et al. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax. 2005;60:282–287.
21. Zhang L, Prietsch SOM, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: effects on growth. Cochrane Database Syst Rev. 2014 July 17;7:CD009471.
22. Pruteanu AI, Chauhan BF, Zhang L, Prietsch SOM, Ducharme FM. Inhaled corticosteroids in children with persistent asthma: dose-response effects on growth. Cochrane Database Syst Rev. 2014 July 17;7:CD009878.
23. Qian CJ, Coulombe J, Suissa S, Ernst P. Pneumonia risk in asthma patients using inhaled corticosteroids: a quasi-cohort study. Br J Clin Pharmacol 2017;83(9):2077–2086.
24. Gamble J, Stevenson M, McClean E, et al. The prevalence of non-adherence in difficult asthma. Am J Respir Crit Care Med. 2009;180:817–822.
25. Tantisira KG, Lasky-Su J, Harada M. Genome wide association between GLCCI1 and response to glucocorticoid therapy in asthma. N Engl J Med. 2011;365:1173–1183.
26. Rodrigo GJ, Castro-Rodrigo JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax. 2005; 60:740–746.
27. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363:1715–1726.

28. Kerstjens HAM, Disse B, Schroder-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. J Allergy Clin Immunol. 2011;128:308–314.
29. Ogale SS, Lee TL, Au DH, et al. Cardiovascular events associated with ipratropium bromide in COPD. Chest. 2010;137:13–19.
30. Celli B, Decramer M, Leimer I, et al. Cardiovascular safety of tiotropium in patients with COPD. Chest. 2010;137:20–30.
31. Sorkness CA, Lemanske RF Jr, Mauger DT, et al. Long-term comparison of 3 controller regiments for mild-moderate persistent childhood asthma: the pediatric asthma controller trial. J Allergy Clin Immunol. 2007;119:64–72.
32. Busse WW, Morgan WJ, Gergen PJ. Randomized trial of omalizumab (Anti-IgE) for asthma in inner-city children. N Engl J Med. 2011;364:1005–1015.
33. Kim HL, Leigh R, Becker A. Omalizumab: practical considerations regarding the risk of anaphylaxis. Allergy Asthma Clin Immunol. 2010;6:32–41.
34. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. U.S. Department of Health and Human Services. U.S. Food and Drug Administration. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm414911.htm. Accessed August 25, 2017.
35. Bel EH, Wenzel SE, Thompson PJ, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198–1207.
36. Fitzgerald JM, Bleecker ER, Parameswaran N, et al. Benralizumab, an anti-interleukin-5 α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016;388(10056):2128–2141.
37. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicenter, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3:355–366.
38. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10095):659–668.
39. Parsons JP, Hallstrand TS, Mastronarde JG, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2013;187:1016–1027.
40. Rogers L, Reibman J. Stepping down asthma treatment: how and when. Curr Opin Pulm Med. 2012;18(1):70–75.
41. Camargo CA Jr, Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department: summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. Proc Am Thorac Soc. 2009;6(4):357–366.
42. Asthma in pregnancy. ACOG practice bulletin no. 90. Washington, DC: American College of Obstetricians and Gynecologists, February 2008. Available from: http://www.guideline.gov/content.aspx?id=12630. Accessed August 27, 2017.

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15 Chronic Obstructive Pulmonary Disease

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LEARNING OBJECTIVES

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

1. Describe the pathophysiology of chronic obstructive pulmonary disease (COPD).
2. Identify signs and symptoms of COPD.
3. List the treatment goals for a patient with COPD.
4. Design an appropriate COPD maintenance treatment regimen based on patient-specific data.
5. Design an appropriate COPD exacerbation treatment regimen based on patient-specific data.
6. Develop a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for COPD.
7. Formulate an appropriate education plan for a patient with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by airflow limitation that is not fully reversible. Previous definitions of COPD included chronic bronchitis and emphysema. Chronic bronchitis is defined clinically as a chronic productive cough for at least 3 months in each of two consecutive years in a patient in whom other causes have been excluded.[1] Emphysema is defined pathologically as destruction of alveoli.[1] The major risk factor for both conditions is cigarette smoking, and many patients share characteristics of each one. Therefore, current guidelines focus instead on chronic airflow limitation.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is an expert panel of health professionals who developed consensus guidelines for the diagnosis and care of patients with COPD that are updated annually.[1]

EPIDEMIOLOGY AND ETIOLOGY

COPD is a major cause of morbidity and mortality and a significant cause of disability worldwide. In 2013, 15.7 million US adults were estimated to have COPD.[2] Chronic lower respiratory diseases are the third leading cause of death in the United States. In 2014, more than 151,000 adults died from COPD.[3] Personal health care spending in the United States on COPD was estimated to be $53.8 billion in 2013.[4]

COPD is caused by repeated inhalation of noxious particles or gases, most commonly cigarette smoke. Marijuana and other forms of tobacco, including secondhand smoke, are also risk factors.[1] Not all smokers develop clinically significant COPD, which suggests that genetic susceptibility plays a role. The best documented genetic factor is a rare hereditary deficiency of α_1-antitrypsin (AAT). Severe deficiency of this enzyme results in premature and accelerated development of emphysema. Factors that potentially reduce maximal attained lung function (eg, maternal smoking, preterm birth, early childhood lung infections, air pollution, childhood asthma, and active smoking during adolescence) increase the risk of COPD.[1,5] Other COPD risk factors include occupational exposure to dusts and chemicals (vapors, irritants, and fumes), biomass smoke inhalation, asthma, and bronchial hyperresponsiveness. Outdoor air pollution has been implicated as a cause, but its exact role is unclear.

PATHOPHYSIOLOGY

LO 1

Repeated exposure to noxious particles and gases causes chronic inflammation, resulting in pathologic changes in the central and peripheral airways, lung **parenchyma**, and pulmonary vasculature that lead to obstruction.[1,6,7] An imbalance between **proteases** and **antiproteases** in the lungs and oxidative stress are also important in the pathogenesis of COPD (**Figure 15–1**).

Inflammation is present in the lungs of all smokers, yet not all smokers develop COPD. In patients with COPD the inflammatory response is amplified, likely due to a genetic predisposition, although the exact mechanisms are unknown. KEY CONCEPT The inflammation of COPD differs from that seen in asthma, so the use of and response to anti-inflammatory medications is different. The inflammation of asthma is mainly mediated through eosinophils and mast cells. In COPD, the primary inflammatory cells are neutrophils, macrophages, and $CD8^+$ T lymphocytes.[6,7] A subset of patients with COPD also have increased eosinophils, which appears to predict a more favorable response to bronchodilators and corticosteroids and may indicate co-existing asthma.[6] Activated inflammatory cells release mediators (eg, interleukin-1, interleukin-8 [CXCL8], tumor necrosis factor-α) and secrete proteases (eg, elastase, proteinase-3, matrix metalloproteinase-9) which sustain and amplify inflammation and damage lung structures.[1,6]

Proteases and antiproteases are part of the normal protective and repair mechanisms in the lungs. An imbalance of protease-antiprotease activity in COPD results from either increased production or activity of destructive proteases or inactivation or reduced production of protective antiproteases. AAT (an antiprotease) inhibits trypsin, elastase, and several other proteolytic enzymes. Deficiency of AAT results in unopposed

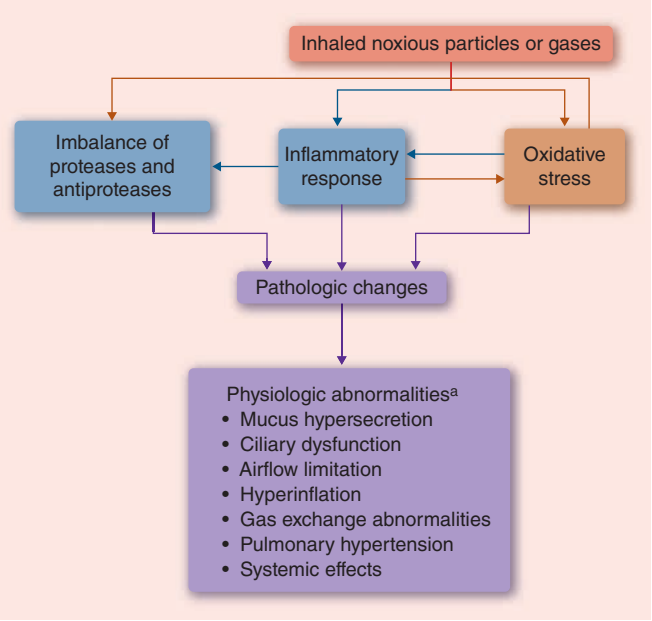

FIGURE 15–1. Pathophysiology of COPD.
[a]The physiologic abnormalities usually develop in this order.

protease activity, which promotes destruction of alveolar walls and lung parenchyma, leading to emphysema.

Oxidative stress occurs from smoke exposure and an increase in activated neutrophils and macrophages. Oxidative stress promotes inflammation and contributes to the protease-antiprotease imbalance by reducing antiprotease activity. In addition, oxidants constrict airway smooth muscle, contributing to reversible airway narrowing.

In the central airways (the trachea, bronchi, and larger bronchioles), inflammatory cells and mediators stimulate mucus gland hyperplasia and mucus hypersecretion. Mucus hypersecretion and ciliary dysfunction lead to chronic cough and sputum production. The major site of airflow obstruction is the peripheral airways (small bronchi and bronchioles). Narrowing of small airways results from **fibrosis**, increased mucus, and accumulation of inflammatory debris.[1,6,7] The reduced airway diameter causes increased resistance to airflow. Parenchymal destruction leads to loss of elasticity and structural support resulting in closure of small airways during expiration, further obstructing airflow.

As airflow obstruction worsens, the rate of lung emptying slows and the interval between inspirations does not allow expiration to the relaxation volume of the lungs. This leads to pulmonary hyperinflation, which initially only occurs during exercise but later is also seen at rest. Hyperinflation contributes to the discomfort associated with airflow obstruction by flattening the diaphragm and placing it at a mechanical disadvantage.

In advanced COPD, airflow obstruction, damaged bronchioles and alveoli, and pulmonary vascular abnormalities lead to impaired gas exchange, resulting in **hypoxemia** and eventually **hypercapnia**. Hypoxemia is initially present only during exercise but occurs at rest as the disease progresses. Inequality in the **ventilation/perfusion ratio (V_A/Q)** is the major mechanism underlying hypoxemia. As hypoxemia worsens, the body may increase erythrocyte production in an attempt to increase oxygen delivery to tissues.

Pulmonary hypertension develops late in the course of COPD, usually after development of severe hypoxemia. It is the most common cardiovascular complication of COPD and can result in **cor pulmonale**, or right-sided heart failure. Progressive loss of skeletal muscle mass in longstanding COPD contributes to exercise limitation and declining health status.

CLINICAL PRESENTATION AND DIAGNOSIS

See accompanying box for the clinical presentation of COPD.

Diagnosis

A suspected diagnosis of COPD should be based on patient symptoms and history of exposure to risk factors. **Spirometry** is required to confirm the diagnosis, using the ratio of **forced expiratory volume in the first second (FEV_1)** to **forced vital capacity (FVC)**. A postbronchodilator FEV_1/FVC ratio less than 70% (0.70) confirms airflow limitation that is not fully reversible.[1] Spirometry results can further be used to classify severity of airflow limitation in these patients. The GOLD classification categories of severity based on postbronchodilator FEV_1 are as follows: GOLD 1, Mild = 80% predicted or greater; GOLD 2, Moderate = 50% to 79% predicted; GOLD 3, Severe = 30% to 49%

Clinical Presentation of COPD

LO 2

General

- Patients are initially asymptomatic. COPD is usually not diagnosed until declining lung function leads to significant symptoms and prompts patients to seek medical care.

Symptoms

- Symptom onset is variable and does not correlate well with severity of airflow limitation measured by FEV_1.[1]
- Initial symptoms include chronic cough (for more than 3 months) that may be intermittent at first, chronic sputum production, and dyspnea on exertion. Patients may complain of a sensation of chest heaviness or increased effort to breathe.
- As COPD progresses, dyspnea at rest and/or orthopnea develop, and ability to perform activities of daily living declines.

Signs

- Inspection may reveal use of accessory muscles of respiration (paradoxical movements of the chest and abdomen in a seesaw-type motion), pursed-lips breathing, and hyperinflation of the chest with increased anterior–posterior diameter ("barrel chest").
- On lung auscultation, patients may have distant breath sounds, wheezing, a prolonged expiratory phase, and **rhonchi**.
- In advanced COPD, signs of hypoxemia may include **cyanosis** and tachycardia.
- Signs of cor pulmonale include increased pulmonic component of the second heart sound, jugular venous distention (JVD), lower extremity edema, and hepatomegaly.

predicted; GOLD 4, Very Severe = less than 30% predicted.[1] Full pulmonary function tests (PFTs) with lung volumes and diffusion capacity and arterial blood gases (ABGs) are not necessary to establish the diagnosis or severity of COPD.

Pulse oximetry should be obtained in patients with signs or symptoms suggestive of cor pulmonale or respiratory failure.[1] If oxygen saturation is less than 92% (0.92), ABGs should be assessed.[1] Patients may exhibit increased arterial carbon dioxide tension ($Paco_2$) and decreased arterial oxygen tension (Pao_2).

A complete blood count (CBC) may reveal an elevated hematocrit that may exceed 55% (0.55; **polycythemia**). An AAT level is recommended in all COPD patients, especially in areas with a high prevalence of AAT deficiency.[1] Chest radiography may show lung hyperinflation and signs of emphysema.

It is important to distinguish COPD from asthma because treatment and prognosis differ. Differentiating factors include age of onset, smoking history, triggers, occupational history, and degree of reversibility measured by prebronchodilator and postbronchodilator spirometry. In some patients, a clear distinction between asthma and COPD is not possible. Management of these patients should be similar to that of asthma.

TREATMENT

Desired Outcomes

LO 3

The goals of COPD management include: (a) smoking cessation if applicable, (b) reducing symptoms, and (c) preventing and treating exacerbations.

General Approach to Treatment

LO 4

KEY CONCEPT An integrated approach of health maintenance (eg, smoking cessation), drug therapy, and supplemental therapy (eg, oxygen and pulmonary rehabilitation) should be used via an individualized approach. Symptom severity, risk of COPD exacerbations, adverse effects, comorbidities, and the patient's response and/or desires should be used to guide therapy decisions.[1]

Either the modified Medical Research Council Questionnaire (mMRC) or COPD Assessment Test (CAT) is recommended for symptom assessment. The CAT is preferred because it provides a more comprehensive assessment.[1] An mMRC grade of 0 or 1 or a CAT score less than 10 indicates fewer symptoms. Patients with more symptoms will have an mMRC grade of 2 or more or a CAT score of 10 or more. These patients require inhaled long-acting bronchodilators on a scheduled basis.[1]

Patient Encounter, Part 1

A 56-year-old African-American man with a past medical history of COPD, type 2 diabetes mellitus, hypertension, gout, tobacco abuse (25 pack year history), and marijuana abuse (over the last 10 years) presents to the clinic complaining of shortness of breath with moderate physical activity, a "heavy" chest, chronic cough, and chronic sputum production for more than 1 year.

What symptoms and/or risk factors does he have that are suggestive of COPD?

What additional information do you need before creating a treatment plan for this patient?

Risk of future COPD exacerbation is assessed using number of exacerbations per year. Patients with a history of two or more exacerbations per year or one or more exacerbation(s) requiring hospitalization are at high risk for future exacerbations. Patients at high risk of COPD exacerbations also require inhaled long-acting bronchodilators on a scheduled basis to reduce the frequency of exacerbations.[1] **Figure 15–2** provides an overview of the management of stable COPD.

Nonpharmacologic Therapy

▶ *Smoking Cessation*

KEY CONCEPT Smoking cessation slows the rate of decline in pulmonary function in patients with COPD.[8,9] Cessation can also reduce cough and sputum production and decrease all-cause mortality.[8] Therefore, it is a critical part of any treatment plan. Unfortunately, achieving and maintaining cessation is a major challenge. A clinical practice guideline from the US Public Health Service recommends a specific action plan depending on the current smoking status and desire to quit (**Figure 15–3**).[10] Brief interventions are effective and can increase cessation rates significantly. The 5 As and the 5 Rs can be used to guide brief interventions (**Table 15–1**).

All tobacco users should be assessed for their readiness to quit and appropriate strategies implemented. Those who are ready to quit should be treated with a combination of behavioral and cognitive strategies and pharmacotherapy. Combination pharmacotherapy is more effective than monotherapy and should be considered in patients with moderate to very severe tobacco dependence.[8] Refer to Tobacco Cessation in Chapter 36.

▶ *Pulmonary Rehabilitation*

Pulmonary rehabilitation results in significant and clinically meaningful improvements in dyspnea, exercise capacity, health status, and health care utilization.[11] Initiating pulmonary rehabilitation within 4 weeks of hospitalization for an acute exacerbation can reduce readmissions and mortality.[1] Benefits have been observed in all grades of COPD severity.[1] A comprehensive pulmonary rehabilitation program should include exercise training, education, and self-management interventions aimed at behavior change.

Rehabilitation programs may be conducted in the inpatient, outpatient (most common), community, or home setting. The minimum length of an effective program is 6 weeks; the longer the program, the more sustained the results.[12] It is important for patients to continue with a home exercise program to maintain the benefits gained from the pulmonary rehabilitation program.

▶ *Long-Term Oxygen Therapy*

Long-term oxygen administration (> 15 hours/day) to patients with chronic respiratory failure has been shown to reduce mortality and improve quality of life.[1,7] Oxygen therapy should be initiated in stable patients with COPD who have severe resting hypoxemia as determined by Pao_2 at or below 55 mm Hg (7.3 kPa) or oxygen saturation (Sao_2) at or below 88% (0.88), or with evidence of pulmonary hypertension, peripheral edema suggesting heart failure, or polycythemia.[1] Patients should be reassessed with repeat ABG or oxygen saturation after 60 to 90 days.

The dual-prong nasal cannula is the standard means of delivering continuous oxygen flow. The goal is to increase the baseline oxygen saturation to at least 90% (0.90) and/or Pao_2 to at least 60 mm Hg (8.0 kPa), allowing adequate oxygenation of vital organs. The flow rate, expressed as liters per minute (L/min),

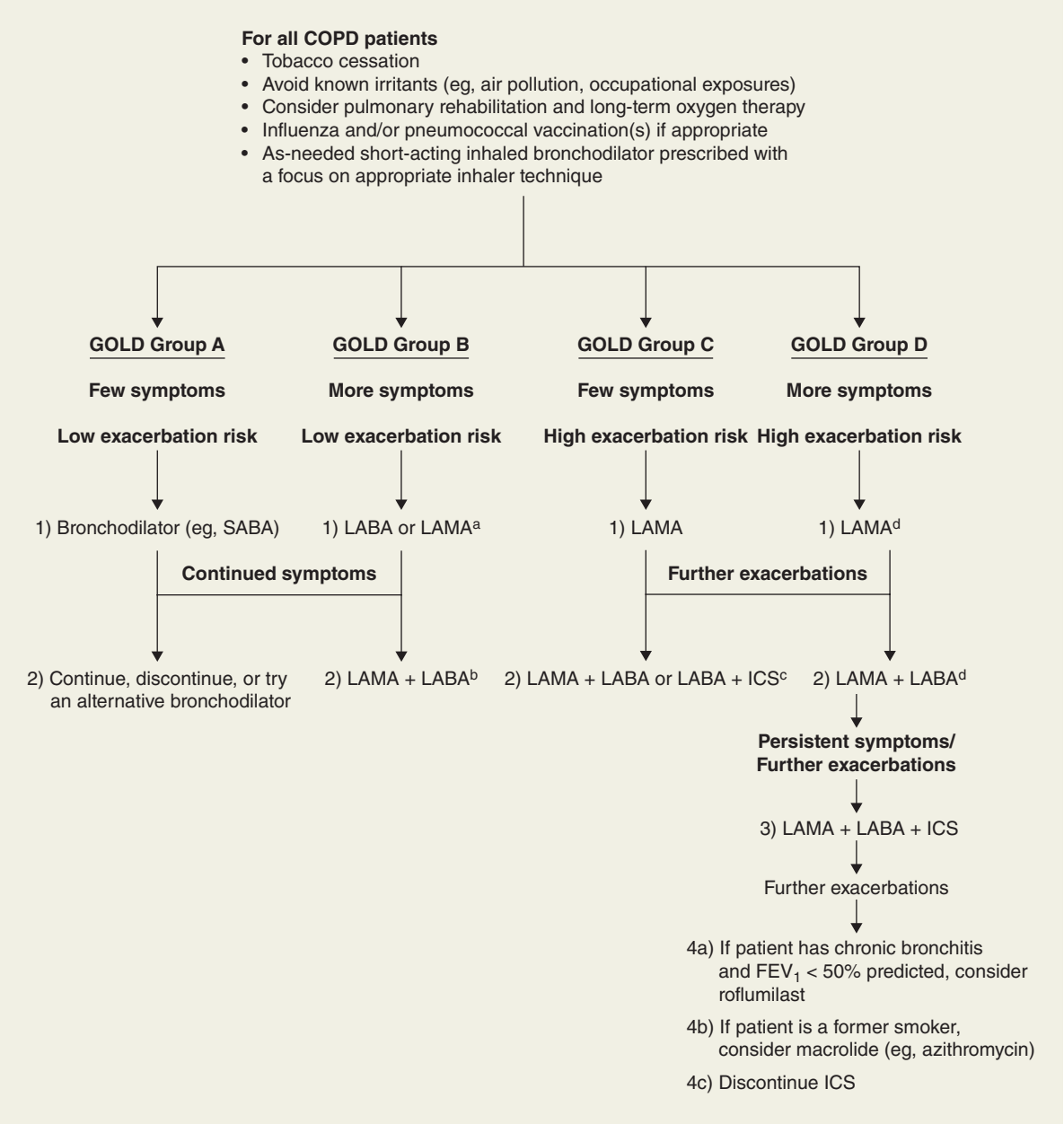

FIGURE 15–2. Treatment algorithm for stable COPD.[1] (ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic-antagonist; SABA, short-acting β_2-agonist.)
[a]If patient is experiencing severe breathlessness, may start with combination LABA/LAMA therapy.
[b]If patient does not improve on combination LABA/LAMA therapy, can de-escalate to a single agent.
[c]ICS therapy increases the risk for development of pneumonia, so LABA/LAMA combination therapy is preferred.
[d]GOLD guidelines suggest starting with combination LABA/LAMA therapy, but if monotherapy is desired, LAMA is the preferred option.

must be increased during exercise and sleep and can be adjusted based on pulse oximetry. Hypoxemia also worsens during air travel; patients requiring oxygen should generally increase their flow rate by 3 L/min during flight.[1]

▶ *Surgery*

Bullectomy, lung volume reduction surgery, and lung transplantation are surgical options for very severe COPD. These procedures may result in improved spirometry, lung volumes, exercise capacity, dyspnea, health-related quality of life, and possibly survival. Patient selection is critical because not all patients benefit.

Pharmacologic Therapy of Stable COPD

Medications available for COPD are effective for reducing or relieving symptoms, improving exercise tolerance, reducing the number and severity of exacerbations, and improving health status. Evidence that medications slow the rate of decline in lung function or improve mortality is inconclusive. An individualized evaluation of symptoms, activity limitation,

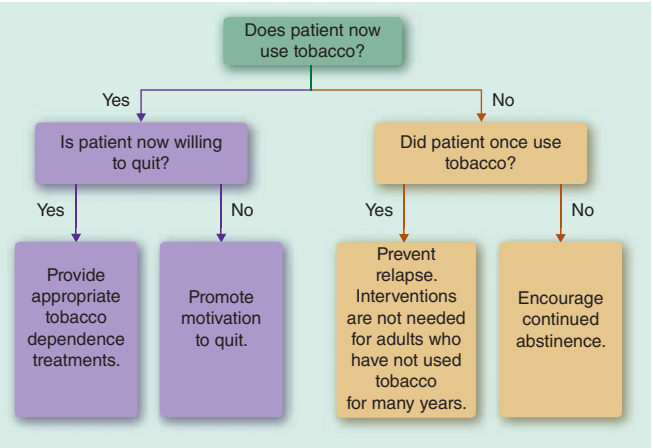

FIGURE 15–3. Algorithm for routine assessment of tobacco use status.[10] (From Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence. Clinical Practice Guideline. U.S. Department of Health and Human Services, 2008, http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/index.html.)

and a patient's future risk for exacerbations should be the guiding principles to determine appropriate pharmacologic management of COPD.[1]

▶ *Bronchodilators*

KEY CONCEPT Bronchodilators are the mainstay of treatment for symptomatic COPD. They can increase FEV_1, reduce symptoms, reduce exacerbation and hospitalization rates, and improve exercise tolerance, pulmonary rehabilitation efficacy, and health status.[1] They can be used as needed for symptoms or on a scheduled basis to prevent or reduce symptoms. The inhaled route is preferred, but attention must be paid to proper inhaler technique. Long-acting bronchodilators are more expensive than short-acting bronchodilators but are superior on important clinical outcomes, including frequency of exacerbations, degree of dyspnea, and health-related quality of life.[1] Importantly, lung function may continue to worsen even with appropriate therapy.

β_2-Agonists These agents cause airway smooth muscle relaxation by stimulating adenyl cyclase to increase formation of cyclic adenosine monophosphate (cAMP). They may also improve mucociliary transport. β_2-Agonists are available in inhalation, oral, and parenteral dosage forms; the inhalation route is preferred because of fewer adverse effects.

These drugs are available in short-acting and long-acting formulations (Table 15–2). The short-acting β_2-agonists (SABAs) used in COPD include albuterol (known as salbutamol outside the United States) and levalbuterol (known as R-salbutamol outside the United States). They are used as "rescue" therapy for acute symptom relief or in those with only occasional symptoms. SABAs are inconvenient as maintenance therapy because of the need for frequent dosing.

Long-acting β_2-agonists (LABAs) include salmeterol, formoterol, arformoterol, indacaterol, olodaterol, and vilanterol. Arformoterol and formoterol are both available for nebulization, providing an alternative for patients with poor inhaler technique. Indacaterol, olodaterol, and vilanterol (only available in combination) are long acting, allowing for once-daily dosing (Table 15–2). While certain studies suggest potential spirometric benefits of one long-acting inhaler over another, definitive data on actual patient outcome differences among long-acting agents is lacking.[13,14] Insurance coverage, patient response, patient preference for type of inhaler device, and prescriber preference are considerations when selecting a LABA. Patients treated with LABAs should also have a SABA such as albuterol for as-needed use ("rescue" medication) but should be advised to avoid excessive use.

Adverse effects of both LABAs and SABAs are dose related and include palpitations, tachycardia, cough, hypokalemia, and tremor. Sleep disturbance may also occur and appears to be worse with higher doses of inhaled LABAs. Increasing doses beyond those clinically recommended is without benefit and could be associated with increased adverse effects.

Antimuscarinics Ipratropium, tiotropium, aclidinium, glycopyrrolate (also known as glycopyrronium bromide), and umeclidinium are all bromide salts available for inhalation treatment of COPD. They produce bronchodilation by competitively blocking muscarinic receptors in bronchial smooth muscle and may also decrease mucus secretion. Tiotropium and umeclidinium have long half-lives allowing for once-daily dosing and are considered long-acting muscarinic antagonists (LAMAs). Other LAMAs include aclidinium and glycopyrrolate, which have shorter half-lives requiring twice-daily dosing. While certain studies suggest potential spirometric benefits of one LAMA over another, definitive data on actual patient outcome differences among LAMAs is still lacking.[15] Choice of LAMA should be based on insurance coverage, patient response and preferences, and prescriber preferences. Ipratropium is not typically recommended because it has a longer onset of action than SABAs and decreased efficacy compared to tiotropium.[16]

LAMAs may be more effective than LABAs for reducing exacerbations in patients with moderate to very severe COPD.[1,17] Patients using a LAMA as maintenance therapy should be prescribed a SABA as their rescue therapy; ipratropium is not recommended as an alternative to albuterol because of the risk of excessive anticholinergic effects when combined with LAMAs.[18]

Inhaled antimuscarinics are well tolerated with the most common adverse effect being dry mouth. Occasional metallic taste has also been reported, most commonly with ipratropium. Other anticholinergic adverse effects include constipation, tachycardia, blurred vision, and precipitation of narrow-angle glaucoma symptoms. Urinary retention could be a problem, especially for patients with concurrent bladder outlet obstruction. Early studies

Table 15–1

Components of Brief Interventions for Tobacco Users

The 5 As for Brief Intervention

Ask: Identify and document tobacco-use status for every patient at every visit
Advise: Urge every tobacco user to quit
Assess: Is the tobacco user willing to make a quit attempt at this time?
Assist: Use counseling and pharmacotherapy to help patients willing to make a quit attempt
Arrange: Schedule follow-up contact, preferably within the first week after the quit date

The 5 Rs to Motivate Smokers Unwilling to Quit at Present

Relevance: Tailor advice and discussion to each smoker
Risks: Help the patient identify potential negative consequences of tobacco use
Rewards: Help the patient identify the potential benefits of quitting
Roadblocks: Help the patient identify barriers to quitting
Repetition: Repeat the motivational message at every visit

Table 15–2

Maintenance Medications for COPD

	Medication	Onset	Peak	Duration	Usual Dose
Short-Acting β_2-Agonists	**Albuterol**[a]				
	Nebulization	5–8 min	1–2 hours	2–6 hours	1.25–5 mg every 4–8 hours as needed
	Inhalation	5–8 min	0.5–1 hour	2–6 hours	MDI (90 mcg/puff) one to two puffs every 4–6 hours as needed
	Oral	30 min	2–3 hours	4–6 hours ER: Up to 12 hours	2–4 mg three to four times a day as needed ER: 4–8 mg every 12 hours (max: 32 mg/day)
	Levalbuterol[a]				
	Nebulization	10–17 min	1.5 hours	5–8 hours	0.63–1.25 mg three times per day, 6–8 hours apart as needed
	Inhalation	5–10 min	1–1.5 hours	3–6 hours	MDI (45 mcg/puff) one to two puffs every 4–6 hours as needed
Long-Acting β_2-Agonists	**Formoterol**				
	Inhalation	1–3 min	1–3 hours	8–12 hours	Only in combination inhalers
	Nebulization	1–3 min	1–3 hours	8–12 hours	20 mcg every 12 hours
	Salmeterol				
	Inhalation	10 min to 1 hour	2–3 hours	12 hours	Powder (50 mcg/inhalation) one inhalation every 12 hours
	Indacaterol				
	Inhalation	5 min	1–4 hours	24 hours	Powder (75 mcg/inhalation) one inhalation every 24 hours
	Olodaterol				
	Inhalation	5 min	10–20 minutes	24 hours	2.5 mcg/inhalation two inhalations every 24 hours
	Vilanterol				
	Inhalation	15–30 min	2 hours	24 hours	Only in combination inhalers
	Arformoterol				
	Nebulization	7–20 min	1–3 hours	12 hours	15 mcg every 12 hours
Short-Acting Muscarinic Antagonists	**Ipratropium**				
	Nebulization	15 min	1–2 hours	4–8 hours	500 mcg every 6–8 hours as needed
	Inhalation	15 min	1–2 hours	2–4 hours	MDI (17 mcg/puff) two puffs four times/day as needed
Long-Acting Muscarinic Antagonists	**Tiotropium**				
	Inhalation	60 min	1.5–3 hours	24 hours	Powder (18 mcg/inhalation) one inhalation every 24 hours Aerosol solution (2.5 mcg/inhalation) two inhalations every 24 hours
	Aclidinium				
	Inhalation	30 min	2–3 hours	12 hours	Powder (400 mcg/inhalation) one inhalation every 12 hours
	Umeclidinium				
	Inhalation	60 min	1–3 hours	24 hours	Powder (62.5 mcg/inhalation) one inhalation every 24 hours
	Glycopyrrolate				
	Inhalation	5 min	5 minutes	12–24 hours	Powder (15.6 mcg/inhalation) one inhalation every 12 hours
	Nebulization	5 min	< 20 minutes	12–24 hours	25 mcg every 12 hours
Methylxanthine	**Theophylline**				
	Oral	15–30 min	Up to 24 hours, depending on formulation	6–24 hours	400–600 mg/day divided every 6–24 hours based on formulation (max: 600 mg/day)[b] Adjust dose to serum concentrations of 5–15 mcg/mL (mg/L; 28–83 µmol/L)
Phosphodiesterase-4 Inhibitor	**Roflumilast**	4 wks	—	—	500 mcg daily[c]
	Oral				

(*Continued*)

Table 15–2

Maintenance Medications for COPD (*Continued*)

Inhaled Corticosteroids	**Beclomethasone**	1–14 days	3–4 weeks	MDI (40, 80 mcg/puff) 40–160 mcg every 12 hours
	Budesonide	1 day	1–2 weeks	Powder (90, 180 mcg/inhalation) 90–180 mcg every 12 hours
	Fluticasone	Variable	1–2 weeks	MDI (44, 110, 220 mcg/puff) 88–440 mcg every 12 hours Powder (50, 100, 250 mcg/inhalation) 50–250 mcg every 12 hours

In elderly patients, start with the lowest recommended dose and increase as necessary.

[a]Albuterol is known as salbutamol and levalbuterol is known as levosalbutamol (or R-salbutamol) outside the United States.

[b]Maximum dose of 400 mg in patients with decreased hepatic function.

[c]Not recommended in patients with moderate or severe hepatic impairment.

ER, extended-release; MDI, metered-dose inhaler.

suggested an increased cardiovascular risk with ipratropium or tiotropium, but subsequent large trials of tiotropium found no increased cardiovascular risk.[1,17,19]

Methylxanthines Theophylline is an oral methylxanthine derivative and nonselective phosphodiesterase inhibitor that increases intracellular cAMP within airway smooth muscle resulting in bronchodilation and may also improve inspiratory function. Its use is limited due to a narrow therapeutic index, multiple drug interactions, and adverse effects. Theophylline should be reserved for patients who cannot use inhaled medications or who remain symptomatic despite appropriate use of inhaled bronchodilators.

Therapeutic drug monitoring is needed to optimize therapy because of wide interpatient variability. Serum concentrations from 5 to 15 mcg/mL (mg/L; 28–83 μmol/L) provide adequate clinical response with a greater margin of safety than the previously recommended range of 10 to 20 mcg/mL (mg/L; 55–111 μmol/L). However, bronchodilatory effects are small when the serum concentration is below 10 mcg/mL (mg/L; 55 μmol/L).[20] Multiple factors can alter theophylline clearance including concomitant medications (through CYP450 interactions), disease states, tobacco smoke, and marijuana. Chemicals in tobacco smoke induce theophylline metabolism and increase its clearance. The most common adverse effects of theophylline include headache, heartburn, insomnia, tachycardia, palpitations, and tremor. Dose-related adverse effects include nausea and vomiting, seizures, and arrhythmias.

▶ *Corticosteroids*

Inhaled corticosteroids (ICS) in combination therapy improve symptoms, lung function, health status, and exacerbation rates in patients with moderate to very severe COPD.[1] However, there appears to be a limited response of COPD-associated inflammation, and the long-term safety of ICS in COPD patients is unclear.[1]

KEY CONCEPT ICS are currently recommended solely for patients with severe to very severe COPD with increased exacerbation risk who are not adequately controlled by first-line long-acting bronchodilators and may be most beneficial in patients with elevated serum eosinophils.[1] Monotherapy with ICS is less effective than combined therapy with a LABA and is therefore not recommended. Combination inhaler devices are convenient and ensure that patients receive both medications (Table 15–3).

The most common adverse effects from ICS include oropharyngeal candidiasis and hoarse voice. These can be minimized by rinsing the mouth after use and by using a spacer device with metered-dose inhalers (MDIs). Increased bruising, decreased bone density, increased risk of diabetes, cataracts, and mycobacterial infections have been reported; an increased pneumonia risk exists with ICS usage and appears to be higher in elderly patients, smokers, or underweight patients.[1,21]

Long-term use of systemic corticosteroids should be avoided due to an unfavorable risk-to-benefit ratio. The steroid myopathy that can result from long-term use of oral corticosteroids weakens muscles, further decreasing the respiratory drive in patients with advanced disease.

▶ *Phosphodiesterase-4 (PDE-4) Inhibitors*

Roflumilast is an oral PDE-4 inhibitor approved for prevention of moderate and severe COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[9] Roflumilast is believed to reduce inflammation by inhibiting breakdown of cAMP but does not cause direct bronchodilation. Roflumilast has more frequent adverse events than inhaled medications, is expensive, and has little effect on quality of life.[22] Adverse effects typically occur early during treatment and include diarrhea, weight loss, nausea, headache, insomnia, decreased appetite, and abdominal pain; neuropsychiatric effects (eg, insomnia, anxiety, depression, suicidal ideation) have also been reported. Roflumilast can be considered in patients with chronic bronchitis, an FEV_1 less than 50%, and exacerbations while being treated with two or three classes of long-acting inhaled medications, particularly if they have had a hospitalization within the previous year.[1,9] It should not be combined with theophylline because both inhibit PDE-4, and it should be avoided in underweight patients or those with depression.[1,20]

▶ *Combination Therapy*

For patients who remain symptomatic on monotherapy, a combination of bronchodilators can be used.[1,9] Combining long-acting inhaled medications is preferred over short-acting agents or theophylline. Combination therapy should include

Table 15–3

FDA-Approved Combination Inhalers for Management of COPD

Inhaled Corticosteroid/Long-acting β_2-Agonist (ICS/LABA)

Brand Name	Corticosteroid	β_2-Agonist	Dosage Strengths	Frequency
Advair Diskus	Fluticasone propionate	Salmeterol	100, 250, 500 mcg/50 mcg	Twice daily
Symbicort	Budesonide	Formoterol	80, 160 mcg/4.5 mcg	Twice daily
Breo	Fluticasone furoate	Vilanterol	100 mcg/25 mcg	Daily

Long-acting Muscarinic Antagonist/Long-acting β_2-Agonist (LAMA/LABA)

Brand Name	Antimuscarinic	β_2-Agonist	Dosage Strengths	Frequency
Anoro	Umeclidinium	Vilanterol	62.5 mcg/25 mcg	Daily
Stiolto	Tiotropium	Olodaterol	2.5 mcg/2.5 mcg	Daily
Bevespi	Glycopyrrolate	Formoterol	9 mcg/4.8 mcg	Twice daily
Utibron	Glycopyrrolate	Indacaterol	15.6 mcg/27.5 mcg	Twice daily

Short-acting Muscarinic Antagonist/Short-acting β_2-Agonist (SAMA/SABA)

Brand Name	Antimuscarinic	β_2-Agonist	Dosage Strengths	Frequency
Combivent	Ipratropium	Albuterol	20 mcg/100 mcg	Four times daily

Long-acting Muscarinic Antagonist/Long-acting β_2-Agonist/Inhaled Corticosteroid (LAMA/LABA/ICS)

Brand Name	Antimuscarinic	β_2-Agonist	Corticosteroid	Dosage Strengths	Frequency
Trelegy	Umeclidinium	Vilanterol	Fluticasone furoate	62.5 mcg/25 mcg/100 mcg	Daily

medications with different mechanisms, which can lower the risk of side effects versus increasing the dose of a single agent.[1] Combining a LABA with a LAMA produces a greater change in spirometry, reduces symptoms and exacerbations, and has a lower pneumonia risk when compared to a LABA/ICS combination.[1,23,24]

Triple therapy with ICS, LABA, and LAMA is commonly used in patients who remain symptomatic on dual therapy. Adding a LAMA to existing LABA/ICS therapy appears to improve lung function and patient reported outcomes including exacerbation risk, while adding ICS to existing LABA/LAMA did not show similar benefits.[1,25] Recent data suggest that ICS may not decrease exacerbation rates more than LABA monotherapy after an exacerbation. Additionally, while spirometry could potentially worsen in the short term, exacerbation rates may not increase when ICS are withdrawn from patients with moderate to severe COPD.[26,27,28] Based on these results, a step-down in therapy can be considered in patients with stable COPD.[29] Potential benefits and risks of any combination therapy should be considered on a case-by-case basis. When combination therapy is indicated, multi-ingredient inhalers should be selected over single-ingredient inhalers to reduce medication administration and cost burden to the patient (Table 15–3).

▶ *Vaccinations*

COPD exacerbations, serious illness, and death in COPD patients can be reduced with annual influenza vaccination. The optimal time for vaccination is usually from early October through mid-November.

Pneumococcal polysaccharide vaccine (PPSV23) should be administered to all adults with COPD. Patients older than 65 years should be revaccinated if it has been more than 5 years since initial vaccination and they were younger than 65 years at the time. Pneumococcal conjugate vaccine (PCV13) is recommended for all persons 65 years old and older who have not previously received PCV13. PCV13 should be administered first, with PPSV23 administered at least 12 months after PCV13 and at least five years after the most recent PPSV23 dose.[30]

▶ *α_1-Antitrypsin Augmentation Therapy*

Augmentation therapy consists of weekly transfusions of pooled human AAT with the goal of maintaining adequate plasma levels of the enzyme. It is recommended for nonsmokers with AAT deficiency and an FEV_1 less than or equal to 65% predicted. In these patients, augmentation therapy appears to minimize the progression of lung disease and slow decline in FEV_1, although large randomized controlled trials are limited. Augmentation therapy appears to be most beneficial in patients with an FEV_1 of 35% to 49% predicted and can be considered even in those with an FEV_1 greater than 65%. It is not recommended for individuals with AAT deficiency who do not have lung disease.[1,31]

▶ *Other Pharmacologic Therapies*

N-acetylcysteine has antioxidant and mucolytic activity, and it may reduce exacerbations and improve health status.[1] While the exact COPD patient population that may benefit from *N*-acetylcysteine has not been defined, it may offer benefits in select patients.[9,32]

Prophylaxis with daily macrolides (eg, azithromycin) significantly reduced exacerbations in select subgroups of COPD patients.[33] However, they are associated with cardiovascular adverse effects, hearing loss, and bacterial resistance. Electrocardiography should be considered prior to starting therapy to detect a prolonged QTc interval, which may predispose to cardiac arrhythmias with macrolide therapy.[34] Their ideal utility appears to be in former smokers with continued exacerbations while on appropriate inhaled therapy.[1,9,34]

Opioids may be effective for dyspnea in severe COPD and may be used to manage symptoms in terminal patients potentially by reducing air hunger. Serious adverse effects are possible, so close monitoring is necessary.[1]

Traditionally, β-blockers were avoided in patients with COPD due to concerns of worsening respiratory status. However, β-blocker use may actually be beneficial in COPD patients because they have been associated with reduced mortality and exacerbation rates without negatively impacting pulmonary function even in patients without overt cardiovascular disease.[35]

While much of their benefit may be derived from cardioprotective properties, other hypotheses include upregulation of β_2-receptors or pleiotropic and/or antioxidant properties. They appear to be safe (particularly β_1-selective agents) and can be continued, particularly when used to treat comorbidities such as coronary artery disease and atrial fibrillation.

Multiple traditional Chinese medicines (eg, Buzhong Yiqi Tang, Bu-Fei Yi-Shen) have reduced exacerbations and improved lung function when added to standard therapy. However, most have been small, flawed studies and large randomized controlled trials are needed to confirm their efficacy.[36]

COPD Exacerbations

An exacerbation is defined as "an acute worsening of respiratory symptoms that result in additional therapy."[1] Exacerbations negatively impact health status, hasten lung function decline, increase rates of hospitalization, and have a reported mortality rate of 10% to 64% when requiring hospitalization.[1,37,38] While it is often difficult to discern what causes an exacerbation, many precipitating factors have been identified, including air pollution and viral (usually rhinovirus) and bacterial (usually *Haemophilus influenzae*) respiratory tract infections; exacerbations associated with viral infections are often more severe.[1,34,37,38]

Exacerbations are classified as mild (only short-acting bronchodilators needed), moderate (additional antibiotics and/or corticosteroids needed), or severe (hospitalization or emergency room visit required, often with acute respiratory failure present) and are based on the patient's clinical status.[1] During an exacerbation, patients often have increased inflammation, increased mucus production, increased gas trapping, and reduced expiratory function, which leads to increased dyspnea with symptoms typically lasting 7 to 10 days.[1,37] Factors associated with an increased risk of exacerbation include a history of exacerbation(s), worsening airflow limitation, and old age.[1,37]

The treatment goals for exacerbations are to limit the impact of the current exacerbation and to prevent future exacerbations. It is estimated that greater than 80% of exacerbations are managed on an outpatient basis.[1] Patients presenting with signs of a severe COPD exacerbation often use accessory muscles to breathe and are tachypneic, hypoxemic, and hypercarbic. Additionally, patients may be cyanotic and have peripheral edema. Life-threatening signs and symptoms include mental status changes, worsening respiratory status despite ventilatory support, hemodynamic instability, and acidosis. Presence of these signs and symptoms should prompt evaluation for hospital and/or intensive care unit admission.

▶ *Nonpharmacologic Management*

Pulse oximetry may be useful for determining whether supplemental oxygen therapy is needed during a COPD exacerbation. If necessary, oxygen should be titrated to a saturation of 88% to 92% (0.88–0.92).[1,37] Blood gases should be checked frequently to confirm appropriate oxygenation without compensatory carbon dioxide retention or acidosis.[1]

If mechanical ventilation is required, it can be provided by noninvasive (nasal or face mask) or invasive (orotracheal tube or tracheostomy) methods. Noninvasive mechanical ventilation (NIV) decreases acute respiratory acidosis, respiratory rate,

Patient Encounter, Part 2: The Medical History, Physical Examination, and Diagnostic Tests

PMH: COPD × 8 years, Hypertension × 15 years, type 2 diabetes mellitus × 10 years, gout × 5 years

Allergies: Anaphylaxis to penicillin and doxycycline

SH: Smokes one pack per day; social intake of alcohol (4–5 drinks per week); use of marijuana on a daily basis; no other illicit drug use

FH: Noncontributory

Meds: Carvedilol 6.25 mg twice daily, albuterol MDI one to two puffs every 4 to 6 hours as needed, metformin 500 mg twice daily, allopurinol 300 mg daily

ROS: (–) fever, chills, or night sweats; (–) nasal congestion, drainage; (–) chest pain, paroxysmal nocturnal dyspnea; (+) orthopnea; (+) shortness of breath, chest heaviness, cough with clear phlegm; (–) wheezing; (–) hemoptysis; (–) heartburn, reflux symptoms, N/V/D, change in appetite, change in bowel habits; (–) pedal edema

PE:

VS: BP 165/100 mm Hg, P 56 beats/min, RR 21/min, T 35.8°C (96.4°F), Wt 90 kg (198 lb), Ht 72 in. (183 cm), BMI 26.9 kg/m^2

HEENT: EOMI; moist mucous membranes; no JVD; no palpably enlarged cervical lymph nodes

Lungs: Clear breath sounds; expiratory phase is diminished; no wheezes or crackles; (+) rhonchi

CV: RRR, normal S_1, S_2; no murmur, gallop, or rub

Abd: Soft, nontender, normoactive bowel sounds, no hepatomegaly

Ext: No cyanosis, edema, or finger clubbing

Pulmonary Function Tests

	Prebronchodilator		Postbronchodilator	
	Actual	% Predicted	Actual	% Predicted
FVC (L)	4.44		4.45	
FEV_1 (L)	1.99	52%	2.01	53%
FEV_1/FVC			45% (0.45)	

CXR: Upper lobe bullous emphysema with hyperexpansion bilaterally

COPD Assessment Test score: 16

History of Exacerbations: 2 previous COPD exacerbations (3 years ago and 6 months ago, both requiring hospitalization)

Given this additional information, what is your assessment of the patient's condition?

What nonpharmacologic and pharmacologic alternatives are available for managing this patient's COPD?

With the data provided, create a care plan for managing the patient's COPD.

length of hospital stay, intubation rates, and mortality and should be attempted prior to invasive methods.[1,37,38]

▶ *Pharmacologic Management*

LO 5

Bronchodilators Administration of a SABA with or without ipratropium is considered standard bronchodilator therapy during a COPD exacerbation.[1,37] Increased doses and/or frequency may provide benefit during an exacerbation, and an MDI with or without a spacer or a nebulizer can be used.[1,37] Maintenance bronchodilator therapy should be continued during an exacerbation or initiated once stable. However, LAMAs should be discontinued if ipratropium is used as part of the exacerbation bronchodilator regimen.

Corticosteroids Systemic corticosteroids, while not having a defined mortality benefit, have been shown to shorten recovery time, improve lung function, reduce the risk of early relapse, reduce the risk of treatment failure, and hasten symptomatic improvement during COPD exacerbations, particularly in patients with higher levels of blood eosinophils (> 2% [0.02]).[1,38,40] A 5-day course of oral prednisone or prednisolone 40 mg daily is recommended, and patients should be monitored closely for hyperglycemia.[1,37,38,41] IV corticosteroids should be used only if the oral route is not tolerated because there is no clinical benefit over oral therapy.[1,40] Nebulized budesonide is more expensive but may be used as an alternative in some patients (eg, those unable to take systemic corticosteroids due to lack of availability or significant systemic adverse effects).[1]

Antibiotics Exacerbations with purulent sputum production have shown increased bacteria, but routine antibiotic use is controversial due to the possibility of nonbacterial causes.[1,42] Approximately 50% of exacerbations are caused by bacterial infections, and there may be benefit to treating most COPD exacerbations with antibiotics.[34,38] Antibiotics, given for 5 to 7 days, reduce recovery time, risk of early relapse, risk of treatment failure, hospitalization duration, and mortality when indicated, particularly in ICU patients.[1,37,38] Procalcitonin, the prohormone of calcitonin, may have value in determining whether to use antibiotics in exacerbations because it has been shown to be elevated in the presence of bacterial respiratory infections.[37,43] Current guidelines recommend antibiotics for patients with increased sputum purulence and either increased sputum volume or increased dyspnea, patients with all three of these symptoms, or patients who require mechanical ventilation.[1] Appropriate antibiotic selections for COPD exacerbations are included in Table 15–4. The oral route is preferred whenever possible, and severity of exacerbation and local resistance patterns should be considered when selecting an antimicrobial regimen.

Other Therapies Hospitalized patients with COPD exacerbations should receive thromboprophylaxis due to increased risk of venous thromboembolism.[1] Fluid balance should be closely monitored. Medication reconciliation, proper inhaler technique, vaccination status evaluation, and patient counseling on the importance of smoking cessation are necessary both during the exacerbation and upon hospital discharge. Patients are at a high risk for recurrence during the first 8 weeks after an exacerbation.[38]

Table 15–4

Recommended Antibiotics for Acute Exacerbations of COPD[1,34]

Suspected Pathogens Causing COPD Exacerbation	Commonly Used Antibiotics[a]
Haemophilus influenzae *Streptococcus pneumoniae* *Moraxella catarrhalis*	Amoxicillin ± β-lactamase inhibitor Azithromycin or clarithromycin Doxycycline
Pseudomonas aeruginosa	Ciprofloxacin[b] or levofloxacin Piperacillin–tazobactam or ticarcillin–clavulanate Cefepime or ceftazidime Meropenem, imipenem–cilistatin, or doripenem Gentamicin, tobramycin, or amikacin[c]
Methicillin-resistant Staphylococcus aureus (MRSA)	Vancomycin[d] Linezolid[d]

[a]Refer to local antibiogram to determine which antibiotic selection is most appropriate.

[b]Limited efficacy against *Streptococcus pneumonia.*

[c]Aminoglycosides are not effective against *Streptococcus pneumoniae.*

[d]Not effective against *Haemophilus influenzae* or *Moraxella catarrhalis.*

OUTCOME EVALUATION

LO 6

- Monitor patients for improvement in symptoms. Ask if there is a difference since starting treatment and if so, is it meaningful to them? Are they less breathless? Can they do more activities and/or sleep better? If treatment response was inadequate and the patient was using the medication correctly, consider discontinuing the medication and selecting another agent.
- Changes in FEV_1 should not be the main outcome assessed because FEV_1 changes correlate weakly with symptoms, exacerbations, and health-related quality of life. The GOLD guidelines recommend annual spirometry to identify patients who are declining quickly.[1]
- The CAT is an eight-item questionnaire that can be used to assess for trends and changes in symptoms and disease impact on daily life.[1] Higher CAT scores may also be predictive of future exacerbations, depression, and mortality.[44] The test can be accessed at www.catestonline.org.
- The Medical Research Council dyspnea scale can be used to monitor physical limitation due to breathlessness. The scale is simple to administer, correlates well with health status, and predicts future mortality risk. However, the CAT is preferred because it is more comprehensive.[1]

Patient Encounter, Part 3

Three months after his last clinic appointment, the patient arrives at the local emergency department complaining of significant shortness of breath even while resting, increasing sputum production, and change in sputum color. Upon examination, he is using accessory muscles and pursed lips to breathe and has an oxygen saturation of 83% (0.83). Based on these findings alone, he is diagnosed with a COPD exacerbation and is admitted to the hospital.

What additional signs and symptoms should be evaluated to determine the severity of his exacerbation?

What nonpharmacologic and pharmacologic alternatives are available for this patient?

With the data provided, create a care plan for managing this COPD exacerbation.

Patient Care Process

Collect Information:

- Review medical history, physical assessment findings, and PFTs.
- Assess the type, frequency, and severity of the patient's symptoms. Use the CAT to measure symptom impact.
- Ask about disease impact on the patient's life, including limitation of activity, missed work, and feelings of depression or anxiety.
- Obtain a thorough history of prescription, nonprescription, and dietary supplement use.
- Speak with the patient and review records to identify smoking history, exacerbation history (number in previous 12 months and whether required hospitalization), immunization status, preferences, health goals, and socioeconomic factors that affect access to medications and/or health care.

Assess the Information:

- Assess efficacy, safety, inhaler technique, and patient adherence.
- Assess appropriateness of each COPD medication based on patient symptoms and exacerbation risk (Figure 15–2).
- Determine symptom burden using the CAT.
- Identify any significant adverse drug effects or interactions.
- Assess for barriers to medication access. COPD medications can be costly even for patients with insurance.
- Assess immunization records for influenza and pneumococcal vaccinations.
- Determine if current smokers are ready to quit.

Develop a Care Plan:

- Design a therapeutic plan including lifestyle modifications (eg, smoking cessation) and optimal drug therapy (Figure 15–2). Consider the need for pulmonary rehabilitation, oxygen therapy, and/or surgery.
- Use combination inhalers when appropriate to minimize drug administration burden.
- Review insurance formularies for medication coverage. Use manufacturer patient assistance programs as needed to ensure medication access.

Implement the Care Plan:

- Provide annual influenza vaccination and pneumococcal vaccination if needed.
- Provide patient education and self-management training: LO 7
  - Smoking cessation including behavioral and cognitive strategies for quitting and proper use of pharmacotherapy.
  - Maintaining or increasing physical activity, ensuring adequate sleep, maintaining a healthy diet.
  - How and when to take medications, importance of adherence, adverse effects and how to minimize them.
  - Signs and symptoms of an exacerbation and what to do if one occurs; provide written action plan.
  - Advanced directives and end-of-life issues for patients with severe disease.
- Address any patient concerns about COPD and its management.
- Refer to pulmonary rehabilitation program, if indicated.

Follow-up: Monitor and Evaluate:

- Follow up within 1 month after an acute exacerbation.
- For stable patients, follow up every 3 to 6 months to assess effectiveness and safety of therapy.
- Review smoking status, oxygen saturation, symptoms, exacerbation frequency and severity, and medication regimen (adherence, inhaler technique, adverse reactions, drug interactions, issues affecting medication access).
- Obtain spirometry annually to assess disease progression.

- Monitor theophylline levels with goal serum concentrations of 5 to 15 mcg/mL (mg/L; 28–83 µmol/L). Obtain trough levels 1 to 2 weeks after initiation of treatment and after any dosage adjustment. Routine levels are not necessary unless toxicity is suspected or symptoms have worsened.
- Monitor the patient for adverse effects of the medications selected.

Abbreviations Introduced in This Chapter

AAT	α_1-Antitrypsin
ABG	Arterial blood gas
cAMP	Cyclic adenosine monophosphate
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled corticosteroid
LABA	Long-acting β_2-agonists
LAMA	Long-acting muscarinic antagonist
MDI	Metered-dose inhaler
mMRC	Modified Medical Research Council
NIV	Noninvasive mechanical ventilation
$Paco_2$	Partial pressure of arterial carbon dioxide
Pao_2	Partial pressure of arterial oxygen
PCV13	Pneumococcal conjugate vaccine
PDE-4	Phosphodiesterase-4
PFTs	Pulmonary function tests
PPSV23	Pneumococcal polysaccharide vaccine
SABA	Short-acting β_2-agonist
SAMA	Short-acting muscarinic antagonist
SaO_2	Arterial oxygen saturation
V_A/Q	Ventilation/perfusion ratio

REFERENCES

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org. Accessed November 29, 2017.
2. Wheaton AG, Cunningham TJ, Ford ES, Croft JB. Employment and activity limitations among adults with chronic obstructive pulmonary disease—United States, 2013. MMWR Morb Mortal Wkly Rep. 2015 March 27;64(11):289–295.
3. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. Trends and patterns of differences in chronic respiratory disease mortality among US counties, 1980–2014. JAMA. 2017;318:1136–1149.
4. Dieleman JL, Baral R, Birger M, et al. US spending on personal health care and public health, 1996–2013. JAMA. 2016;316:2627–2646.
5. Martinez F. Early-life origins of chronic obstructive pulmonary disease. N Engl J Med. 2016;375:871–878.
6. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2016; 138: 16–27.
7. Mehta GR, Mohammed R, Sarfraz S, et al. Chronic obstructive pulmonary disease: a guide for the primary care physician. Dis Mon. 2016;62:164–187.
8. Tashkin D. Smoking cessation in chronic obstructive pulmonary disease. Semin Respir Crit Care Med. 2015;36:491–507.
9. Criner GC, Bourbeau J, Diekemper RL, et al. Executive summary: prevention of acute exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. Chest. 2015;147:883–893.
10. Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence. Clinical Practice Guideline. U.S. Department of Health and Human Services, 2008, Available from: http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/index.html. Accessed November 29, 2017.
11. Nici L, ZuWallack R. Chronic obstructive pulmonary disease—evolving concepts in treatment: advances in pulmonary rehabilitation. Semin Respir Crit Care Med. 2015:36:567–574.
12. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13–e64.
13. Geake JB, Dabscheck EJ, Wood-Baker R, Cates CJ. Indacaterol, a once-daily beta2-agonist, versus twice-daily beta2-agonists or placebo for chronic obstructive pulmonary disease (Review). Cochrane Database Syst Rev. 2015:CD010139.
14. Latorre M, Novelli F, Vagaggini B, et al. Differences in the efficacy and safety among inhaled corticosteroids (ICS)/long-acting beta2-agonists (LABA) combinations in the treatment of chronic obstructive pulmonary disease (COPD): role of ICS. Pulm Pharmacol Ther. 2015;30:44–50.
15. Feldman G, Maltais F, Khindri S, et al. A randomized, blinded study to evaluate the efficacy and safety of umeclidinium 62.5 μg compared with tiotropium 18 μg in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:719–730.
16. Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease (Review). Cochrane Database Syst Rev. 2015:CD009552.
17. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364:1093–1103.
18. Stephenson A, Seitz D, Bell CM, et al. Inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease: a population-based study. Arch Intern Med. 2011;171:914–920.
19. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008; 359:1543–1554.
20. Barnes PJ. Theophylline. Am J Respir Crit Care Med. 2013; 188:901–906.
21. Finney L, Berry M, Singanayagam A, et al. Inhaled corticosteroids and pneumonia in chronic obstructive pulmonary disease. Lancet Respir Med. 2014;2:919–932.
22. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013;11:CD002309.
23. Horita N, Goto A, Shibata Y, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD) (Review). Cochrane Database Syst Rev. 2017:CD012066.
24. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. N Engl J Med. 2016;374:2222–2234.
25. Frith PA, Thompson PJ, Ratnavadivel R, et al. Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study—a randomised controlled trial. Thorax. 2015;70:519–527.
26. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014;371:1285–1294.
27. Rossi A, van der Molen T, del Olmo R, et al. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. Eur Respir J. 2014;44:1548–1556.
28. Kunz LIZ, Postma DS, Klooster K, et al. Relapse in FEV 1 decline after steroid withdrawal in COPD. Chest. 2015;148(2):389–396.
29. Kaplan AG. Applying the wisdom of stepping down inhaled corticosteroids in patients with COPD: a proposed algorithm for clinical practice. Int J Chron Obstruct Pulmon Dis. 2015; 10:2535–2548.
30. Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older—United States, 2017. MMWR Morb Mortal Wkly Rep. 2017;66:136–138.
31. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. Chronic Obstr Pulm Dis. 2016;3(3):668–682.
32. Poole P, Chong J, Cates CJ. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease (Review). Cochrane Database Syst Rev. 2015:CD001287.
33. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med. 2011; 365:689–698.
34. Santos S, Marin A, Serra-Batlles J, et al. Treatment of patients with COPD and recurrent exacerbations: the role of infection and inflammation. Int J Chron Obstruct Pulmon Dis. 2016;11:515–525.
35. Etminan M, Jafari S, Carleton B, FitzGerald JM. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. BMC Pulm Med. 2012;12:48.
36. Haifeng W, Hailong Z, Jiansheng L, et al. Effectiveness and safety of traditional Chinese medicine on stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. Complement Ther Med. 2015;23:603–611.
37. Dixit D, Bridgeman MB, Andrews LB, et al. Acute exacerbations of chronic obstructive pulmonary disease: diagnosis, management, and prevention in critically ill patients. Pharmacotherapy. 2015;35(6):631–648.

38. Pavord ID, Jones PW, Burgel PR, Rabe KF. Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:21–30.
39. Ceviker Y, Sayiner A. Comparison of two systemic steroid regimens for the treatment of COPD exacerbations. Pulm Pharmacol Ther. 2014;27:179–183.
40. Walters JAE, Tan DJ, White CJ, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease (Review). Cochrane Database Syst Rev. 2014:CD001288.
41. Leuppi JD, Schuetz P, Bingisser R, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. JAMA. 2013;309:2223–2231.
42. Vollenweider DJ, Jarrett H, Steurer-Stey CA, et al. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012:CD010257.
43. Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, Vestbo J. Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis. Eur Respir Rev. 2017;26:160073.
44. Karloh M, Mayer AF, Maurici R, et al. The COPD Assessment Test: what do we know so far? A systematic review and meta-analysis about clinical outcomes prediction and classification of patients into GOLD stages. Chest. 2016;149:413–425.

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16 Cystic Fibrosis

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LEARNING OBJECTIVES

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

1. Explain the pathophysiology of cystic fibrosis (CF) and its multiorgan system involvement.
2. Describe the common clinical presentation and diagnosis of CF.
3. Consider long-term treatment goals with respect to clinical course and prognosis of CF.
4. Identify nonpharmacologic therapies for CF management.
5. Recommend appropriate pharmacologic therapies for chronic CF management.
6. Design appropriate antibiotic regimens for acute pulmonary exacerbations of CF.
7. Apply pharmacokinetic principles when calculating drug doses in CF patients.
8. Formulate monitoring plans for acute and chronic CF pharmacotherapy.

INTRODUCTION

Cystic fibrosis (CF) is an inherited multiorgan system disorder affecting children and, increasingly, adults. It is the most common life-shortening genetic disease among whites and the major cause of severe chronic lung disease and pancreatic insufficiency in children. Disease generally manifests as mucosal obstruction of exocrine glands caused by defective ion transport within epithelial cells. Due to the array of affected organ systems and complicated medical therapies, appropriate CF treatment necessitates interprofessional team collaboration.

EPIDEMIOLOGY AND ETIOLOGY

In the United States, CF most commonly occurs in whites, affecting approximately 1 in 3200 individuals. CF is less common in Hispanics (1 in 9200 to 13,500), African Americans (1 in 15,000), and Asian Americans (1 in 35,000).[1] CF is inherited as an autosomal recessive trait, and approximately 1 in 25 whites are **heterozygous** carriers. Offspring of a carrier couple (each parent being heterozygous) have a 1 in 4 chance of having the disease (**homozygous**), a 1 in 2 chance of being a carrier (heterozygous), and a 1 in 4 chance of receiving no trait. The *CFTR* gene mutation is found on the long arm of chromosome 7 and encodes for the CF transmembrane regulator (CFTR) protein, which functions as a chloride channel to transport water and electrolytes. Over 2000 mutations have been described in the *CFTR* gene; however, the *Phe508del* mutation (also known as *F508del* or *ΔF508*) is most common and is present in approximately 70% to 90% of CF patients.[1-5]

PATHOPHYSIOLOGY

LO 1

CF is a disease of exocrine gland epithelial cells where CFTR expression is prevalent. Normally, these cells transport chloride through CFTR chloride channels with sodium and water accompanying this flux across the cell membrane (**Figure 16–1**). CFTR is regulated by protein kinases in response to varying levels of the intracellular second messenger cyclic-3′,5′-adenosine monophosphate (cAMP). CFTR also downregulates the epithelial sodium channel and regulates calcium-activated chloride and potassium channels, and it may function in exocytosis and formation of plasma membrane molecular complexes and proteins important in inflammatory responses and mucociliary clearance.[2,6] KEY CONCEPT In CF, the CFTR chloride channel is dysfunctional and usually results in decreased chloride secretion and increased sodium absorption, leading to altered viscosity of fluid excreted by the exocrine glands and mucosal obstruction. *CFTR* gene mutations are assigned to classes (I–VI) based on degree of residual CFTR protein function. Class I (absent CFTR synthesis), II (blocked CFTR trafficking), and III (blocked CFTR regulation or gating) mutations result in no CFTR function. Class IV (altered CFTR conductance), Class V (reduced CFTR synthesis), and Class VI (shortened CFTR life span) mutations have some remaining functional protein.[1,2,5]

Pulmonary System

Chronic lung disease leads to death in 90% of patients. KEY CONCEPT Pulmonary disease is characterized by thick mucus secretions, impaired mucus clearance, chronic airway infection and colonization, obstruction, and an exaggerated neutrophil-dominated inflammatory response.[1,4] This process leads to air trapping, **atelectasis**, mucus plugging, **bronchiectasis**, cystic lesions, pulmonary hypertension, and eventual respiratory failure. Pulmonary function declines approximately 1% to 2% per year; an individual's rate of decline depends on severity of CFTR dysfunction and comorbidities.[7] Sinusitis and nasal polyps are also common, and microbial colonization is similar to that of the lungs.

Bacterial pathogens are often acquired in age-dependent sequence. Early infection is most often caused by *Staphylococcus aureus* (usually methicillin sensitive) and nontypeable

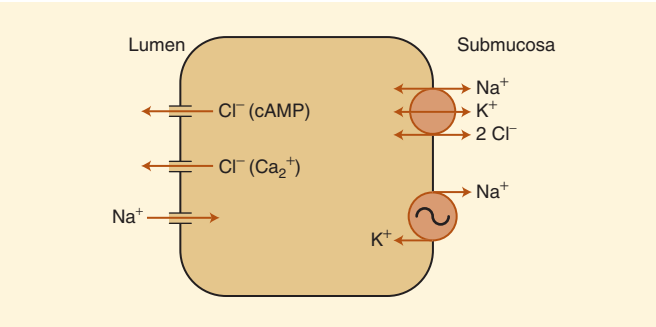

FIGURE 16–1. Electrolyte transport in the airway epithelial cell. (Ca, calcium; cAMP, cyclic-3′, 5′-adenosine monophosphate; Cl, chloride; Na, sodium; K potassium.) (From Milavetz G, Smith JJ. Cystic fibrosis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 7th ed. New York, NY: McGraw-Hill; 2008:536.)

Haemophilus influenzae. *Pseudomonas aeruginosa* infection is the most significant CF pathogen among all age groups. *P. aeruginosa* expresses extracellular toxins that perpetuate lung inflammation. Mucoid strains of *P. aeruginosa* produce an alginate biofilm layer that interferes with antibiotic penetration. Methicillin-resistant *S. aureus* (MRSA) is also a significant CF pathogen, and incidence is on the rise in some geographic areas. Organisms identified later in the disease course include *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex, fungi including *Candida* and *Aspergillus* species, and nontuberculous mycobacteria among others.[2,7] Cultured organisms may represent initial infection, chronic colonization, or microbial overgrowth in an acute exacerbation.

Gastrointestinal System

Gastrointestinal (GI) involvement often presents as **meconium** ileus, small-bowel obstruction shortly after birth due to abnormally thick meconium. Older CF patients may develop distal intestinal obstruction syndrome (DIOS) due to fecal impaction in the terminal ileum and cecum.

Maldigestion due to pancreatic enzyme insufficiency is present in 85% to 90% of CF patients.[1,8] Thick pancreatic secretions and cellular debris obstruct pancreatic ducts and lead to fibrosis. Volume and concentration of pancreatic enzymes and bicarbonate are reduced, leading to maldigestion of fat and protein and subsequent malabsorption of fat-soluble vitamins (A, D, E, and K). Symptoms include abdominal distention, **steatorrhea**, flatulence, and malnourishment despite voracious appetite. Maldigestion is progressive and may develop later in a previously pancreatic-sufficient patient. Other complications may include GI reflux, dysmotility, salivary dysfunction, **intussusception**, **volvulus**, **atresia**, **rectal prolapse**, complications related to corrective surgery for meconium ileus, and an increased risk of GI cancers later in life.

Hepatobiliary disease occurs due to bile duct obstruction from abnormal bile composition and flow. Hepatomegaly, splenomegaly, and cholecystitis may be present. Hepatic **steatosis** may be present due to effects of malnutrition. Progression from cholestasis (impaired bile flow) to cirrhosis, esophageal varices, and portal hypertension takes several years. Many patients are compensated and asymptomatic but may be susceptible to acute decompensation in the event of extrinsic hepatic insult from viruses, medications, or other factors.[1,9]

Endocrine System

CF-related diabetes (CFRD) occurs in 20% of adolescents and 40% to 50% of adults, disproportionally affecting women. Although it shares characteristics of both type 1 and type 2 diabetes mellitus, CFRD is categorized separately. Reduced functional pancreatic islet cells and increased islet **amyloid** deposition results in insulin insufficiency, the primary cause of CFRD. Insulin secretion is delayed in response to glucose challenge, and absolute insulin secretion over time is reduced. Some insulin resistance may also be present in CFRD and may fluctuate in relation to infection and inflammation.[2,7,10,11]

Postprandial hyperglycemia is common, but because some basal insulin secretion is maintained, fasting hyperglycemia is less severe and ketosis is rare. Diet, acute and chronic infection, and corticosteroid use lead to fluctuation in glucose tolerance over time.[10] CFRD is associated with greater nutritional failure, increased pulmonary disease, and earlier mortality. Pulmonary function decline and nutritional consequences associated with progressive CFRD have historically overshadowed risks of long-term macrovascular and microvascular complications; however, these complications are now emerging with longer life expectancy.[7]

Reproductive System

CF patients often experience delayed puberty. In females, menarche occurs 18 months later than average; menstrual irregularity is common, and fertility is reduced due to increased cervical mucus viscosity. Due to increasing life expectancy, pregnancy is becoming more common; however, outcomes depend on prepartum nutritional and pulmonary status. Almost all males with CF are **azoospermic** due to congenital absence of the vas deferens with resultant obstruction; however, conception still occurs occasionally. Conception can also occur through application of assisted reproductive technologies.[12]

Musculoskeletal System

Several factors contribute to development of bone disease in CF: (a) malabsorption of vitamins D and K and calcium, (b) poor nutrition and decreased body mass, (c) physical inactivity, (d) corticosteroid therapy, and (e) delayed puberty. Chronic pulmonary infection, through release of inflammatory cytokines, can increase bone resorption and decrease formation. Osteopenia, osteoporosis, pathological fractures, and **kyphosis** can occur.[13,14] Episodic or chronic arthritis may occur due to immune complex formation in response to chronic inflammation.[7] Digital **clubbing** is common and is a marker for chronic hypoxia.[1]

Hematological System

Anemia may be present due to impaired erythropoietin regulation, nutritional factors (vitamin E and iron malabsorption), or chronic inflammation. Increased cytokine production can lead to shortened red blood cell survival, reduced erythropoietin response, and impaired mobilization of iron stores. Additionally, with chronic hypoxia, normal hemoglobin and hematocrit values may represent relative anemia.[15] Increased red blood cell production is a physiological response to hypoxia; however, this response may be blunted in CF and may result in symptoms of anemia despite normal lab values.

Abnormal bleeding or clotting may also be observed as a result of vitamin K malabsorption, antibiotic-associated depletion of GI flora and vitamin K synthesis, reduced coagulation factor synthesis due to liver disease, and/or a procoagulant state due to inflammation.

Clinical Presentation of Cystic Fibrosis

General

- Usually diagnosed in neonates (meconium ileus or newborn screening) or during early childhood. May present later in life due to less severe symptoms or misdiagnosis.

Symptoms

- Pulmonary: Chronic cough, sputum production, decreased exercise tolerance, and recurrent pneumonia and sinusitis. Exacerbations may be marked by increased cough, sputum changes (darker, thicker), hemoptysis, dyspnea, and fever.
- GI: Numerous large, foul-smelling loose stools (steatorrhea), flatulence, and abdominal pain. Intestinal obstruction may present as abdominal pain and distention and/or decreased bowel movements.
- Nutritional: Poor weight gain despite voracious appetite and hunger. Dry skin, skin rash, and visual disturbances may be noted in vitamin deficiency.
- CFRD: Weight loss, increased thirst, and more frequent urination.

Signs

- Obstructive airways disease: Tachypnea, dyspnea, cyanosis, wheezes, crackles, sternal retractions, digital clubbing, and barrel chest.
- Failure to thrive: Below age-based normal of both height and weight in children; adults may be near/below ideal body weight or have a low body mass index (BMI).
- Salty taste to the skin.
- Hepatobiliary disease: Hepatomegaly, splenomegaly, and prolonged bleeding may occur.
- Recurrent pancreatitis (usually in pancreatic-sufficient patients): Episodic epigastric abdominal pain, persistent vomiting, and fever.

Laboratory Tests

- Leukocytosis with increase in polymorphonuclear (PMN) leukocytes and bands may occur in acute pulmonary exacerbations.
- Maldigestion: Decreased serum levels of fat-soluble vitamins (A, D, E, and K). Decreased vitamin K levels may result in elevated prothrombin time (PT) and international normalized ratio (INR).
- Glucose intolerance: Blood glucose between 140 and 199 mg/dL (7.8–11 mmol/L) 2 hours after an oral glucose-tolerance test.
- CFRD: Blood glucose 200 mg/dL (11.1 mmol/L) or higher 2 hours after an oral glucose-tolerance test or fasting hyperglycemia (fasting blood glucose 126 mg/dL [7 mmol/L] or more regardless of the post-glucose challenge level).
- Hepatobiliary disease: Serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase, and bilirubin may be elevated.

Other Tests

- Microbial cultures (sputum, throat, bronchoalveolar lavage, or sinus): Isolation of *P. aeruginosa, S. aureus, S. maltophilia,* and other CF-related organisms.
- Pulmonary function tests (PFTs): Decreased forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), typically lower during acute pulmonary exacerbations.
- Chest x-ray or CT scan: Infiltrates, atelectasis, bronchiectasis, and mucus plugging.
- Abdominal x-ray or CT scan: Intestinal obstruction may be manifested as meconium ileus, DIOS, or intussusception. Rectal prolapse may be noted on physical examination.
- Maldigestion: Elevated fecal fat content, reduced pancreatic stool elastase (< 200 mcg/g of feces).

Integumentary System

Sweat contains abnormally high concentrations of sodium and chloride due to impaired reabsorption within the sweat duct from loss of CFTR channels. This may impart a characteristic salty taste to the skin. Patients are usually otherwise asymptomatic.[4] In rare instances such as hot weather or excessive sweating during physical activity, patients may become dehydrated and experience symptoms of hyponatremia (nausea, headache, lethargy, and confusion).

CLINICAL PRESENTATION AND DIAGNOSIS

LO 2

See the accompanying box for the clinical presentation of CF.

Diagnosis

Testing for CF is part of required newborn screening panels in all US states in an effort to identify patients prior to symptom development, initiate early treatment, and improve long-term outcomes.[16] A positive newborn screen for CF is not diagnostic (due to false-positive results among CF carriers), nor does a negative screen universally exclude the diagnosis. All "positive screens," as well as individuals presenting with signs and symptoms of CF, are referred to a CF care center for sweat chloride test and genetic evaluation. Diagnosis of CF is based on two separate elevated sweat chloride concentrations of 60 mEq/L (mmol/L) or greater obtained through pilocarpine **iontophoresis** ("sweat test"). Genetic testing (*CFTR* mutation analysis) is performed to confirm the diagnosis and determine eligibility for precision medicine therapy, screen in utero, or detect carrier status. More than 70% of diagnoses are made by 12 months of age.[1,16]

Clinical Course and Prognosis

Clinical course varies because of multiple genetic mutations and the heterogeneous profile of the *Phe508del* mutation. Some patients develop severe lung disease early in childhood and reach end-stage disease by adolescence, whereas others maintain near-normal lung function into adulthood. Newly diagnosed adults tend to have *CFTR* mutations associated with residual CFTR function and may present with milder respiratory symptoms, pancreatitis, or infertility.[2]

Life expectancy has greatly increased from a predicted survival of 16 years of age in 1970 to more than 40 years for patients born in the 1990s.[1,2,7] According to the Cystic Fibrosis Foundation Registry, 51.6% of patients are over 18 years of age.[17]

Patient Encounter Part 1

A 6-week-old female term neonate is being evaluated at CF clinic due to an abnormal newborn screen (elevated immunoreactive trypsinogen; one copy of gene mutation *G551D* on initial testing). Sweat chloride testing is performed on bilateral thighs with results reported as follows:

Sample 1: Sweat chloride 112 mEq/L (mmol/L)

Sample 2: Sweat chloride 98 mEq/L (mmol/L)

Upon parental interview, the infant is a voracious eater and has six to nine loose stools per day that have an oily appearance. She is mostly breastfed, with some supplemental 20 kcal/ounce (0.67 kcal/mL; 2.8 kJ/mL) infant formula, and she weighs 3.25 kg (birth weight of 3.6 kg). Parents also report that she needed oral laxatives and enemas to help pass her meconium while in the newborn nursery.

What information is consistent with a diagnosis of CF?

What are the next steps in the CF diagnostic process?

The parents are overwhelmed with the diagnosis of CF and are very worried about life expectancy. How would you explain the infant's prognosis?

TREATMENT

Desired Outcomes

LO 3 Therapeutic outcomes in CF care relate to chronic and acute treatment goals. With chronic management, the primary goals are to delay disease progression and optimize quality of life. KEY CONCEPT Maximizing nutritional status through pancreatic enzyme replacement and vitamin and nutritional supplements is necessary for normal growth and development and for maintaining long-term lung function. Reduction of airway inflammation and infection and aggressive preventive therapies minimize acute pulmonary exacerbations and delay pulmonary decline. In pulmonary exacerbations, therapy is directed toward reducing acute airway inflammation and obstruction through aggressive airway clearance and antibiotic therapy with a goal of returning lung function to pre-exacerbation levels or greater.

Nonpharmacologic Therapy

▶ *Airway Clearance Therapy*

KEY CONCEPT Airway clearance therapy is a necessary routine for all CF patients to clear secretions and control infection, even at diagnosis prior to becoming symptomatic. Waiting until development of a first pulmonary exacerbation or daily symptoms delays benefits and may accelerate pulmonary decline. The LO 4 traditional form of chest physiotherapy (CPT) is percussion and postural drainage. Areas of the patient's chest, sides, and back are rapidly "clapped" by hand in different patient positions, followed by cough or forced expiration to mobilize secretions. Patients may also be taught autogenic drainage, which consists of deep breathing exercises followed by forced cough.

Several airway clearance devices are also available. Flutter valve devices use oscillating positive expiratory pressure (OPEP) to cause vibratory airflow obstruction and an internal percussive effect to mobilize secretions. Intrapulmonary percussive ventilation (IPV) provides continuous oscillating pressures during inhalation and exhalation. High-frequency chest compression (HFCC) with an inflatable vest that provides external oscillation is most commonly used and often preferred because patients can perform therapy independently from an early age.[1,18]

Effective cough and expectoration of mucus are essential for good clearance technique. Airway clearance therapy is typically performed once or twice daily for maintenance care and is increased to three or four times per day during acute exacerbations.

▶ *Nutrition*

Most CF patients have increased caloric needs due to increased energy expenditure through increased work of breathing, increased basal metabolism, and maldigestion. Prevention LO 4 of malnutrition requires early patient-specific nutritional intervention. Caloric requirements to promote age-appropriate weight gain or maintenance are typically 110% to 200% of the recommended daily allowance (RDA) for age, gender, and size and increase as disease progresses.[11]

Nutrition in malnourished patients consists of baseline required calories plus additional calories for weight gain via a high-calorie high-fat diet. Even with aggressive diet and oral supplements, placement of a **gastrostomy** or **jejunostomy** tube for nighttime supplemental feeds may be necessary.[11] Patients with refractory malabsorption, CFRD, and/or tube feedings have unique caloric needs. Collaboration with dieticians specially trained in CF nutrition is essential.

Pharmacologic Therapy

▶ *Airway Clearance Therapy*

LO 5 Airway clearance therapy is often accompanied by bronchodilator treatment with albuterol (known as salbutamol outside the United States) to stimulate mucociliary clearance and prevent bronchospasm associated with therapy (Table 16–1).

A mucolytic agent is administered subsequently to reduce sputum viscosity and enhance clearance. Dornase alfa (Pulmozyme) is a recombinant human (rh) DNase that selectively cleaves extracellular DNA released during neutrophil degradation in viscous CF sputum. Nebulization of dornase alfa improves daily pulmonary symptoms and function, reduces pulmonary exacerbations, and improves quality of life.[19,20] Daily dosing is most common, but some patients benefit from twice daily administration.[20] Hypertonic saline for inhalation (HyperSal) 7% or 3.5% is often used as an alternative or add-on mucolytic agent for osmotic effects in airway surface liquid or sputum. It must be preceded by a bronchodilator due to greater incidence of bronchospasm and may not be tolerated by some patients.[19,20] *N*-acetylcysteine is another mucolytic agent, but its unpleasant odor and taste limit patient acceptance.

CF guidelines do not recommend β_2-agonists or inhaled corticosteroids in patients without asthma or allergic bronchopulmonary aspergillosis (ABPA).[19] Inhaled corticosteroids may attenuate reactive airways and reduce airway inflammation in some patients; however, clear benefit in CF has not been established.[19-21] Patients with asthma or recurrent wheezing or dyspnea who improve with albuterol (salbutamol) should be considered for maintenance asthma therapy, as should patients with bronchodilator-responsive PFTs. Drug delivery to the site of inflammation is limited by mucus plugging, which may limit efficacy. Patients on asthma therapies should administer these medications after airway clearance to optimize drug delivery.

LO 5 Montelukast, antihistamines, and/or intranasal steroids are used for CF patients with allergic or rhinosinusitis symptoms.

Table 16–1

Common Medications Used in Cystic Fibrosis

Medication	Pediatric Dose	Adult Dose
Albuterol (salbutamol)	2.5 mg nebulized with chest physiotherapy two to four times daily; alternatively, two puffs via metered-dose inhaler may be substituted	2.5 mg nebulized with chest physiotherapy two to four times daily; alternatively, two puffs via metered-dose inhaler may be substituted
Dornase alfa	2.5 mg nebulized once or twice daily	2.5 mg nebulized once or twice daily
Hypertonic saline 7%, 3.5%, or 3%	4 mL nebulized one to four times per day	4 mL nebulized one to four times per day
Ibuprofen[a]	20–30 mg/kg/dose given twice daily	20–30 mg/kg/dose given twice daily
Azithromycin	Body weight 25–39 kg: 250 mg on Mondays, Wednesdays, and Fridays	Body weight 40 kg or more: 500 mg on Mondays, Wednesdays, and Fridays
Ivacaftor[b]	50–150 mg every 12 hours	150 mg every 12 hours
Lumacaftor/ivacaftor[c]	200–400 mg/250 mg every 12 hours	400 mg/250 mg every 12 hours

[a]Adjusted to achieve peak serum concentrations of 50 to 100 mcg/mL (243–485 µmol/L). Maintain chronic dosing with same dosage form and manufacturer. Note that therapy is not always continued into adulthood.

[b]Dose may require adjustment in patients with moderate or severe hepatic impairment and/or when coadministered with moderate or strong CYP3A inhibitors.

[c]Dose may require adjustment in patients with moderate or severe hepatic impairment and/or when coadministered with strong CYP3A inhibitors.

Long-term systemic corticosteroids reduce airway inflammation and improve lung function. However, beneficial effects diminish upon discontinuation, and concern for long-term adverse effects limits use as maintenance therapy.[19,21] Systemic corticosteroids may be used short term in acute exacerbations or for treatment of allergic response to *Aspergillus* colonization (ABPA); however, dose and duration of therapy should be minimized.

High-dose ibuprofen targeting peak concentrations of 50 to 100 mcg/mL (243–485 µmol/L) has been shown to slow disease progression, particularly in children 6 to 17 years of age with mild lung disease (FEV_1 > 60% predicted). At high doses, ibuprofen inhibits the lipoxygenase pathway, reducing neutrophil migration and function as well as release of lysosomal enzymes. At lower concentrations achieved with analgesic dosing, neutrophil migration increases, potentially increasing inflammation.[19] A dose of 20 to 30 mg/kg given twice daily is usually needed to attain target levels, but interpatient variability necessitates serum concentration monitoring.[21] Due to monitoring requirements and concerns regarding long-term safety and tolerability, only a few CF centers prescribe high-dose ibuprofen.

Azithromycin is a macrolide antibiotic commonly used in CF as an anti-inflammatory agent to improve overall lung function and reduce exacerbations in patients colonized with *Pseudomonas* and to reduce exacerbations in those without *Pseudomonas*.[19,20,22] Proposed mechanisms include interference with *Pseudomonas* alginate biofilm production, bactericidal activity during stationary *Pseudomonas* growth, neutrophil inhibition, cytokine inhibition, and reduction in sputum viscosity.[22] Due to its long tissue half-life, azithromycin is typically dosed 3 days/week (Monday, Wednesday, and Friday). Alternatively, patients may take 500 or 250 mg either daily or only Monday through Friday, based on the same weight parameters.[22] Patients should have a screening acid-fast bacillus sputum culture prior to initiation and then every 6 to 12 months, because isolation of nontuberculous mycobacteria is a contraindication to chronic azithromycin therapy.[19]

▶ *Antibiotic Therapy*

KEY CONCEPT Antibiotic therapy is used in three distinct situations: (a) eradication and delay of colonization in early lung disease (treatment of positive cultures regardless of symptoms), (b) suppression of bacterial growth once colonization is present, and (c) reduction of bacterial load in acute exacerbations in an attempt to return lung function to pre-exacerbation levels or greater.[23] KEY CONCEPT Antibiotic selection is based on periodic culture and sensitivity data, typically covering all organisms identified during the preceding year. If no culture data are available, empirical antibiotics should cover the most likely organisms for the patient's age group. Due to altered pharmacokinetics and microorganism resistance, dose optimization is key (Table 16–2).

Oral Antibiotic Therapy Severity of pulmonary symptoms also guides antibiotic selection. For recent-onset or mild symptoms, patients may be treated with outpatient oral and inhaled antibiotics for 10 to 14 days. Oral fluoroquinolones are a mainstay for *P. aeruginosa* treatment in CF, even in children. Despite concerns regarding cartilage and tendon toxicity in young animals, clinical practice has not shown an increased risk in human children.[24] Inhaled tobramycin, aztreonam, or colistin is usually continued or added for double coverage if the patient is not on suppressive inhaled antibiotics. Methicillin-sensitive *S. aureus* (MSSA) may be treated with oral amoxicillin–clavulanic acid, dicloxacillin, first- or second-generation cephalosporins, trimethoprim–sulfamethoxazole, clindamycin, doxycycline, or minocycline, depending on sensitivity. MRSA may be treated with oral trimethoprim–sulfamethoxazole, clindamycin, doxycycline, minocycline, or linezolid. *H. influenzae* often produces β-lactamases but can usually be treated with amoxicillin–clavulanic acid, a cephalosporin, or trimethoprim–sulfamethoxazole. Oral trimethoprim–sulfamethoxazole or minocycline may be used to treat *S. maltophilia*.

Intravenous Antibiotic Therapy For severe infections or patients failing outpatient therapy, IV antibiotic therapy is often prescribed for 10 to 21 days as inpatient therapy. Some patients may be discharged to finish their IV course or even receive their entire IV course at home. KEY CONCEPT Typical regimens for severe infections include an antipseudomonal β-lactam plus an aminoglycoside for added synergy and delay of resistance development.[25,26] Cephalosporins tend to be better tolerated and offer the benefit of less frequent administration. Extended-spectrum penicillins have been associated with a higher incidence of allergy. Aztreonam offers little cross-reactivity in penicillin- or cephalosporin-allergic patients; however, it has no gram-positive coverage. Meropenem should be reserved for organisms resistant to all other antibiotics to minimize development of resistance in the carbapenem drug class.

Table 16–2

Selected Antibiotic Dosing in Cystic Fibrosis[a]

Antibiotic	Pediatric Dose (mg/kg/day)	Adult Maximum Daily Dose	Interval (hours)
Intravenous			
Tobramycin, gentamicin[b]	10–15	None	8–24
Amikacin[b]	30–45	None	8–24
Ceftazidime	150–400	8–12 g	6–8
Cefepime	150–200	6–8 g	8
Piperacillin–tazobactam[c]	400–600	18–24 g	6
Ticarcillin–clavulanate[c]	400–600	12–18 g	4–6
Meropenem	120	6 g	8
Imipenem–cilastatin[c]	100	2–4 g	6
Aztreonam	200–300	8–12 g	6
Ciprofloxacin	30	1.2 g	8–12
Levofloxacin	10–20	750 mg	12–24
Nafcillin	200	12 g	4–6
Vancomycin[b]	60–80	None	6–12
Linezolid	30	1.2 g	8–12
Colistin	5–8	480 mg	8–12
Chloramphenicol[b]	60–80	4 g	6
Oral			
Amoxicillin ± clavulanic acid[c]	90	4 g	12
Dicloxacillin	100	2 g	6
Cephalexin	50–100	4 g	6–8
Trimethoprim–sulfamethoxazole[d]	12–20	1280 mg	6–12
Clindamycin	30	1.8 g	6–8
Ciprofloxacin	40	2 g	12
Levofloxacin	10–20	750 mg	12–24
Doxycycline[e]	4	200 mg	12–24
Minocycline[e]	4	200 mg	12
Linezolid	30	1.2 g	8–12
Inhaled			
Tobramycin	160–600 mg/day	600 mg	12
Aztreonam lysine	225 mg/day	225 mg	8
Colistin	75–150 mg/day	300 mg	12

[a]All doses assume normal renal and hepatic function. Consult a specialized drug reference for dosage adjustment if function is impaired. Dose and/or interval may require adjustment.

[b]Empirical starting doses only. Adjust dose per therapeutic drug monitoring.

[c]Dose based on β-lactam component.

[d]Dose based on trimethoprim component.

[e]Children older than 8 years.

Tobramycin IV is generally the first-line aminoglycoside. Isolates are usually resistant to gentamicin, and amikacin is reserved for tobramycin-resistant strains. Pharmacokinetic targets are listed in Table 16–3. Higher peak serum concentrations are desired to maximize efficacy, whereas lower trough levels reduce risk of toxicity. Once-daily dosing targets higher peaks and lower troughs, optimizing the concentration-dependent killing of aminoglycosides (eg, tobramycin 10–15 mg/kg/day or amikacin 30–45 mg/kg/day) and is preferred over three times daily dosing.[25] However, time below the minimum inhibitory concentration (MIC) is prolonged with once-daily administration in some children, possibly leading to loss of synergy for a substantial portion of the dosing interval or development of resistance. Traditional dosing may be used in these patients. Incorporation of patient-specific pharmacokinetic history is essential for optimal aminoglycoside dosing. Long-term studies are needed to examine the efficacy and resistance patterns associated with once-daily aminoglycosides in CF patients.[25,26]

As with Pseudomonas infections, most other serious gram-negative infections are also treated with combination therapy. *S. maltophilia* is highly resistant and most often treated with trimethoprim–sulfamethoxazole, minocycline, or ticarcillin–clavulanate (if available). There are few therapeutic options for *A. xylosoxidans* and *B. cepacia*.

An oral fluoroquinolone may be substituted for an IV aminoglycoside based on sensitivity data or presence of renal dysfunction and/or ototoxicity. Due to excellent bioavailability, fluoroquinolones, trimethoprim–sulfamethoxazole, doxycycline, minocycline, and linezolid should be used orally for most patients able to take enteral medications. Due to toxicity risk, colistin IV and chloramphenicol IV are reserved for life-threatening or highly resistant infections.

Inpatient treatment of MRSA can consist of IV vancomycin or oral agents as previously described, depending on the severity of infection and concomitant organisms.

LO 5

Inhaled Antibiotic Therapy Chronic or rotating inhaled antibiotic maintenance therapy may be used to suppress *P. aeruginosa* colonization in CF patients of all ages; however, long-term systemic antibiotics are not recommended due to emergence of resistance.[19,27,28] Inhaled antibiotic therapy is also recommended for eradication of initial *P. aeruginosa* infection.[29] Inhaled tobramycin (TOBI, Bethkis) is typically administered to patients 6 years of age and older in alternating 28-day cycles of 300 mg nebulized twice daily, followed by a 28-day washout period to minimize development of resistance. Long-term cyclical administration improves pulmonary function, decreases microbial burden, and reduces hospitalization for IV therapy.[20] A dry powder formulation of tobramycin (TOBI Podhaler, 112 mg inhaled twice daily) can also be used in 28-day on/off cycles with reduced administration time.[30] Due to minimal systemic absorption, pharmacokinetic monitoring is not necessary with normal renal function. Lower doses of nebulized tobramycin solution for injection have been used in younger children, and *Pseudomonas* eradication studies used 300 mg twice daily in children as young as 6 months.[31]

Aztreonam lysine for inhalation (Cayston) is also used for *P. aeruginosa* suppression in 28-day on/off cycles for CF patients 6 years of age and older.[19] It has been used in children as young as 3 months of age for *P. aeruginosa* eradication.[32] A dose of 75 mg three times daily is given via the Altera nebulizer system, a high-efficiency drug delivery device with shorter administration time.

Nebulized colistin using the IV formulation may be an option in patients with tobramycin-resistant strains or intolerance to inhaled tobramycin or aztreonam lysine.[33] Pretreatment with albuterol is necessary due to increased risk of bronchoconstriction.

Selection of inhaled antibiotics is based on culture data and patient preference. Alternating inhaled antibiotic regimens are sometimes used in patients with more advanced lung disease.[20] Inhaled antibiotics are typically stopped during acute exacerbations requiring IV therapy because drug delivery is reduced with increased sputum production, and concomitant use of IV aminoglycosides may increase risk of toxicity.[25]

Table 16–3

Target Intravenous Antibiotic Serum Concentrations in Cystic Fibrosis

	Traditional Units of Measurement		SI Units of Measurement	
Antibiotic	**Goal Peak[a] (mcg/mL)**	**Goal Trough[b] (mcg/mL)**	**Goal Peak[a] (μmol/L)**	**Goal Trough[b] (μmol/L)**
Tobramycin, gentamicin	10–12[c]	< 1.5[c]	21–26[c]	< 3.2[c]
	20–40[d]	< 1[d]	42–84[d]	< 2.1[d]
Amikacin	30–40[c]	< 5[c]	51–68[c]	< 8.6[c]
	60–120[d]	< 3[d]	103–206[d]	< 5.1[d]
Vancomycin	–[e]	15–20	–[e]	10–14

Note: Values reported in mcg/mL are numerically equivalent to mg/L.

[a]Peaks calculated 30 minutes after end of infusion for aminoglycosides.

[b]Troughs calculated immediately prior to the time the dose is due.

[c]Goals refer to traditional dosing (every 8 or 12 hours). Higher peaks may be targeted with corresponding lower trough concentrations for aminoglycosides based on center practice.

[d]Goals refer to once-daily (high-dose extended interval) dosing (preferred).

[e]Not routinely measured.

LO 7

Pharmacokinetic Considerations KEY CONCEPT CF patients have larger volumes of distribution for many antibiotics due to an increased ratio of lean body mass to total body mass and lower fat stores. CF patients also have enhanced total body clearance, although the exact mechanism has not been determined; both renal and extrarenal processes have been proposed.[26]

Because of these pharmacokinetic changes, higher doses of aminoglycosides are needed to achieve target serum levels and adequate tissue penetration.[26] Higher doses of β-lactam antibiotics are also needed to achieve and sustain levels above the MIC.[26] Trimethoprim–sulfamethoxazole displays enhanced renal clearance and hepatic metabolism in the CF population. Higher doses of fluoroquinolones, vancomycin, and linezolid may also be needed to attain inhibitory serum and tissue concentrations against CF pathogens.[26,34]

Although most CF patients have shorter drug half-lives and larger volumes of distribution than non-CF patients, some patients exhibit decreased renal clearance because of concomitant nephrotoxic medications, diabetic nephropathy, or other reasons.

► *Gastrointestinal Therapy*

LO 5

Pancreatic Enzyme Replacement This is the mainstay of GI therapy. Most enzyme products available in the United States are formulated as capsules containing enteric-coated microspheres or microtablets that escape enzyme inactivation by gastric acid and promote dissolution in the more alkaline duodenum (Table 16–4). Capsules may be opened and the microbeads swallowed with food (for infants and young children), as long as they are not chewed or mixed with alkaline or hot foods (which denature enzymes). Although products may contain similar enzyme ratios, they are not bioequivalent and cannot be interchanged.

Pancreatic enzymes are initiated at 1000 units/kg/meal of lipase component (because fats are most difficult to digest) with half-doses given for snacks. Enzymes should be taken at the beginning or divided throughout the meal and must be given with any fat-containing snack. Infants are typically started at 1500 to 2500 units of lipase/120 mL of formula or breast milk and may require division of capsule contents via visual estimation to obtain appropriate doses. Pancreatic enzymes cannot be placed in formula bottles due to inability to pass consistently through the nipple slit. Instead, enzyme microbeads are placed on a small dot of infant applesauce (or moistened infant rice cereal) and administered via infant spoon with subsequent nursing or bottle-feeding to facilitate swallowing. The oral mucosa must be examined afterward to ensure that all enzymes are swallowed because remnant microbeads can cause oral erosions (ulcers).

Table 16–4

Common Pancreatic Enzyme Replacement Products

Trade Name	Lipase (Units)	Amylase (Units)	Protease (Units)
CREON 3000	3000	15,000	9500
CREON 6000	6000	30,000	19,000
CREON 12,000	12,000	60,000	38,000
CREON 24,000	24,000	120,000	76,000
CREON 36,000	36,000	180,000	114,000
Pancreaze MT 2[a]	2600	10,850	6200
Pancreaze MT 4[a]	4200	17,500	10,000
Pancreaze MT 10[a]	10,500	43,750	25,000
Pancreaze MT 16[a]	16,800	70,000	40,000
Pancreaze MT 20[a]	21,000	61,000	37,000
Pertzye 4000	4000	15,125	14,375
Pertzye 8000	8000	30,250	28,750
Pertzye 16,000	16,000	60,500	57,500
Pertzye 24,000	24,000	90,750	86,250
Viokace[b]	10,440	39,150	39,150
Viokace[b]	20,880	78,300	78,300
Zenpep 3000	3000	16,000	10,000
Zenpep 5000	5000	27,000	17,000
Zenpep 10,000	10,000	55,000	34,000
Zenpep 15,000	15,000	82,000	51,000
Zenpep 20,000	20,000	84,000	63,000
Zenpep 25,000	25,000	136,000	85,500
Zenpep 40,000	40,000	168,000	126,000

[a]The number after a trade name refers to the approximate number of thousands of units of lipase contained per dosage form.

[b]Nonenteric coated enzyme. Must be given with a gastric acid suppressant. Often administered via feeding tube.

KEY CONCEPT Titration of pancreatic enzyme doses is based on control of steatorrhea, stool output, and abdominal symptoms. Infants should have no more than three to four stools per day, whereas older patients should have no more than two to three (children) or one to two (adolescents/adults) well-formed stools per day. Doses are titrated at 2- to 3-week intervals in increments of 150 to 250 units of lipase/kg/meal (or the next easily administered capsule or half-capsule) up to 2500 units/kg/meal. Maximum infant doses are typically 4000 units of lipase/120 mL of formula. Higher doses should be used cautiously due to risk of fibrosing colonopathy observed with doses above 6000 units of lipase/kg/meal for more than 6 months.[1,11] Patients receiving enteral formulas via feeding tubes (either at nighttime or continuously) may receive intermittent doses of oral enzymes. They may also receive enzymes that are administered directly through the feeding tube using a vehicle such as an applesauce bolus, or they may receive crushed enzymes that are given as either intermittent doses via the feeding tube or added to the enteral formula bags in the actual feedings. An *ex vivo* cartridge device containing immobilized lipase (RELiZORB) may also be used with some enteral formulas to predigest fat within the tube feeding apparatus prior to the formula reaching the patient.

Patients responding poorly to maximal doses of one product may benefit from changing to another product and/or addition of a histamine H_2-receptor antagonist or proton pump inhibitor. Acid suppression may boost the effective enzyme dose, if duodenal pH is not alkaline enough to neutralize residual gastric acid and dissolve enteric coating.[11] Acid suppression also treats concomitant gastroesophageal reflux disease, which is common in CF.[8,20]

Fat-Soluble Vitamin Supplementation This is usually required in pancreatic insufficiency. Specially formulated products for CF patients (AquADEKs, DEKAs, MVW Complete, Choiceful) are usually sufficient to attain normal serum vitamin levels at a dose of 1 mL daily for infants, one tablet daily for younger children, and one tablet/capsule twice daily for teenagers and adults taken with food and pancreatic enzymes. Additional supplementation may be needed in uncontrolled malabsorption or for replacement of severe vitamin deficiency based on serum vitamin levels.[1,11] Appetite stimulants such as cyproheptadine, dronabinol, mirtazapine, or megestrol may be an option for promoting nutrition and weight gain, but must be balanced with potential side effects which can range in severity from drowsiness (cyproheptadine, dronabinol, mirtazapine) to adrenal suppression (megestrol).[11]

Liver Disease Ursodiol at 20 mg/kg/day in two divided doses may slow progression of liver disease. It improves bile flow and may displace toxic bile acids that accumulate in a cholestatic liver, stimulate bicarbonate secretion into the bile, offer a cytoprotective effect, and reduce elevated liver enzymes.[1,9]

Intestinal Obstruction Treatment of DIOS consists of enteral administration of polyethylene glycol (PEG) electrolyte solutions. Severe presentations may require surgical resection. Enemas may also be used to facilitate stool clearance. IV fluids are often required to correct dehydration due to vomiting or decreased oral intake. Reevaluation of enzyme adherence and dosing is essential to prevent recurrence, and some patients may require daily PEG administration (MiraLAX).[1,11]

▶ *CF-Related Diabetes*

Patients with mild CFRD may be managed with carbohydrate modification if nutritional status is optimal. However, most patients present with poor nutrition and weight loss and require more aggressive treatment. KEY CONCEPT Because CFRD results from insulin insufficiency, exogenous insulin replacement is usually required. Many patients can be successfully managed by meal coverage with short- or rapid-acting insulin (regular, lispro, or aspart) dosed per carbohydrate counting. Patients with fasting hyperglycemia or patients receiving nighttime tube feedings typically also require longer-acting basal insulin. Regular home glucose monitoring is essential to appropriate therapy. Oral antidiabetic agents have not been studied adequately in CFRD, and routine use is not recommended.[10]

▶ *Bone Disease and Arthritis*

CF patients with low bone mineral density and low serum vitamin D levels may improve bone health through supplemental vitamin D analogs beyond those found in standard CF vitamins. The CF Foundation recommends 25-hydroxyvitamin D levels of at least 30 ng/mL (75 nmol/L) for all patients. For cholecalciferol (or ergocalciferol), a minimum of 400 to 500 IU and 800 to 1000 IU should be taken daily by infants and patients 1 to 10 years of age, respectively. Patients older than 10 years should take 800 to 2000 IU daily. Vitamin D concentrations should be measured annually in the winter for evaluation of dosing.[14] Total weekly or biweekly doses of 12,000 IU for children younger than 5 years of age and 50,000 IU for patients 5 years of age and older may be required to achieve target vitamin D concentrations. Supplemental calcium should be provided if 1300 to 1500 mg of elemental calcium intake cannot be achieved through diet.[13]

Antiresorptive agents (oral or IV bisphosphonates) may be used to treat adult CF patients with osteoporosis. Remaining upright daily for 30 minutes after dosing may be difficult for patients needing to perform airway clearance therapy, so products offering less frequent dosing should be considered. Pamidronate 30 mg IV every 3 months or zoledronic acid 5 mg IV once yearly may be considered in adult CF patients.[7,13] Androgen replacement may benefit bone health in some male CF patients with documented hypogonadism.[7]

▶ *Precision Therapy*

Since the discovery of the CF gene and the CFTR protein defect, research has focused on gene mutation-specific pharmacologic therapy to correct or modulate dysfunctional CFTR protein. Ivacaftor (Kalydeco, VX-770) is a CFTR potentiator that activates defective CFTR at the cell surface and improves CFTR function in patients with gating mutations. Ivacaftor is indicated for treatment of CF patients 2 years and older who have at least

Patient Encounter Part 2

The parents received education about CF and met with the multidisciplinary CF team. Additional laboratory testing was sent to confirm the CF genotype. The team would like to initiate first-line CF therapies because the baby displays symptoms of pancreatic insufficiency (see Part 1). The neonate weighs 3.25 kg and is 54 cm long.

Given this information, what is your assessment of the infant's nutritional status?

What are the treatment goals for this patient?

What nonpharmacologic therapy should be initiated?

What pharmacologic therapy should be initiated?

one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. Ivacaftor treatment (added to standard CF care) is associated with improved lung function (approximately 10% increase in FEV_1), decreased pulmonary exacerbations, weight gain, and increased quality of life.[19,35] Ivacaftor given alone is not effective for patients homozygous for *Phe508del*. Ivacaftor should not be recommended, prescribed, or dispensed without first verifying that the patient has an appropriate *CFTR* gene mutation that has been identified to be responsive to ivacaftor.

The ivacaftor dose is 150 mg orally every 12 hours with food containing at least 20 g of fat for patients age 6 years and older. Patients 2 to 5 years of age should receive 50 mg (< 14 kg) or 75 mg (> 14 kg) orally every 12 hours. Dosage must be reduced in moderate to severe hepatic impairment (Child-Pugh Class B or C) and when coadministered with moderate or strong CYP3A inhibitors (eg, azole antifungals, clarithromycin, erythromycin). Use with strong CYP3A inducers (eg, rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine) is contraindicated. Ivacaftor therapy is generally well tolerated, although elevated liver enzymes have been reported; hepatic enzymes should be monitored quarterly in the first year of therapy.

LO 5

Another precision therapy contains a combination of lumacaftor and ivacaftor (Orkambi, VX-809/VX-770) to treat CF in patients 6 years and older who are homozygous for *Phe508del* and has been shown to reduce pulmonary exacerbations.[35] Lumacaftor stabilizes the CFTR protein so more reaches the cell surface, whereas ivacaftor potentiates ion transport. Lumacaftor/ivacaftor should not be recommended, prescribed, or dispensed without first verifying that the patient has two copies of the *Phe508del* gene mutation. Dosing is lumacaftor 400 mg/ivacaftor 250 mg orally every 12 hours for patients age 12 years and older, and lumacaftor 200 mg/ivacaftor 250 mg orally every 12 hours for patients 6 to 11 years of age. Dosage must be reduced in moderate to severe hepatic impairment (Child-Pugh Class B or C). Dose titration may be needed when imitated in patients already on strong CYP3A inhibitors, and use with strong CYP3A inducers is contraindicated. Lumacaftor is also a strong inducer of several CYP enzymes, and interactions with many medications may require dose adjustment or alternative therapy. Careful review of drug interactions is essential.

In February 2018, a third precision therapy consisting of tezacaftor and ivacaftor (Symdeko, VX-661/VX-770) was approved for CF patients 12 years and older who are homozygous for *Phe508del* or who have at least one gene responsive to therapy. Dosing is tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening. Dosage must be reduced in moderate to severe hepatic impairment (Child-Pugh Class B or C) and when coadministered with moderate or strong CYP3A inhibitors. Use with strong CYP3A inducers is contraindicated. Quarterly monitoring of hepatic enzymes is also recommended. Triple combination therapies are also currently being investigated.[35]

OUTCOME EVALUATION

Pulmonary Function

- Monitor for changes in pulmonary symptoms (cough, sputum production, respiratory rate, and oxygen saturation). Symptoms should improve with antibiotics and aggressive airway clearance therapy. PFTs should be markedly increased after 1 week and trend back to pre-exacerbation levels after 2 weeks of therapy. If improvement lags, 3 weeks of therapy may be needed.

Patient Encounter Part 3

The infant is now 11 months old (weight: 9 kg) and is brought to a routine CF clinic appointment. Her parents report that she has had a runny nose, cough productive of yellow sputum for the past week, and an intermittent fever of up to 101.3°F (38.5°C) at home. Also, the baby has had some post-tussive emesis, reduced oral intake, and has been sleeping more. Vital signs are as follows: BP 82/44 mm Hg, HR 130 beats/min, RR 44/min, 100.8°F (38.2°C), oxygen saturation 94% (0.94). Review of throat cultures since diagnosis reveals the following organisms:

- *S. aureus*: sensitive to nafcillin, trimethoprim–sulfamethoxazole, minocycline, linezolid, and vancomycin; resistant to clindamycin and erythromycin
- *P. aeruginosa*: sensitive to ceftazidime, cefepime, piperacillin/tazobactam, aztreonam, meropenem, ciprofloxacin, and tobramycin; resistant to levofloxacin, amikacin, and gentamicin
- *A. xylosoxidans*: sensitive to trimethoprim–sulfamethoxazole, minocycline, and piperacillin/tazobactam; resistant to ceftazidime, meropenem, and ciprofloxacin

The infant has no known drug allergies.

Based on the information available, design an antibiotic regimen for outpatient therapy of this first pulmonary exacerbation.

What antibiotic(s) and dose(s) would you recommend for inpatient therapy?

Develop a monitoring plan to assess antibiotic response.

- For IV antimicrobial therapy, obtain serum drug levels for aminoglycosides and/or vancomycin and perform pharmacokinetic analysis. Adjust the dose, if needed, according to the targets in Table 16–3. Obtain follow-up trough levels and serum creatinine at least weekly or more frequently if renal function is unstable.

Gastrointestinal Function

- Monitor short- and long-term nutritional status through evaluation of height, weight, and BMI. Ideally, parameters should be near the normals (50th percentile) for non-CF patients.
- Evaluate the patient's stool patterns. Steatorrhea indicates suboptimal enzyme replacement or noncompliance. Infants should have two to three well-formed stools daily, whereas older children and adults may have one or two stools daily.
- Monitor efficacy of vitamin supplementation through yearly serum vitamin levels. Obtain levels more frequently if treating a deficiency.

CF-Related Diabetes

- Monitor morning fasting and 2-hour postprandial blood glucose in patients with CFRD or those taking systemic corticosteroids. Follow A1C levels on an outpatient basis to assess long-term glucose control. Levels may be falsely low in CF due to a shorter red blood cell half-life.

Patient Care Process

Collect Information:

- Conduct a history of prescription, nonprescription, and alternative medications. Review drug allergies and intolerances, especially antibiotics.
- Review the medical history and physical assessment findings with a focus on frequency and quality of cough, sputum production, dyspnea, respiratory rate, oxygen saturations, temperature, and PFT trends. Review the patient's airway clearance methods and order of inhaled therapies.
- Speak with the patient and/or caregivers and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Evaluate for signs and symptoms of pulmonary exacerbation. If present, determine if antibiotics are indicated.
- Review culture and sensitivity tests over the last 1 to 2 years. Review pharmacokinetic history. What antibiotics were used previously? Was response better to a particular regimen?
- Review other available laboratory tests (renal and hepatic function, complete blood count, vitamin levels, IgE level, blood glucose, A1C, bone density). Identify presence of CF comorbidities (eg, diabetes, liver disease, bone disease).
- Determine nutritional status, weight, height, and BMI trends. Assess GI symptoms: quantity and quality of bowel movements, gastroesophageal reflux, bloating, flatulence, or abdominal pain. Are oral supplements or tube feedings being used?
- Evaluate medications for effectiveness, drug interactions, and adverse reactions. Are all appropriate maintenance medications prescribed and dosed appropriately for weight and age?
- Assess adherence, including timing of inhaled medications with respect to airway clearance therapies and timing of enzymes and insulin with regard to meals.

Develop a Care Plan:

- Devise an appropriate IV or oral/inhaled antibiotic regimen for a pulmonary exacerbation. Optimize doses based on pharmacokinetic and pharmacodynamic parameters.
- Optimize maintenance therapies, doses, and schedules that promote efficacy and ease care burden.

Implement the Care Plan:

- Educate the patient and family about any changes in drug therapy, medication administration requirements, and potential side effects. Emphasize importance of therapy adherence.
- Review the patient's practices and technique for self-administration or caregiver-administration of therapies.
- Determine if the patient has insurance coverage, if there are any specialty pharmacy medication access restrictions, and if recommended agents are included on the institution's formulary. Determine if the patient qualifies for any patient assistance programs.

Follow-up: Monitor and Evaluate:

- For antibiotic regimens, evaluate pulmonary symptoms daily if inpatient or every 1 to 2 weeks if outpatient.
- For IV antibiotic regimens, obtain drug levels and perform pharmacokinetic dose adjustments as necessary. Monitor renal function at least weekly. Evaluate fluid intake and urine output daily.
- Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status. Assess effectiveness and safety of maintenance therapies at least quarterly.
- Assess medication adherence and access at least quarterly.

Abbreviations Introduced in This Chapter

ABPA	Allergic bronchopulmonary aspergillosis
CF	Cystic fibrosis
CFRD	Cystic fibrosis-related diabetes
CFTR	Cystic fibrosis transmembrane regulator
CPT	Chest physiotherapy
DIOS	Distal intestinal obstruction syndrome
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HFCC	High-frequency chest compression
IPV	Intrapulmonary percussive ventilation
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
OPEP	Oscillating positive expiratory pressure
PEG	Polyethylene glycol
PFT	Pulmonary function test
PMN	Polymorphonuclear
PT	Prothrombin time
RDA	Recommended daily allowance

REFERENCES

1. Paranjape SM, Mogayzel PJ. Cystic fibrosis. Pediatr Rev. 2014;35(5):194–205.
2. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519–2531.
3. The Clinical and Functional Translation of CFTR (CFTR2). US CF Foundation, Johns Hopkins University, The Hospital for Sick Children. Available from: http://cftr2.org. Accessed August 31, 2017.
4. Davies JC, Ebdon AM, Orchard C. Recent advances in the management of cystic fibrosis. Arch Dis Child. 2014;99(11):1033–1036.
5. Boyle MP, De Boeck K. A new era in the treatment of cystic fibrosis: correction of the underlying CFTR defect. Lancet Respir Med. 2013;1(2):158–163.
6. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. Nat Rev Genet. 2015;16(1):45–56.
7. Quon BS, Aitken ML. Cystic fibrosis: what to expect now in the early adult years. Paediatr Respir Rev. 2012;13(4):206–214.
8. Li L, Somerset S. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. Dig Liver Dis. 2014;46(10):865–874.

9. Flass T, Narkewicz MR. Cirrhosis and other liver disease in cystic fibrosis. J Cyst Fibros. 2013;12(2):116–124.
10. Moran A, Pillay K, Becker DJ, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2014. Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes. 2014;15 Suppl 20:65–76.
11. Schindler T, Michel S, Wilson AW. Nutrition management of cystic fibrosis in the 21st century. Nutr Clin Pract. 2015;30(4): 488–500.
12. Ahmad A, Ahmed A, Patrizio P. Cystic fibrosis and fertility. Curr Opin Obstet Gynecol. 2013;25(3):167–172.
13. Marquette M, Haworth CS. Bone health and disease in cystic fibrosis. Paediatr Resp Rev. 2016;20:2–5.
14. Tangpricha V, Kelly A, Stephenson A, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. J Clin Endocrinol Metab. 2012;97(4):1082–1093.
15. von Drygalski A, Biller J. Anemia in cystic fibrosis: incidence, mechanisms, and association with pulmonary function and vitamin deficiency. Nutr Clin Pract. 2008;23(5):557–563.
16. Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017;181S:S4–S15.
17. Cystic Fibrosis Foundation Patient Registry 2015 Annual Data Report [updated 2016]. Available from: https://www.cff.org/Our-Research/CF-Patient-Registry/2015-Patient-Registry-Annual-Data-Report.pdf. Accessed December 9, 2017.
18. Main E, Grillo L, Rand S. Airway clearance strategies in cystic fibrosis and non-cystic fibrosis bronchiectasis. Semin Respir Crit Care Med. 2015;36(02):251–266.
19. Mogayzel PJ Jr., Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013;187(7):680–689.
20. Cohen-Cymberknoh M, Shoseyov D, Kerem E. Managing cystic fibrosis. Am J Respir Crit Care Med. 2011;183(11):1463–1471.
21. Chmiel JF, Konstan MW, Elborn JS. Antibiotic and anti-inflammatory therapies for cystic fibrosis. Cold Spring Harb Perspect Med. 2013;3(10):a009779.
22. Principi N, Blasi F, Esposito S. Azithromycin use in patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis. 2015;34(6):1071–1079.
23. Chmiel JF, Aksamit TR, Chotirmall SH, et al. Antibiotic management of lung infections in cystic fibrosis. I. The microbiome, methicillin-resistant Staphylococcus aureus, gram-negative bacteria, and multiple infections. Ann Am Thorac Soc. 2014;11(7):1120–1129.
24. Yee CL, Duffy C, Gerbino PG, et al. Tendon or joint disorders in children after treatment with fluoroquinolones or azithromycin. Pediatr Infect Dis J. 2002;21(6):525–529.
25. Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines. Am J Respir Crit Care Med. 2009;180(9): 802–808.
26. Zobell JT, Young DC, Waters CD, et al. Optimization of anti-pseudomonal antibiotics for cystic fibrosis pulmonary exacerbations: VI. Executive summary. Pediatr Pulmonol. 2013;48(6):525–537.
27. Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. Pediatrics. 2016;137(4):e20151784.
28. Borowitz D, Robinson KA, Rosenfeld M, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009;155(6, Suppl): S73–S93.
29. Mogayzel PJ, Naureckas ET, Robinson KA, et al. Cystic Fibrosis Foundation pulmonary guideline. pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection. Ann Am Thorac Soc. 2014;11(10): 1640–1650.
30. Lam J, Vaughan S, Parkins MD. Tobramycin Inhalation Powder (TIP): an efficient treatment strategy for the management of chronic Pseudomonas aeruginosa infection in cystic fibrosis. Clin Med Insights Circ Respir Pulm Med. 2013;7:61–77.
31. Ratjen F, Munck A, Kho P, Angyalosi G. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. Thorax. 2010;65(4):286–291.
32. Tiddens HAWM, De Boeck K, Clancy JP, et al. Open label study of inhaled aztreonam for Pseudomonas eradication in children with cystic fibrosis: The ALPINE study. J Cyst Fibros. 2015;14(1):111–119.
33. Koerner-Rettberg C, Ballmann M. Colistimethate sodium for the treatment of chronic pulmonary infection in cystic fibrosis: an evidence-based review of its place in therapy. Core Evid. 2014;9:99–112.
34. Fusco NM, Toussaint KA, Prescott WA, Jr. Antibiotic management of methicillin-resistant Staphylococcus aureus–associated acute pulmonary exacerbations in cystic fibrosis. Ann Pharmacother. 2015;49(4):458–468.
35. Paranjape SM, Mogayzel PJ, Jr. Cystic fibrosis in the era of precision medicine. Paediatr Respir Rev. 2018;25:64–72.

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17 Gastroesophageal Reflux Disease

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LEARNING OBJECTIVES

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

1. Explain the underlying causes of gastroesophageal reflux disease (GERD).
2. Understand the difference between typical, atypical, and alarm symptoms.
3. Determine when diagnostic tests should be recommended based on the clinical presentation.
4. Identify the desired therapeutic outcomes for patients with GERD.
5. Recommend appropriate nonpharmacologic and pharmacologic interventions for patients with GERD.
6. Educate patients on appropriate lifestyle modifications and drug therapy issues including adherence, adverse effects, and drug interactions.
7. Formulate a monitoring plan to assess the effectiveness and safety of pharmacotherapy for GERD.

INTRODUCTION

Gastroesophageal reflux is the retrograde, effortless movement of stomach contents into the esophagus. When troublesome symptoms or mucosal damage occurs as a result of this process, this is defined as gastroesophageal reflux disease (GERD).[1,2] Treatment is usually initiated based on symptom presentation rather than laboratory tests or invasive monitoring and consists of various lifestyle interventions and pharmacotherapy. Lack of response to empiric therapies may require further evaluation to identify potential underlying complicating conditions.[1,3]

EPIDEMIOLOGY AND ETIOLOGY

GERD is one of the most common gastrointestinal conditions. Up to 40% of Americans report intermittent GERD symptoms, with 10% to 20% of the US population reporting at least weekly symptoms.[1] GERD symptoms can result in morbidity and decreased work productivity. The incidence of **erosive esophagitis** and **Barrett esophagus** increases with age, especially in Caucasian men over 50 years of age with symptoms for more than 10 years.[3,4]

The precise etiology of GERD is difficult to determine in most patients. Increased intraabdominal pressure or decreased **lower esophageal sphincter (LES)** tone may allow gastric refluxate to enter the esophagus causing GERD symptoms in some patients. These processes can be transient and are often due to physical activity, food, or medications.

PATHOPHYSIOLOGY

LO 1

Retrograde movement of gastric contents into the esophagus, oral cavity, or lungs is the origin of symptoms or complications that define GERD. Reflux is normally prevented through muscle tone of the LES. Reduction in LES function or tone may allow reflux of gastric contents into the esophagus. Other physiologic and mucosal defense mechanisms may also become compromised and affect the refluxate composition and development of GERD. Such mechanisms include slowed esophageal clearance, decreased salivary buffering, impaired mucosal resistance, delayed gastric emptying, and increased intraabdominal pressure.

Lower Esophageal Sphincter Pressure

In the normal state, the LES maintains a tonic pressure that separates gastric contents from the esophagus, relaxing during swallowing to allow esophageal contents to pass into the stomach. Decreased LES pressure can occur via spontaneous relaxation, increased intraabdominal pressure, and an atonic LES. Spontaneous relaxation of the LES occurs during vomiting, belching, retching, and esophageal distention. Transient increases in intraabdominal pressure may occur during straining, exercise, bending over, or **Valsalva maneuver**. An atonic LES allows unopposed passage of refluxate from stomach into the esophagus. A **hiatal hernia** may cause or worsen GERD symptoms by increasing intragastric pressure and decreasing LES tone. Some foods and medications may worsen LES dysfunction, whereas others can directly irritate the esophageal mucosa (**Table 17–1**).

Esophageal and Mucosal Protection

Several normal processes protect the esophageal tissue and mucosal barrier from irritants such as refluxed gastric fluid. Swallowing enhances esophageal clearance by increasing salivary flow, which contains bicarbonate that buffers the acidic gastric contents. This usually maintains a neutral esophageal pH; however, salivary production decreases during sleep and in older persons, which may contribute to GERD symptoms. Mucus-secreting glands in the esophageal mucosa and submucosa also help neutralize acidic refluxate by releasing bicarbonate. Most patients with GERD do not produce abnormally large amounts

Table 17–1

Foods and Medications That May Worsen GERD Symptoms

Decreased LES Pressure	
Foods	
Fatty meal/fried foods	Coffee, caffeinated drinks
Carminatives (eg, peppermint)	Garlic
Chocolate	Onions
	Chili peppers
Medications	
Anticholinergics	Ethanol
Barbiturates	Isoproterenol
Benzodiazepines	Nicotine
Caffeine	Nitrates
Dihydropyridine calcium channel blockers	Opioids (eg, morphine)
	Phentolamine
Dopamine	Progesterone
Estrogen	Theophylline
Direct Irritants to the Esophageal Mucosa	
Foods	
Carbonated beverages	Orange juice
Citrus fruits	Spicy foods
Coffee	Tomatoes
Medications	
Aspirin	Iron
Bisphosphonates	NSAIDs
Dabigatran	Quinidine
Doxycycline	Potassium chloride

GERD, gastroesophageal reflux disease; LES, lower esophageal sphincter; NSAIDs, nonsteroidal anti-inflammatory drugs.

Adapted from May DB, Thiman M, Rao S. Gastroesophageal reflux disease. In: DiPiro JT, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill, 2017:437, with permission.

of acid, but slowed esophageal clearance of gastric contents increases contact time of refluxate with esophageal mucosa, possibly leading to symptoms or erosion. Refluxate contains gastric acid, pepsin, bile acids, and pancreatic enzymes that promote mucosal erosion and GERD symptoms.

Gastric Emptying and Increased Abdominal Pressure

Gastric fluid volume depends on the rate of gastric acid secretion, stomach emptying time, and the amount of gastric fluid that refluxes from the duodenum into the stomach. Prolonged stomach emptying time increases the volume of fluid in the stomach, thereby increasing intragastric pressure. Increased gastric volume can increase the amount and frequency of fluid being refluxed, which may cause or worsen GERD symptoms. Factors that increase gastric volume and/or decrease gastric emptying, such as smoking and high-fat meals, are often associated with reflux.

Obesity is a risk factor for developing GERD symptoms and complications. Obesity has been linked to GERD due to increased abdominal pressure. Even weight gain in patients with a normal body mass index may cause new-onset GERD symptoms.[3] Morbidly obese patients may also have more transient LES relaxations, incompetent LES function, and impaired esophageal motility.[5]

Patient Encounter 1, Part 1

A 53-year-old African-American man complains of constant heartburn and regurgitation. He reports no recent weight loss or dyspepsia. He has been self-medicating with over-the-counter calcium carbonate tablets for the last month with no improvement. His weight is 200 kg and his height is 5'11" (180 cm). He has no known drug allergies.

Are this patient's symptoms consistent with GERD?

Would the patient's symptoms be described as typical, atypical, or alarm?

What risk factors does he have that may worsen GERD symptoms?

CLINICAL PRESENTATION AND DIAGNOSIS

LO 2

KEY CONCEPT Patients with GERD may have symptoms classified as: (a) typical, (b) atypical, or (c) alarm (see accompanying box Clinical Presentation of GERD).[3]

Diagnosis of GERD

LO 3

Diagnosis of GERD is assumed with typical patient symptoms and a positive response to a trial of acid-suppressing therapy. Diagnostic testing should be reserved for patients with atypical or alarm symptoms. **Endoscopy** is preferred for assessing mucosal injury and to identify complications such as **esophageal strictures** (which can cause difficulty swallowing) and erosive esophagitis due to repeated and prolonged exposure to gastric refluxate. A mucosal biopsy should be taken to identify Barrett esophagus, which is associated with an increased risk of developing esophageal cancer. Endoscopy may also be performed in patients not responding to an adequate trial of a twice-daily proton pump inhibitor (PPI).[1,3] **Ambulatory esophageal reflux monitoring** identifies excessive esophageal acid exposure and the frequency of reflux episodes. **Esophageal manometry** may be beneficial for patients who have failed twice-daily PPIs and have

Clinical Presentation of GERD

Symptoms

- *Typical symptoms* (may be aggravated by activities that worsen gastroesophageal reflux such as recumbent position, bending over, or eating a high-fat meal): Heartburn, often described as a substernal sensation of warmth or burning rising up from the abdomen that may radiate to the neck and may be waxing and waning in character; hypersalivation; regurgitation; belching
- *Atypical symptoms* (associated with GERD, but causality should only be considered if typical symptoms are also present): Chronic cough, laryngitis, hoarseness, wheezing, noncardiac chest pain, asthma (~50% with asthma have GERD)
- *Alarm symptoms* (may indicate GERD complications such as Barrett esophagus, esophageal strictures, or esophageal adenocarcinoma and require further diagnostic evaluation): Dysphagia, odynophagia, weight loss, bleeding

normal endoscopic findings or those contemplating antireflux surgery. These tests help to determine whether symptoms are acid related and may also be useful in patients not responding to acid suppression therapy or prior to antireflux surgery.

GERD and **dyspepsia** (often occurring with peptic ulcer disease) commonly overlap in presentation. Dyspepsia is characterized predominantly by epigastric pain but can also be associated with other upper GI symptoms including heartburn.[6] Care should be taken when evaluating patient symptom history to differentiate GERD from dyspepsia due to differing treatment strategies. Patients reporting epigastric pain for at least 1 month should be evaluated for dyspepsia. Although *Helicobacter pylori*-positive patients frequently present with gastritis, symptomatic reflux does not correlate well with an active *H. pylori* infection. Routine screening for *H. pylori* in patients with GERD is controversial and not currently recommended.[3,7,8]

TREATMENT

Desired Outcomes

LO 4

KEY CONCEPT The goals of GERD treatment are to alleviate symptoms, decrease the frequency of recurrent disease, promote healing of mucosal injury, and prevent complications.

General Approach to Treatment

KEY CONCEPT Treatment for GERD involves one or more of the following modalities: (a) patient-specific lifestyle changes, (b) pharmacologic intervention primarily with acid-suppressing therapy, or (c) antireflux surgery (Table 17–2).[3,9] The best initial therapeutic option depends on the frequency and severity of symptoms, degree of esophagitis, and presence of complications (Figure 17–1).[1,3,10]

Nonpharmacologic Therapy

▶ *Lifestyle Modifications*

Although most patients do not respond to lifestyle changes alone, it is helpful to maintain these changes throughout therapy to potentially reduce the need for long-term pharmacologic therapies. The most beneficial lifestyle changes include: (a) losing weight if overweight or obese, and (b) elevating the head of the bed with a foam wedge if symptoms are worse when recumbent. Elevating the head of the bed decreases the contact time of gastric acid with the esophageal mucosa at night. A reduction in body mass index in obese patients, particularly those who reduce waist circumference, may improve GERD symptoms.[11]

Table 17–2

Therapeutic Approach to GERD in Adults

Recommended Regimen	Brand Name	Oral Dose	Comments
INTERMITTENT, MILD HEARTBURN (individualized lifestyle modifications + patient-directed therapy with antacids and/or nonprescription H_2RA *or* PPI)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Patient-directed therapy with antacids (≥ 12 years old)			
Magnesium hydroxide/aluminum hydroxide with simethicone	Maalox®	10–20 mL as needed or after meals and at bedtime	If symptoms are unrelieved with lifestyle modifications and nonprescription medications after 2 weeks, patient should seek medical attention; do not exceed 16 teaspoonfuls per 24 hours
Antacid/alginic acid	Gaviscon®	2–4 tablets or 10–20 mL after meals and at bedtime	Note: Content of alginic acid varies greatly among products; the higher the alginic acid, the better
Calcium carbonate	Tums®	500 mg, 2–4 tablets as needed	
Patient-directed therapy with nonprescription H_2RA (up to twice daily) (≥ 12 years old)			
Cimetidine	Tagamet HB®	200 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription H_2RA after 2 weeks, patient should seek medical attention
Famotidine	Pepcid AC®	10–20 mg	
Nizatidine	Axid AR®	75 mg	
Ranitidine	Zantac®	75–150 mg	
Patient-directed therapy (> 18 years old) with nonprescription PPI (taken once daily)			
Esomeprazole	Nexium® 24HR	20 mg	If symptoms are unrelieved with lifestyle modifications and nonprescription PPI after 2 weeks, patient should seek medical attention
Lansoprazole	Prevacid® 24HR	15 mg	
Omeprazole	Prilosec OTC®	20 mg	
Omeprazole/sodium bicarbonate	Zegerid OTC®	20 mg/1100 mg	

(*Continued*)

Table 17–2

Therapeutic Approach to GERD in Adults (*Continued*)

Recommended Regimen	Brand Name	Oral Dose	Comments
SYMPTOMATIC RELIEF OF GERD (individualized lifestyle modifications + prescription-strength H_2RA *or* PPI)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient
Prescription-strength H_2RA (for 6–12 weeks)			
Cimetidine (off-label use)	Tagamet®	400 mg four times daily or 800 mg twice daily	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy • If symptoms recur, consider maintenance therapy. Note: Most patients require standard doses for maintenance therapy
Famotidine	Pepcid®	20 mg twice daily	
Nizatidine	Axid®	150 mg twice daily	
Ranitidine	Zantac®	150 mg twice daily	
Prescription-strength PPI (for 4–8 weeks)			
Dexlansoprazole	Dexilant®	30 mg once daily for 4 weeks	• For typical symptoms, treat empirically with prescription-strength acid suppression therapy • Patients with moderate to severe symptoms should receive a PPI as initial therapy • If symptoms recur, consider maintenance therapy
Esomeprazole	Nexium®	20–40 mg once daily	
Lansoprazole	Prevacid®	15 mg once daily	
Omeprazole	Prilosec®	20 mg once daily	
Omeprazole/sodium bicarbonate	Zegerid®	20 mg once daily	
Pantoprazole (Off-label use)	Protonix®	40 mg once daily	
Rabeprazole	Aciphex®	20 mg once daily	
HEALING OF EROSIVE ESOPHAGITIS OR TREATMENT OF MODERATE TO SEVERE SYMPTOMS OR COMPLICATIONS (individualized lifestyle modifications + high-dose H_2RA *or* PPI *or* antireflux surgery)			
Individualized lifestyle modifications			Lifestyle modifications should be individualized for each patient.
PPI (up to twice daily for up to 8 weeks)			
Dexlansoprazole	Dexilant®	60 mg daily	• For atypical or alarm symptoms, obtain endoscopy with biopsy to evaluate mucosa • If symptoms are relieved, consider maintenance therapy. PPIs are the most effective maintenance therapy for patients with atypical symptoms, complications, and erosive disease. Start with twice-daily PPI therapy if reflux chest syndrome present • Patients not responding to pharmacologic therapy should be evaluated via manometry and/or ambulatory reflux monitoring • Twice daily dosing of PPIs is considered off-label use
Esomeprazole	Nexium®	20–40 mg daily	
Lansoprazole	Prevacid®	30 mg once or twice daily	
Omeprazole	Prilosec®	20 mg once or twice daily	
Rabeprazole	Aciphex®	20 mg once or twice daily	
Pantoprazole	Protonix®	40 mg once or twice daily	
High-dose H_2RA (for 8–12 weeks)			
Cimetidine	Tagamet®	400 mg four times daily or 800 mg twice daily	Note: If high-dose H_2RA needed, may consider using PPI to lower cost, increase convenience, and increase tolerability Note: Four times daily use is considered off-label for nizatidine
Famotidine	Pepcid®	20–40 mg twice daily	
Nizatidine	Aciphex®	150 mg two–four times daily	
Ranitidine	Zantac®	150 mg four times daily	
Interventional therapy			
Antireflux surgery			

GERD, gastroesophageal reflux disease; H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

From May DB, Thiman M, Rao S. Gastroesophageal reflux disease. In: DiPiro JT, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill, 2017:442–443, with permission.

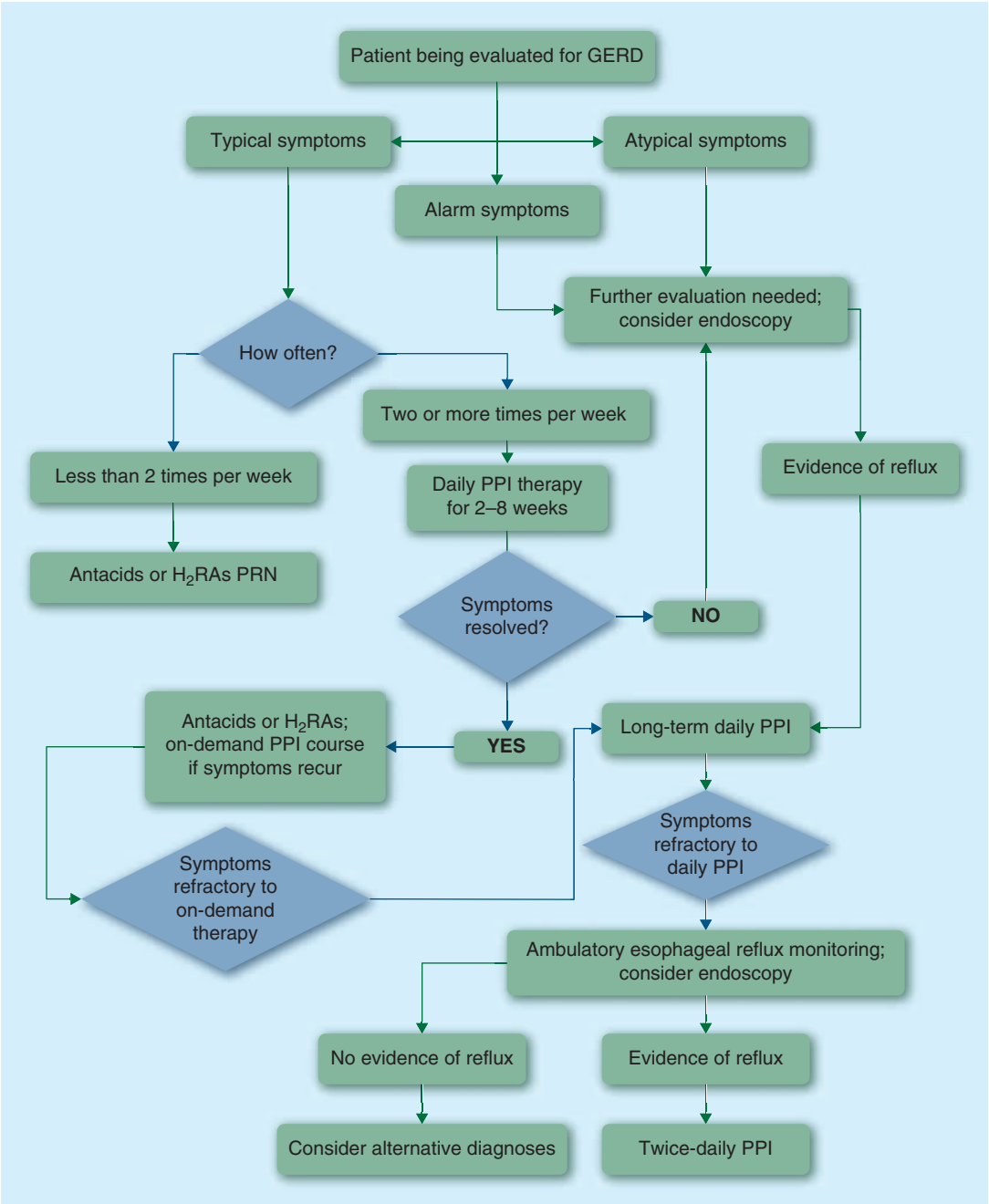

FIGURE 17–1. GERD treatment algorithm for adults. (GERD, gastroesophageal reflux disease; H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor, PRN, as needed.)

Other lifestyle modifications should be considered based on patient circumstances. These might include: (a) eating smaller meals and avoiding meals 3 hours before sleeping, (b) avoiding foods or medications that exacerbate GERD, (c) smoking cessation, and (d) avoiding alcohol. The patient's medication and food histories should be evaluated to identify potential factors that may exacerbate GERD symptoms (Table 17–1).

▶ *Surgical Treatment*

Antireflux surgical options may be considered when pharmacologic management is undesirable due to side effects or adherence challenges in patients with well-documented GERD.[7] Fundoplication increases LES pressures by wrapping the fundus of the stomach around the distal esophagus; the wrap may include the total esophageal circumference (Nissen fundoplication), only the posterior circumference (Toupet), or only the anterior circumference (Dor). The LINX procedure consists of placing a band of interlinked titanium beads with magnetic cords around the LES to aid in maintaining LES pressure. LES stimulators are surgically inserted to modulate LES pressures and reduce refluxate from the stomach.[12]

The goal of surgery is to reestablish the antireflux barrier, position the LES within the abdomen where it is under positive (intraabdominal) pressure, and close any associated hiatal defect. Antireflux surgery provided more symptom control than omeprazole in patients with esophagitis in a 7-year follow-up study.[13]

The evidence for surgery is not as strong in patients who do not respond to PPI therapy.[3,7] Roux-en-Y gastric bypass has been shown to reduce symptoms of GERD in obese patients; however, not all forms of bariatric surgery, such as vertical banded gastroplasty, have been shown to improve GERD symptoms.[3,14]

Surgical options may be considered at any time during therapy; however, surgery is not recommended for patients who respond to adequate PPI therapy. Surgical therapies have significant inherent risks including risk of mortality; therefore, surgery may be an appropriate option if a patient has a strong desire to discontinue medication therapy, the presence of a large hiatal hernia, or refractory GERD symptoms.[3]

Pharmacologic Therapy

Pharmacologic therapy for GERD involves increasing the pH of gastric contents through either direct gastric acid neutralization or reducing acid production through inhibition of stimulation pathways, thereby reducing GERD symptoms and tissue damage. Pharmacologic options can be stratified by effectiveness: antacids are inferior to histamine-2 receptor antagonists (H_2RAs) due to brief neutralization of gastric acid and lack of acid-suppressive properties. H_2RAs decrease acid secretion to a lesser extent than PPIs because PPIs block the rate-limiting step in acid secretion from gastric parietal cells, thereby blocking all pathways for gastric acid secretion.[3]

▶ *Antacids*

Antacids are useful for intermittent treatment of GERD symptoms and can be used for patients with infrequent typical reflux symptoms. They are effective for immediate, symptomatic relief but require frequent dosing (Table 17–2). Aluminum or magnesium-containing antacids may result in electrolyte abnormalities, particularly in patients with renal impairment. Antacids are usually well tolerated, but potential side effects include constipation or diarrhea depending on the formulation being used. Antacids may also chelate with medications such as fluoroquinolones, tetracyclines, iron products, and thyroid hormones; therefore, doses should be separated by several hours to avoid decreased efficacy.

▶ *Histamine-2 Receptor Antagonists*

The H_2RAs (cimetidine, famotidine, nizatidine, ranitidine) decrease acid secretion by blocking histamine$_2$-receptors in gastric parietal cells. H_2RAs provide relief from typical acute GERD symptoms and can also be administered prophylactically. H_2RAs are more effective than antacids at controlling chronic GERD symptoms but less effective than PPIs. H_2RAs may be dosed intermittently or on a scheduled basis depending on the degree of symptom control (Table 17–2). LO 5

H_2RAs are generally well tolerated; side effects are mild and most commonly include headache and nausea. Cimetidine is a weak inhibitor of the cytochrome P-450 system with many common drug interactions; other H_2RAs have limited drug interactions. Cimetidine also has unique adverse effects such as gynecomastia and vitamin B_{12} deficiency, which limits patient tolerance in chronic therapy.[15] Most H_2RAs are renally eliminated and may require dose adjustment in kidney dysfunction.

▶ *Proton Pump Inhibitors*

KEY CONCEPT PPIs (eg, omeprazole, lansoprazole) block gastric acid secretion by inhibiting gastric H^+/K^+-adenosine triphosphatase in gastric parietal cells, producing a profound, long-lasting antisecretory effect capable of maintaining the gastric pH above 4, even during acid surges occurring postprandially. LO 5 Primary uses of PPIs are treating frequent reflux symptoms and healing of gastric or esophageal ulcerations. KEY CONCEPT PPIs provide significant reduction in gastric acid and the greatest relief of symptoms, especially in patients with moderate to severe GERD, with high rates of healing erosive disease. PPIs are available as both prescription and nonprescription products with various formulations available (Table 17–2).

Because PPIs degrade in acidic environments, they are typically formulated in delayed-release capsules or tablets. For patients unable to swallow intact capsules (including children) or those with nasogastric tubes, the capsule contents can be mixed in applesauce or orange juice.[16] The acidic juices help maintain the integrity of the enteric-coated pellets until they reach the small intestine.[16] Esomeprazole pellets can be mixed with water prior to delivery through a nasogastric tube.[16]

Most patients should be instructed to take their PPI in the morning, 30 to 60 minutes before breakfast to maximize efficacy, because these agents inhibit only actively secreting proton pumps. Due to their slow onset of action, PPIs are most effective when taken on a scheduled basis. Patients with nighttime symptoms may benefit from taking the PPI prior to the evening meal. If a second daily dose is needed, it should be taken before the evening meal and not at bedtime. Dexlansoprazole and the combination product omeprazole–sodium bicarbonate may be taken without regard to food.[9] All PPIs can decrease the absorption of medications that require an acidic environment to be absorbed (eg, dabigatran, encapsulated itraconazole, dipyridamole) and are all metabolized by the cytochrome P-450 system to some extent.[17,18]

LO 6 PPIs are generally well tolerated; the most common side effects are headache and GI effects such as diarrhea and nausea. Several concerns have been raised about consequences of long-term PPI use. Renal complications (acute kidney injury and chronic kidney disease), bone fractures, and dementia have been reported from retrospective observational studies and case reports; however, prospective data are limited and additional study is needed to determine causality.[19] LO 6 Reduced absorption of micronutrients such as calcium, magnesium, and vitamin B_{12} with long-term use has also been reported in observational studies.[10] However, routine screening and supplementation of these vitamins and minerals based solely on chronic PPI use is not warranted.[3,7,10] In patients with documented hypocalcemia, it is reasonable to replete calcium with the citrate rather than the carbonate salt due to improved absorption in a less acidic environment.[20]

LO 6 Concerns for drug interactions with clopidogrel and PPIs that inhibit CYP 2C19 were initially raised by pharmacodynamic studies showing possible attenuation of clopidogel's antiplatelet function. Clopidogrel is a prodrug requiring a two-step activation via CYP2C19, which may be competitively depleted due to metabolism of PPIs via the same enzyme.[21,22] However, the 2010 COGENT study found no meaningful interaction or increase in the incidence of myocardial infarction in patients who used omeprazole with aspirin and clopidogrel.[23] Although the COGENT study had limitations, the interaction between clopidogrel and PPIs is not considered to be clinically significant, and use of PPIs may decrease GI-related events such as upper GI bleed when used with dual antiplatelet agents. Use of a PPI with clopidogrel should be considered based on the individual patient's cardiovascular and bleeding risk. If patients or providers wish to avoid the combination, alternatives include switching to a P2Y12 inhibitor not activated by CYP2C19, switching to a PPI with less CYP2C19 metabolism (omeprazole is most affected), or substituting an H_2RA for a PPI.[24]

Infectious complications attributed to chronic PPI use include spontaneous bacterial peritonitis, small intestinal bacterial overgrowth, *Clostridium difficile* infection, and pneumonia.[25] Studies have been mostly small observational trials attributing a low to moderate overall increased infection risk with PPI treatment. PPIs have been postulated to increase the risk of gastrointestinal malignancies by facilitating *H. Pylori* proliferation and by causing hypergastrinemia as a result of profound gastric acid suppression. Although no clinical studies have found an association with PPIs and increased cancer risk, hypergastrinemia does have a trophic effect in colonic cells in mice and in vitro human colorectal cancers.[19,26] Further monitoring of this possible complication will be necessary due to the slow growth of some colonic tumors.[19] The potential risks of chronic PPI use must be evaluated on an individual basis, and judicious use should guide clinical decisions.

▶ *Prokinetic Agents*

Metoclopramide, a central dopamine antagonist, accelerates gastric emptying and can increase LES pressure. Metoclopramide has been studied for GERD symptom relief in conjunction with a PPI; however, potential side effects can be significant and include extrapyramidal effects and tardive dyskinesia.[3] Domperidone is a peripherally acting dopamine antagonist that does not have central nervous system toxicities; however, it is not approved for use in the United States and requires monitoring for QT prolongation. In patients without gastroparesis, there is no clear role for the use of prokinetic agents for treatment of GERD.[3]

▶ *Alternative Pharmacologic Agents*

Baclofen, a gamma-aminobutyric acid (GABA) agonist, has been shown to provide some benefit in reducing GERD symptoms by increasing gastric pH. Due to limited efficacy data and potential side effects including dizziness, somnolence, and constipation, baclofen is not recommended for treatment of GERD without diagnostic evaluation.[3]

Sucralfate, a nonabsorbable aluminum salt of sucrose octasulfate, has limited value in the treatment of GERD. Sucralfate is suboptimal compared with PPI therapy and has no role in nonpregnant patients with GERD.[3]

Initial Therapy of GERD

LO 7

On presentation to a health care provider, patients may have already attempted an over-the-counter (OTC) trial of self-directed therapy with all three of the major pharmacologic agents. After confirmation of the diagnosis of GERD, a trial of a scheduled PPI for 8 weeks is typically recommended, monitoring for symptomatic improvement. Most patients with nonerosive GERD respond positively to a PPI trial and therefore should be evaluated for an appropriate long-term maintenance therapy. Adherence and appropriate administration should be monitored throughout therapy. For patients with refractory nocturnal symptoms or symptoms not controlled with daily therapy, a trial of twice daily PPIs may provide benefit.[10]

Patients with erosive esophagitis on endoscopy should be treated with at least 8 weeks of twice-daily PPI therapy. PPIs are superior to H_2RAs for healing erosive lesions.[3] Maintenance therapy in these patients should be individualized after the initial treatment period; if PPIs are continued, they should be used at the lowest effective dose and schedule.[3]

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Dyslipidemia, hypertension, and depression

FH: Mother had breast cancer, father has hypertension and depression

SH: Recently went on disability; lives at home with wife and teenage daughter. Smokes 2½ packs of cigarettes per day and drinks 1–2 large caffeinated energy drinks daily. Reports drinking about 6 alcoholic beverages per week

Meds: Hydrochlorothiazide 12.5 mg once daily, amlodipine 10 mg once daily, atorvastatin 20 mg at bedtime, citalopram 10 mg once daily

ROS: (+) Heartburn, regurgitation; (–) chest pain, nausea, vomiting, diarrhea, weight loss, change in appetite, shortness of breath or cough

PE:

VS: BP 125/72 mm Hg, P 82 beats/min, RR 16 breaths/min, T 37°C (98.6°F)

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Abd: Soft, nontender, nondistended; (+) bowel sounds, (–) hepatosplenomegaly, heme (–) stool

Given this additional information, what factors could be contributing to the patient's GERD symptoms?

Does this patient require further diagnostic evaluation based on his clinical presentation? If so, which procedure would you recommend?

What nonpharmacologic and pharmacologic changes would you recommend for his GERD therapy?

Maintenance GERD Therapy

KEY CONCEPT Maintenance therapy may be necessary in patients with refractory symptoms while on maximal acid suppression (Table 17–2).[3,7,10] KEY CONCEPT Adding an H_2RA to a PPI regimen may provide initial benefit for refractory symptoms but may result in tachyphylaxis with continued use. While maintenance daily PPI therapy may be necessary in some patients, on-demand PPI dosing may also be effective. On-demand therapy consists of stopping PPI therapy upon resolution of GERD symptoms, with reinitiation of therapy for 2 to 4 weeks if symptoms occur two or more times within 7 days while off therapy.[10] In a large prospective study of GERD patients (most of whom had erosive esophagitis) who used on-demand therapy, 70% had 0 or 1 relapse and only 30% changed to chronic daily PPI therapy after almost one year of follow-up.[27] Other studies found that on-demand therapy can decrease PPI exposure by 60% to 80%, with more than 80% of patients being willing to continue the dosing strategy when given the option.[28]

KEY CONCEPT Patients who wish to stop long-term PPI therapy should be slowly titrated off using a stepwise or prolonged taper due to the potential for rebound gastric acid hypersecretion with sudden withdrawal. Rebound hypersecretion can occur with continual PPI use for at least 2 months. For these reasons, the PPI dose and frequency should be tapered slowly, using H_2RAs for breakthrough symptoms. The duration of the taper must be individualized; rebound hypersecretion symptoms can last 3 months or longer after PPI discontinuation.[29]

Special Populations

▶ *Children with GERD*

Generally, reflux is a common physiologic process in children that occurs several times per day with no clinical consequence; however, as with adults, GERD is present when symptoms become troublesome or if complications are present.[30,31] Regurgitation is common in children and may occur daily in as many as 50% of infants younger than 3 months.[30] Most babies who "spit up" are "happy spitters"; they are comfortable, gaining weight, and have no breathing problems caused by vomiting. More troublesome symptoms may include vomiting, apnea, poor weight gain, sleep disturbances, and refusing to eat.[31]

Reflux episodes are common during transient LES relaxations not related to swallowing because of developmental immaturity of the LES.[30] Other causes include impaired luminal clearance of gastric acid and infant diet. Formula-fed infants are more likely than breastfed infants to exhibit GERD symptoms.[32] Children with neurologic impairment and impaired swallowing, obesity, repaired congenital abnormalities of the esophagus, cystic fibrosis, or hiatal hernia are at a higher risk for developing GERD.[30]

Lifestyle modifications are emphasized in pediatric patients with uncomplicated GERD. Symptoms usually resolve by 12 to 18 months of life and respond to supportive therapy, including dietary adjustments such as smaller meals, more frequent feedings, switching to an extensively hydrolyzed protein or amino acid-based formula, or thickening infant formula with rice cereal. However, excessive thickening of infant formula is discouraged, particularly in preterm infants due to concerns of increased risk for necrotizing enterocolitis.[31] Postural management (ie, positioning the infant in an upright position, especially after meals) may be helpful. Changes in maternal diet such as restricting eggs and milk may be useful in breast-fed infants with GERD symptoms because milk protein allergy in infants can mimic the presentation of GERD.[31]

If lifestyle modifications are not effective, medical therapy may be indicated. Acid suppression with either an H_2RA or PPI is the mainstay of pharmacologic therapy for pediatric GERD.[30] Chronic use of antacids or routine use of prokinetics or sucralfate is not recommended. Monotherapy with an H_2RA is commonly used; however, chronic use may lead to tachyphylaxis, as with adults.

Increased use of PPIs in children has led to concerns because long-term safety is unknown. Therefore, clinicians must carefully weigh potential risks versus benefits along with appropriate indications for therapy and duration of treatment.[30]

▶ *GERD During Pregnancy*

GERD is common during pregnancy, and 30% to 50% of pregnant women report heartburn symptoms. Lifestyle modifications such as eating smaller meals can reduce heartburn and regurgitation. Mild to moderate GERD symptoms can be treated with antacids that have limited systemic absorption, such as calcium carbonate. Pregnant patients with severe, frequent heartburn can be started on a PPI. A large retrospective cohort of over 5000 patients found no increase in the number of birth defects in infants exposed to PPIs in utero.[33]

OUTCOME EVALUATION

- Monitor for symptom relief and the presence of symptoms.
- Record the frequency and severity of symptoms by interviewing the patient after 4 to 8 weeks of acid-suppressing

Patient Care Process

Collect Information:

- Perform a medication history to determine use of prescription, nonprescription, and dietary supplements.
- Identify patient allergies and intolerances that may affect current or planned pharmacotherapy.
- Review the patient's medical and surgical history for issues that may be related to GERD.

Assess the Information:

- Determine whether the patient is taking medications or eating foods that may worsen GERD symptoms (Table 17–1).
- Document severity, characteristics, and frequency of GERD symptoms (eg, typical or alarm symptoms).
- Assess the efficacy, safety, and patient adherence of current therapies and identify any significant adverse effects or interactions.

Develop a Care Plan:

- Implement lifestyle modifications that the patient is willing to do in order to reduce GERD symptoms.
- Decide if self-treatment is an option or if the patient should be referred to a physician.
- Choose medications and doses that are appropriate considering symptoms, drug or food interactions, and the patient's ability to obtain the chosen therapies that will likely improve quality of life.

Implement the Care Plan:

- Educate the patient about the chosen drug therapy including medication administration, potential adverse effects, and follow-up parameters.
- Educate the patient about symptoms that suggest the presence of complications requiring immediate medical attention, such as dysphagia or odynophagia.
- Discuss the importance of weight loss and dietary changes (if appropriate) for reducing GERD symptoms.
- Address any patient concerns about the GERD management plan.

Follow-up: Monitor and Evaluate:

- Instruct the patient on the proper time for reassessment if symptoms have not resolved.
- Review medication adherence and timing of doses.
- Monitor for adverse drug effects and determine a plan if symptoms recur.
- Refer patients with atypical or alarm symptoms to their physician for further diagnostic evaluation.
- Determine if long-term maintenance therapy is necessary after completion of the initial course of therapy.

Patient Encounter 2

A 63-year-old, 110-kg woman with a history of hypertension, diabetes, glaucoma, and GERD presents for her annual appointment after 2 years of daily PPI therapy, with symptoms well controlled. She reports concern about her PPI therapy after reading a news article about adverse health risks of long-term PPI use.

What is your response to the patient's concerns about risks of long-term PPI therapy?

What alternative treatment options are available for the patient?

Create a pharmacotherapy plan for this patient.

What counseling points should be discussed with the patient regarding the regimen change?

How would you monitor for effectiveness of the treatment plan?

therapy. Continued symptoms may indicate the need for long-term maintenance therapy.

- KEY CONCEPT Review the patient profile for drugs that may aggravate GERD.
- Monitor for adverse drug reactions, drug–drug interactions, and adherence.
- Reassess the need for continued PPI therapy at the completion of the recommended treatment regimen (Table 17–2).

Abbreviations Introduced in This Chapter

GABA	Gamma-aminobutyric acid
GERD	Gastroesophageal reflux disease
H$_2$RA	Histamine-2 receptor antagonist
LES	Lower esophageal sphincter
PPI	Proton pump inhibitor

REFERENCES

1. Savarino E, Bredenoord AJ, Fox M, et al. International Working Group for Disorders of Gastrointestinal Motility and Function. Expert consensus document: advances in the physiological assessment and diagnosis of GERD. Nat Rev Gastroenterol Hepatol. 2017;14(11):665–676.
2. Maqbool A, Pauwels A. Cystic fibrosis and gastroesophageal reflux disease. J Cyst Fibros. 2017;16(Suppl 2):S2–S13.
3. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108(3):308–328.
4. Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG clinical guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol. 2016;111(1):30–50.
5. Herbella FA, Patti MG. Gastroesophageal reflux disease: from pathophysiology to treatment. World J Gastroenterol. 2010;16(30):3745–3749.
6. Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017;112(7):988–1013.
7. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology. 2008;135(4):1383–1391.
8. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112(2):212–239.
9. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490–1494.
10. Laine L, Nagar A. Long-term PPI use: balancing potential harms and documented benefits. Am J Gastroenterol. 2016;111(7):913–915.
11. Park SK, Lee T, Yang HJ, et al. Weight loss and waist reduction is associated with improvement in gastroesophageal disease reflux symptoms: a longitudinal study of 15,295 subjects undergoing health checkups. Neurogastroenterol Motil. 2017 May;29(5).
12. DeMeester TR. Surgical options for the treatment of gastroesophageal reflux disease. Gastroenterol Hepatol (NY). 2017 February;13(2):128–129.
13. Lundell L, Miettinen P, Myrvold HE, et al. Seven-year follow-up of a randomized clinical trial comparing proton-pump inhibition with surgical therapy for reflux oesophagitis. Br J Surg. 2007;94:198–203.
14. Gagne DJ, Dovec E, Urbandt JE. Laparoscopic revision of vertical banded gastroplasty to Roux-en-Y gastric bypass: outcomes of 105 patients. Surg Obes Relat Dis. 2011;7:493–499.
15. Tagamet(R) [package insert]. Tarrytown, NY: Medtech Products, Inc; 2014.
16. Williams NT. Medication administration through enteral feeding tubes. Am J Health Syst Pharm. 2008;65:2347–2357.
17. Bolek T, Samoš M, Stančiaková L, et al. The impact of proton pump inhibition on dabigatran levels in patients with atrial fibrillation. Am J Ther. 2017 April 25 [Epub ahead of print].
18. Lahner E, Annibale B, Delle Fave G. Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy. Aliment Pharmacol Ther. 2009;15;29(12):1219–1229.
19. Johnson DA, Katz PO, Armstrong D, et al. The safety of appropriate use of over-the-counter proton pump inhibitors: an evidence-based review and delphi consensus. Drugs. 2017;77(5):547–561.
20. Yang YX. Chronic proton pump inhibitor therapy and calcium metabolism. Curr Gastroenterol Rep. 2012;14(6):473–479.
21. Sibbing D, Morath T, Stegherr J, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost. 2009;101:714–719.
22. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol. 2008;51:256–260.
23. Bhatt DL, Cryer BL, Contant CF, et al; COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010;363(20):1909–1917.
24. Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. World J Gastrointest Pharmacol Ther. 2015;6(2):17–21.
25. Thompson ABR, Sauve MD, Kassam N, Kamitakahara H. Safety of long-term use of proton pump inhibitors. World J Gastroenterol. 2010;16(19):2323–2330.
26. Watson SA, Durrant LG, Morris DL. Growth-promoting action of gastrin on human colonic and gastric tumour cells cultured in vitro. Br J Surg. 1988;75(4):342–345.
27. Bardhan KD, Müller-Lissner S, Bigard MA, et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. BMJ. 1999;318(7182):502–507.

28. Pace F, Tonini M, Pallotta S, et al. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken "on-demand." Aliment Pharmacol Ther. 2007;26(2):195–204.
29. Haastrup P, Paulsen MS, Begtrup LM, et al. Strategies for discontinuation of proton pump inhibitors: a systematic review. Fam Pract. 2014;31(6):625–630.
30. Vandenplas Y, Rudolph CE, Di Lorenz C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49:498–547.
31. Lightdale Jr, Gremse DA; Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013;131(5):e1684–e1695.
32. Orenstein SR, McGowan JD. Efficacy of conservative therapy as taught in the primary care setting for symptoms suggesting infant gastroesophageal reflux. J Pediatr. 2008;152(3):310–314.
33. Pasternak B, Hviid A. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med. 2010;363(22):2114–2123.

18 Peptic Ulcer Disease

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LEARNING OBJECTIVES

LO

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

1. Recognize differences between ulcers induced by *Helicobacter pylori*, nonsteroidal anti-inflammatory drugs (NSAIDs), and stress-related mucosal damage (SRMD) in terms of risk factors, pathogenesis, signs and symptoms, clinical course, and prognosis.
2. Identify desired therapeutic outcomes for patients with *H. pylori*–associated ulcers and NSAID-induced ulcers.
3. Identify factors that guide selection of an *H. pylori* eradication regimen and improve adherence with these regimens.
4. Determine the appropriate management for a patient taking a nonselective NSAID who is at high risk for ulcer-related gastrointestinal (GI) complications (eg, GI bleed) or who develops an ulcer.
5. Employ an algorithm for evaluation and treatment of a patient with signs and symptoms suggestive of an *H. pylori*–associated or NSAID-induced ulcer.
6. Given patient-specific information and the prescribed treatment regimen, formulate a monitoring plan for drug therapy either to eradicate *H. pylori* or to treat an active NSAID-induced ulcer or GI complication.

INTRODUCTION

Peptic ulcer disease (PUD) refers to a defect in the gastric or duodenal mucosal wall that extends through the **muscularis mucosa** into the deeper layers of the submucosa.[1] PUD is a significant cause of morbidity and is associated with substantial health care costs.[2,3] Although there are many etiologies of PUD, the three most common are (a) *H. pylori* infection, (b) use of nonsteroidal anti-inflammatory drugs (NSAIDs), and (c) stress-related mucosal damage (SRMD).

Complications of PUD include gastrointestinal (GI) bleeding, perforation, and obstruction. Complications of untreated or undiagnosed *H. pylori* infection include gastric cancer and PUD. This chapter focuses mainly on pharmacotherapy of PUD related to *H. pylori* infection or NSAID use. Prophylaxis of SRMD in hospitalized patients is also discussed briefly.

EPIDEMIOLOGY AND ETIOLOGY

PUD affects approximately 10% of women and 12% of men in the United States, resulting in 4 million cases annually.[4] The mean direct medical cost (including pharmacy, inpatient, and outpatient costs) was $23,819 per patient per year in one study evaluating workplace absences, short-term medical disability, worker's compensation, and medical and pharmacy claims for six large US employers.[5]

The prevalence of *H. pylori* infection in the United States and Canada is about 30%, whereas the global prevalence is greater than 50%. Factors that influence the incidence and prevalence of *H. pylori* infection include age, ethnicity, sex, geography, and socioeconomic status.

Helicobacter Pylori

LO 1

H. pylori is usually contracted in the first few years of life and tends to persist indefinitely unless treated. The infection normally resides in the stomach and is transmitted through ingestion of fecal-contaminated water or food. The organism causes **gastritis** in all infected individuals, but fewer than 10% actually develop symptomatic PUD.

Nonsteroidal Anti-Inflammatory Drugs

Chronic NSAID ingestion causes nausea and dyspepsia in nearly half of patients. Peptic ulceration occurs in up to 30% of chronic NSAID (including aspirin) users, with GI bleeding or perforation occurring in 1.5% of patients who develop an ulcer.[2] Ulcer-related complications result in 100,000 hospitalizations and more than 20,000 deaths in the United States each year.[2]

Risk factors for NSAID-induced PUD and complications are presented in Table 18–1. Risk factors are generally additive. Corticosteroid therapy is not an independent risk factor for ulceration but increases PUD risk substantially when combined with NSAID therapy.[6] Whether *H. pylori* infection is a risk factor for NSAID-induced ulcers remains controversial; however, *H. pylori* and NSAIDs act independently to increase ulcer risk and ulcer-related bleeding and also appear to have synergistic effects.[7,8]

Stress-Related Mucosal Damage

SRMD occurs most frequently in critically ill patients due to mucosal defects caused by gastric mucosal ischemia and intraluminal acid.[9] The ulcers are usually superficial, but SRMD may also penetrate into the submucosa and cause significant GI bleeding. Physiologically stressful situations that lead to SRMD include sepsis, organ failure, prolonged mechanical ventilation, thermal injury, and surgery. Critical care patients with the specific characteristics listed above are at highest risk.[10]

Table 18–1

Risk Factors for Ulcers and GI Complications Related to NSAID Use

- Age older than 65 years
- Concomitant anticoagulant use
- Preexisting coagulopathy (elevated INR or thrombocytopenia)
- Concomitant corticosteroid therapy
- Previous PUD or PUD complications (bleeding/perforation)
- Cardiovascular disease and other comorbid conditions
- Multiple NSAID use (eg, low-dose aspirin plus another NSAID)
- Longer duration of NSAID use
- High-dose NSAID use

GI, gastrointestinal; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.

From Lanza FL, Chan FKL, Quigley EMM, et al. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728–738.

Zollinger–Ellison Syndrome

Zollinger–Ellison syndrome (ZES) is caused by a gastrin-producing tumor called a gastrinoma. The resulting gastric acid hypersecretion causes diarrhea and malabsorption. Ulcers tend to be numerous and have a high risk of perforation and bleeding.[11] Treatments include surgical resection when feasible and high-dose oral proton pump inhibitor (PPI) therapy.

Other Causative Factors

Cigarette smoking is associated with a higher prevalence of ulcers in *H. pylori*-infected patients.[2] The detrimental effects of smoking on the gastric mucosa may involve increased pepsin secretion, duodenogastric reflux of bile salts, elevated levels of free radicals, and reduced prostaglandin-2 (PG_2) production, resulting in decreased mucus and bicarbonate secretion.[12]

Although psychosocial factors such as life stress, personality patterns, and depression may influence PUD prevalence, a clear causal relationship has not been demonstrated.[2]

Dietary factors such as coffee, tea, cola, alcohol, and spicy foods may cause dyspepsia but have not been shown to independently increase PUD risk.

PATHOPHYSIOLOGY

LO 1

Ulcers related to *H. pylori* infection more commonly affect the duodenum (duodenal ulcers [DUs]), whereas NSAID-related ulcers more frequently affect the stomach (gastric ulcers [GUs]) (Figure 18–1). However, ulcers may be found in either location from either cause.[11]

Ulcer formation in the GI tract results from disrupted homeostasis between factors that break down food (eg, gastric acid and pepsin) and those that promote mucosal defense and repair (eg, bicarbonate, mucus secretion, and PGs).

Gastric Acid and Pepsin

Hydrochloric acid and pepsin are the primary substances that cause gastric mucosal damage in PUD. Three different stimuli (eg, histamine, acetylcholine, and gastrin) cause acid secretion through interactions with the histaminic, cholinergic, and gastrin receptors on the surface of parietal cells. Gastric acid output occurs in two stages: (a) basal acid output during fasting, and (b) maximal acid output in response to meals. Basal acid secretion follows a circadian cycle and is modulated by the effects of acetylcholine and histamine on parietal cells.[13]

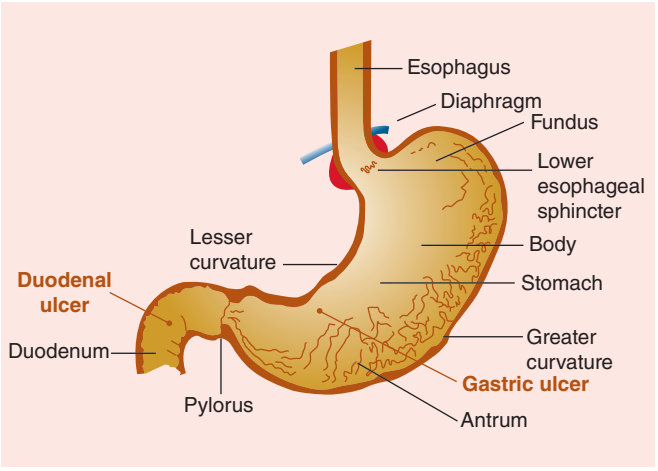


FIGURE 18–1. Anatomic structure of the stomach and duodenum and most common locations of gastric and duodenal ulcers. (From Love B, Thoma MN. Peptic ulcer disease. In: DiPiro JT, Talbert RA, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014 with permission. www.accesspharmacy.com.)

Food increases gastric acid secretion in two ways: (1) vagus nerve stimulation in response to sight, smell, or taste; and (2) stomach distention during the gastric and intestinal phases of acid secretion.

After stimulation by histamine, acetylcholine, and gastrin, acid is secreted by the H^+-K^+-ATPase$^+$ (proton) pump, located on the luminal side of parietal cells. Acid secretion in PUD is usually normal or only slightly elevated. NSAID ingestion does not usually affect acid secretion, whereas *H. pylori* infection often slightly increases acid output.[13]

Pepsinogen released from chief cells in the body of the stomach is converted to pepsin in an acidic environment; pepsin initiates protein digestion and collagen proteolysis and serves as a signal for the release of other digestive enzymes such as gastrin and cholecystokinin.[14] The proteolytic activity of pepsin appears to influence ulcer formation.

Mucosal Defense and Repair

Several normal processes prevent mucosal damage and subsequent ulcer formation. The buffering action of the mucus/phospholipid and bicarbonate barrier shields the gastric epithelial surface from gastric acid.[2] This allows an acidic environment in the gastric lumen but a near neutral pH on the epithelial lining.

PGs inhibit gastric acid secretion and protect gastric mucosa by stimulating mucus, bicarbonate, and phospholipid production. PGs also increase mucosal blood flow and stimulate epithelial cell regeneration.[2] Damage to the mucosal defense system is the primary method by which *H. pylori* and NSAIDs cause peptic ulcers.

▶ *Helicobacter pylori*

H. pylori, a gram-negative rod, is found on the surface of the gastric epithelium. Flagella provide motility that allows the organism to penetrate the mucous gel barrier and infect epithelial cells.[15] Cellular invasion by *H. pylori* is necessary for an active infection. The organism survives in the acidic milieu of the stomach by producing urease, an enzyme that hydrolyzes urea in gastric juice into carbon dioxide and ammonia.[15]

H. pylori may cause gastroduodenal mucosal injury through (a) direct mucosal damage, (b) alterations in host inflammatory responses, and (c) hypergastrinemia and elevated acid secretion.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs can cause gastric mucosal damage by two mechanisms: (1) direct irritation of the gastric epithelium, and (2) systemic inhibition of endogenous mucosal PG synthesis. Direct irritation occurs because NSAIDs are weak acids. Less acidic agents, such as nonacetylated salicylates, may confer decreased GI toxicity.[16] Direct irritant effects contribute to NSAID-induced gastritis but play a minor role in the development of NSAID-induced PUD.

Systemic inhibition of PG synthesis is the primary means by which NSAIDs cause PUD. NSAID inhibition of PG production by blocking the cyclooxygenase-2 (COX-2) enzyme produces beneficial analgesic and anti-inflammatory effects. However, NSAIDs may also block the COX-1 enzyme, which produces PGs that provide gastroprotection. NSAIDs given parenterally (eg, ketorolac) and rectally (eg, indomethacin) have an incidence of PUD similar to oral NSAIDs. Topical NSAIDs (eg, diclofenac) are unlikely to cause PUD because very low serum concentrations are achieved. The antiplatelet effects of NSAIDs may worsen bleeding complications associated with PUD.

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

See text box for the clinical presentation of PUD. Dyspepsia (upper abdominal discomfort) is found in 10% to 40% of the general population. PUD is found in 5% to 15% of patients with dyspepsia.

PUD can be classified as uncomplicated or complicated. Uncomplicated disease is typically characterized by mild epigastric pain, whereas complicated disease involves acute upper GI complications such as GI bleeding, obstruction, or perforation. Bleeding may be occult or may present as **melena** or **hematemesis**. Up to 20% of patients who develop a PUD-related hemorrhage do not have prior symptoms. Gastric outlet obstruction is usually caused by ulcer-related inflammation or scar formation. Patients typically present with early satiety after meals, nausea, vomiting, abdominal pain, and weight loss. Perforation requires emergent surgical intervention, and these patients should not undergo endoscopy.

Diagnosis

Radiologic and/or endoscopic procedures are usually required to document the presence of ulcers. Because endoscopic testing is invasive and expensive, it is only indicated in patients 60 years of age or older with new-onset dyspepsia.[17] Patients with dyspepsia who are younger than 60 years may forego endoscopy but should be tested for *H. pylori* using noninvasive testing and treated if positive.[17] Those who test negative for *H. pylori* should be offered a trial (4–8 weeks) of acid suppression therapy or proceed to endoscopy. Persistent dyspepsia despite a trial of acid suppressive therapy warrants upper endoscopy evaluation.[1]

Testing for *H. pylori* infection is indicated in patients with active PUD, history of documented PUD, low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or history of endoscopic resection of early gastric cancer.[18] Diagnostic tests to detect *H. pylori* presence can be either endoscopic or nonendoscopic.[15,18] Endoscopic diagnosis involves extraction of gastric tissue samples that are subsequently tested for *H. pylori*.[18] Histology is the standard identification method, but culture, polymerase chain reaction (PCR), and the rapid urease test can also identify *H. pylori* in tissue samples.[19]

Nonendoscopic testing methods for *H. pylori* include the urea breath test, serologic testing, and stool antigen assay.[15,18] These tests are less invasive and less expensive than endoscopy. The urea breath test is usually first line because of its high sensitivity and specificity and short turnaround time.[19] Concomitant acid-suppressive or antibiotic therapy may give false-negative results.[19] The urea breath test can also be used to confirm eradication of *H. pylori* infection.[19]

Serologic testing provides a quick (within 15 minutes) office-based assessment of exposure to *H. pylori*, but it cannot differentiate active infection from previously treated infection; patients can remain **seropositive** for years after eradication. Serologic testing is also less sensitive and specific than the urea breath test.[15] Serologic testing is recommended in patients with recent or current antibiotic or acid-suppressive therapy.[19]

Stool antigen assays can be useful for initial diagnosis or to confirm *H. pylori* eradication. They have high sensitivity and specificity and are affected less by concomitant medication use.[15] Use of antimicrobial agents within 4 weeks, PPIs within 2 weeks, and histamine-2 receptor antagonists (H_2RAs) within 24 hours of testing can suppress the infection and reduce the sensitivity of testing.[15]

TREATMENT

The treatment selected for PUD depends on the etiology of the ulcer, whether the ulcer is new or recurrent, and whether complications have occurred. **Figure 18–2** shows an algorithm for evaluation and treatment of a patient with signs and symptoms suggestive of an *H. pylori*–associated or NSAID-induced ulcer.

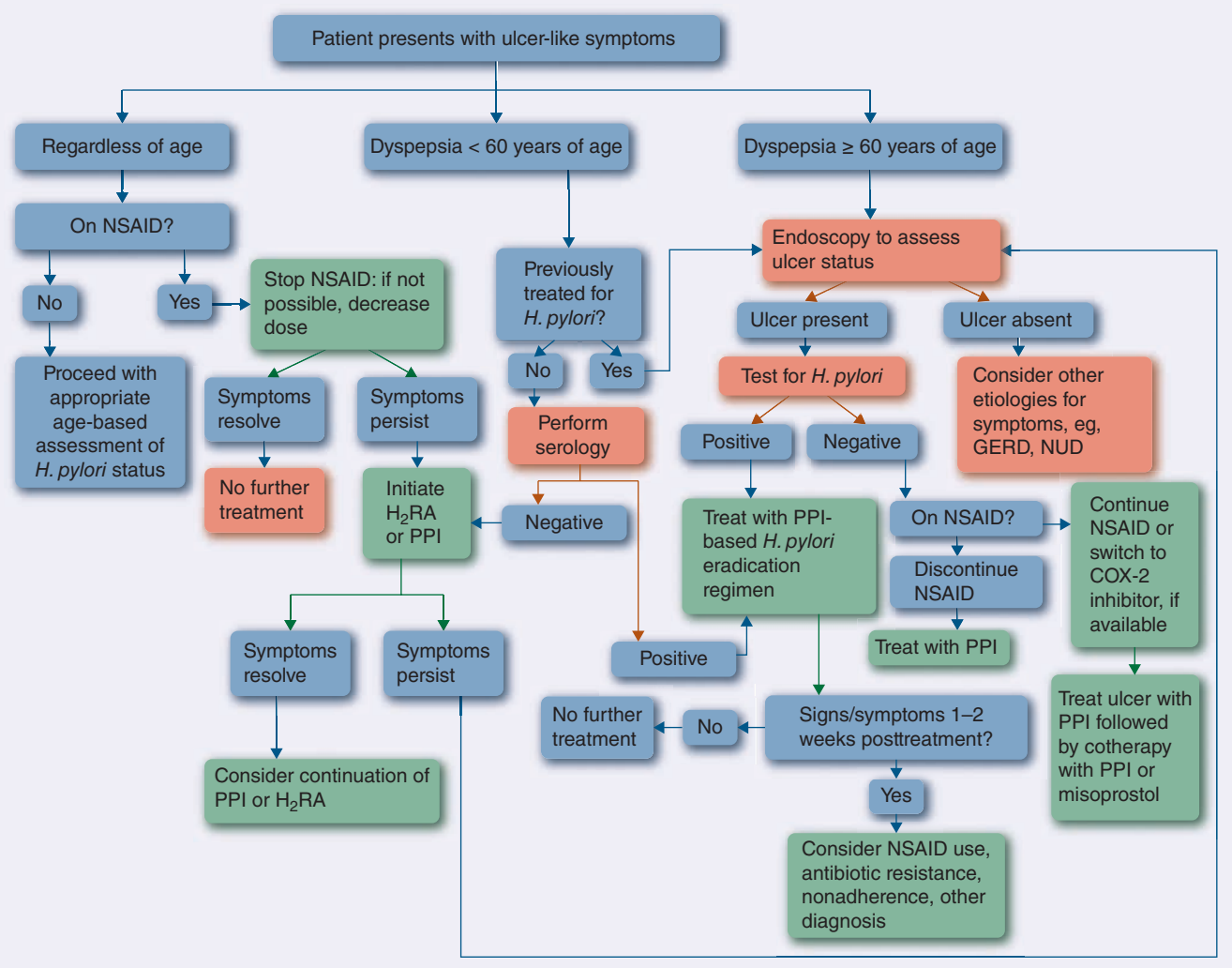
Clinical Presentation of PUD

Symptoms

- Dyspepsia and mild epigastric pain that may be described as burning, gnawing, or aching in character.
- Epigastric pain with DUs typically occurs 1 to 3 hours after meals or at night and is often relieved by food.
- Pain with GUs is often aggravated by food.
- Abdominal pain may be described as burning or a feeling of discomfort.
- Pain severity often fluctuates and the character can vary from dull to sharp.
- Patients may also complain of heartburn, belching, bloating, nausea, or vomiting.

Signs

- Weight loss may be associated with nausea and vomiting.
- Complications such as bleeding, perforation, or obstruction may occur.
- Alarm findings include family history of upper GI malignancy, unintentional weight loss, overt GI bleeding, iron deficiency anemia, progressive dysphagia or odynophagia, early satiety, persistent vomiting, palpable mass, or lymphadenopathy.



LO 5 **FIGURE 18–2.** Guidelines for the evaluation and management of a patient who presents with dyspeptic or ulcer-like symptoms. (COX-2, cyclooxygenase-2; GERD, gastroesophageal reflux disease; H_2RA, H_2-receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor.) (Adapted from Love BL, Mohorn PL. Peptic ulcer disease. In: DiPiro JT, Talbert RA, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017, with permission. www.accesspharmacy.com.)

LO 2

Desired Outcomes

The goals of PUD therapy are to resolve symptoms, reduce acid secretion, promote epithelial healing, prevent ulcer-related complications, and prevent ulcer recurrence. For *H. pylori*–related PUD, eradication of *H. pylori* is an additional outcome.

Nonpharmacologic Therapy

▶ *Risk Factor Avoidance*

KEY CONCEPT Patients with PUD should avoid exposure to factors known to worsen the disease, exacerbate symptoms, or lead to ulcer recurrence. Patients should be advised to reduce psychological stress and avoid cigarette smoking, alcohol consumption, and NSAID or aspirin use if possible. Patients who require chronic NSAID therapy (eg, for rheumatoid arthritis) may be given prophylaxis with misoprostol or a PPI (see Prevention of NSAID-Induced Ulcers section).

▶ *Surgery*

The high success rates of medical therapies have reduced the need for surgical procedures. Elective surgeries performed for PUD have decreased by more than 70% since the 1980s mainly due to *H. pylori* eradication.[20] Surgical interventions are generally reserved for complicated or refractory PUD.

For patients with acute GI bleeding, endoscopic hemostasis can be achieved using contact thermal therapy, mechanical therapy using clips, or epinephrine injection followed by either thermal or mechanical therapy.[21] Angiography with embolization of bleeding lesions can be used if the bleeding cannot be stopped endoscopically and the patient is either high risk for surgery or not a surgical candidate.[22]

Pharmacologic Therapy

▶ *Treatment of* H. pylori*–Associated Ulcers*

The goal of *H. pylori* therapy is to eradicate the organism using an effective antibiotic-containing regimen. KEY CONCEPT Reliance on conventional acid-suppressive drug therapy alone as an alternative to H. pylori eradication is inappropriate because it is associated with a higher incidence of ulcer recurrence and ulcer-related complications. Reinfection rates are generally low after the initial course of therapy as long as the patient was

adherent. In addition to proven efficacy, the optimal treatment regimen should cause minimal adverse events, have low risk for development of bacterial resistance, and be cost-effective.[15,18]

LO 3

H. pylori treatment regimens are presented in Table 18–2. KEY CONCEPT Eradication therapy should be pursued in all patients who test positive for *H. pylori* infection. Several regimens are recommended as first-line eradication therapy. Different antibiotics should be used if a second course of *H. pylori* eradication therapy is required. The cure rates of *H. pylori* with H_2RAs in combination with antibiotics are lower than with PPIs.[18]

Important considerations in selecting first-line treatment regimens include presence of a penicillin allergy and previous exposure to macrolide antibiotics. Acceptable first-line regimens that carry strong recommendations include bismuth quadruple therapy as well as concomitant therapy. Other acceptable regimens for first-line treatment with weak recommendations include: (1) clarithromycin triple therapy in regions with clarithromycin resistance less than 15% when a patient has no previous macrolide exposure, (2) sequential therapy, (3) hybrid therapy, (4) levofloxacin triple therapy, and (5) fluoroquinolone sequential therapy. Substitution of one PPI for another is acceptable and does not affect eradication rates. Alcohol consumption must be considered prior to selecting a metronidazole containing treatment regimen.[18]

The duration of therapy for *H. pylori* eradication is controversial; US guidelines recommend either 10 or 14 days.[18] Compared with 7 days of triple therapy, a 10-day duration increases eradication rates by 4% and 14 days increases eradication rates by 5% to 12%.[26] Longer treatment courses may decrease adherence and increase drug costs; ultimately, the most effective eradication regimens still fail in 10% to 20% of patients.[11]

Bismuth-based four-drug regimens have clinical cure rates similar to three-drug PPI-based regimens.[25] Bismuth salts promote ulcer healing through antibacterial and mucosal protective effects. Disadvantages of bismuth-based regimens include frequency of administration (four times a day), risk for salicylate toxicity in renal impairment, and bothersome side effects (eg, stool and tongue discoloration, constipation, nausea, vomiting).[11]

Pylera™ and PrevPac® are proprietary products designed to improve regimen adherence (Table 18–2). Pylera™ is a combination product, whereas PrevPac® is a conveniently packaged eradication regimen. Both products are substantially more expensive than their individual generic and nonprescription components.

Recent literature has indicated a potential role for probiotics in first-line treatment of *H. pylori*. These data associated probiotic therapy with increased cure rates and reduced side effects compared to conventional eradication regimens. However, further study is needed due to limitations of the available evidence. Current guidelines reinforce several areas for additional research regarding optimal dosing of probiotic therapy.[18]

Patients may remain infected with *H. pylori* after the initial treatment course because of reinfection, nonadherence, or antimicrobial resistance. Factors associated with decreased adherence include polypharmacy, need for frequent drug administration or long treatment duration, and use of drugs that may cause intolerable side effects. Potential adverse drug effects include taste disturbances (clarithromycin and metronidazole), nausea, vomiting, abdominal pain, and diarrhea. Superinfections with oral thrush or vaginal candidiasis can occur. Alcohol should be avoided during treatment with metronidazole or tinidazole due to the potential for a disulfiram-like reaction.

Resistance data for *H. pylori* in the United States are limited. Recent data from a Veterans Affairs Medical Center demonstrated

Table 18–2

Drug Regimens to Eradicate *Helicobacter pylori*

Treatment Regimen	Medications	Duration
Clarithromycin triple therapy	Clarithromycin 500 mg BID + amoxicillin 1 g BID OR metronidazole 500 mg TID + PPI BID	14 days
Bismuth quadruple therapy[a]	Bismuth subsalicylate 300 mg QID + metronidazole 250–500 mg QID + tetracycline 500 mg QID + PPI BID	10–14 days
Concomitant[a] therapy	Clarithromycin 500 mg BID + amoxicillin 1 g BID + nitroimidazole[c] 500 mg BID + PPI BID	10–14 days
Sequential therapy	Amoxicillin 1 g BID + PPI BID followed by clarithromycin 500 mg BID + nitroimidazole[c] 500 mg BID + PPI BID	5–7 days 5–7 days
Hybrid therapy	Amoxicillin 1 g BID + PPI BID followed by amoxicillin 1 g BID + clarithromycin 500 mg BID + nitroimidazole[c] 500 mg BID + PPI BID	7 days 7 days
Levofloxacin triple therapy	Levofloxacin 500 mg daily + amoxicillin 1 g BID + PPI BID	10–14 days
Levofloxacin sequential therapy	Amoxicillin 1 g BID + PPI BID followed by amoxicillin 1 g BID + levofloxacin 500 mg daily + nitroimidazole[c] 500 mg BID + PPI BID	5–7 days 5–7 days
Rifabutin triple therapy[b]	Rifabutin 300 mg daily + amoxicillin 1 g (BID or TID)[d] + PPI BID	10 days
High-dose dual therapy	Amoxicillin (1 g TID or 750 mg QID) + PPI (TID or QID)	14 days
Combination Therapies		
PREVPAC®	Clarithromycin 500 mg BID + amoxicillin 1 g BID + lansoprazole 30 mg BID (contained in blister pack cards)	10–14 days
Pylera™	(Bismuth subcitrate potassium 140 mg + metronidazole 125 mg + tetracycline 125 mg) three capsules QID + omeprazole 20 mg BID	10 days

[a]Regimens with strong recommendation based on current guidelines.

[b]Salvage regimen only.

[c]Metronidazole or tinidazole.

[d]Dosing varied in clinical trials.

BID, twice daily; H_2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; QID, four times daily; TID, three times daily.

From Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: treatment of Helicobacter pylori infection. Am J Gastroenterol. 2017;112:212–238.

Patient Encounter 1

A 62-year-old man presents with abdominal pain and heartburn that occur two to three times per week. He also reports a 10-pound (4.5-kg) weight loss in the last 6 weeks, despite not dieting or increasing physical activity. He does not report any recent antibiotic use.

PMH: Hypertension × 5 years

FH: Mother alive at 84 with hypertension, type 2 diabetes; father deceased at 68 following MI

SH: Smokes half pack per day; no alcohol or illicit drug use

Allergies: Penicillin

Meds: Lisinopril/hydrochlorothiazide 20/25 mg daily, acetaminophen 500 mg as needed for headache

Based on this patient's clinical presentation, what is the most appropriate course of action to establish a diagnosis?

The patient receives a diagnosis of H. pylori *infection based on the diagnostic method recommended. What eradication therapy would you recommend?*

The patient completed the course of eradication therapy recommended; however, he returns with similar symptoms 3 months later. What regimen would you recommend for eradication therapy?

Patient Encounter 2

A 52-year-old man presents with persistent epigastric pain and heartburn. His chief complaint today is, "I think my ulcer is back again!"

PMH: Hypertension × 2 years

FH: Mother deceased at age 70, cancer; father alive with hypertension, dyslipidemia

SH: Nonsmoker, 1 to 2 alcoholic beverages three times weekly, no illicit drug use

Allergies: NKDA

Meds: Hydrochlorothiazide 25 mg daily, amlodipine 5 mg daily

The patient previously completed the following courses for *H. pylori* eradication:

- Clarithromycin 500 mg + amoxicillin 1 g + lansoprazole 30 mg, each given twice daily
- Pylera + omeprazole 20 mg twice daily for 10 days

H. pylori recurrence is confirmed with a urea breath test.

Discuss possible reasons for treatment failure in this patient.

What regimen would you recommend for salvage eradication therapy?

clarithromycin resistance rates exceeding the threshold for use in current guidelines. A threshold of 15% to 20% is recommended to differentiate between regions of high and low clarithromycin resistance. In the setting of resistance, efficacy of a three-drug regimen containing clarithromycin can decrease to 10% to 30%. Culture and sensitivity tests are not routinely performed with *H. pylori* infection unless a patient has already failed two different treatment regimens; these tests are also not widely available in the United States.[18,26]

Initiation of a second *H. pylori* treatment regimen after failure of initial treatment is usually associated with a lower success rate. Reasons for failure are often the same as failure of the initial regimen. Selection of a salvage treatment regimen should be based on the initial treatment the patient received, history of quinolone exposure, and penicillin allergy status.

- If clarithromycin triple therapy was used as the initial treatment regimen and the patient is not penicillin allergic, recommended salvage therapies include: (1) bismuth quadruple therapy, (2) levofloxacin triple therapy, (3) rifabutin triple therapy, or (4) high-dose dual therapy. For patients who received initial clarithromycin triple therapy and are penicillin allergic, bismuth quadruple therapy is recommended.
- When bismuth quadruple therapy was the initial treatment regimen and the patient is not penicillin allergic, recommended salvage regimens include: (1) levofloxacin triple therapy, (2) concomitant therapy, (3) rifabutin triple therapy, or (4) high-dose dual therapy. Levofloxacin triple therapy should be avoided in patients with previous quinolone exposure. Salvage regimens are less well defined for patients who received bismuth quadruple therapy as initial treatment and are penicillin allergic. There is no standard third-line therapy for *H. pylori* treatment.[18]

LO 6 Confirmation of *H. pylori* infection eradication is recommended in all treated patients.[18] Testing should occur at least 4 weeks after completion of the eradication regimen and 1 to 2 weeks after discontinuation of PPI.[18] Eradication may be confirmed by either the urea breath test or stool antigen testing. Eradication may also be confirmed by endoscopy, but this should only be done when endoscopy is required because it is more expensive and invasive.[15]

► Treatment of NSAID-Induced Ulcers

LO 4

Treatment recommendations to heal NSAID-induced ulcers or provide maintenance therapy in patients receiving NSAIDs are shown in Table 18–3. Choice of regimen depends on whether NSAID use is to be continued. NSAIDs should be discontinued and replaced with alternatives (eg, acetaminophen), when possible. For patients who cannot discontinue NSAID therapy, PPIs, H_2RAs, or sucralfate are effective for ulcer healing and to prevent further recurrences.[11] PPIs are usually preferred because they provide more rapid relief of symptoms, have the strongest acid suppression, and heal ulcers more quickly than H_2RAs or sucralfate.[11] Standard doses of H_2RAs effectively heal DUs but are minimally effective in GUs. A PPI provides equivalent efficacy with treatment duration of only 4 weeks. PPI therapy should only be continued for longer than 4 weeks if an ulcer is confirmed to still be present or if the patient develops severe complications from PUD.

► Prevention of NSAID-Induced Ulcers

Prophylactic regimens against PUD are often required in patients receiving long-term NSAID or aspirin therapy for osteoarthritis, rheumatoid arthritis, or cardioprotection.[27] Misoprostol, H_2RAs, PPIs, and COX-2 selective inhibitors have been evaluated in controlled trials to reduce the risk of NSAID-induced PUD. KEY CONCEPT In patients at risk for NSAID-induced ulcers, PPIs at standard doses reduce the risk of both gastric and DUs as effectively as misoprostol and more effectively than H_2RAs. In addition, PPIs are generally better tolerated than misoprostol.

Table 18–3

Oral Drug Regimens to Heal Peptic Ulcers or Maintain Ulcer Healing in the Absence of Antibiotic Therapy

Drug	DU or GU Healing (mg/day)	Maintenance of DU or GU Healing (mg/day)
Mucosal Protectant		
Sucralfate	1 g four times a day 2 g two times a day	1 g four times a day 1–2 g two times a day
H_2-Receptor Antagonists		
Cimetidine	300 mg four times a day 400 mg two times a day 800 mg at bedtime	400–800 mg daily
Famotidine	20 mg two times a day 40 mg at bedtime	20–40 mg daily
Nizatidine	150 mg two times a day 300 mg at bedtime	150–300 mg daily
Ranitidine	150 mg two times a day 300 mg at bedtime	150–300 mg daily
Proton Pump Inhibitors		
Dexlansoprazole	30–60 mg daily	30–60 mg daily
Esomeprazole	20–40 mg daily	20–40 mg daily
Lansoprazole	15–30 mg daily	15–30 mg daily
Omeprazole	20–40 mg daily	20–40 mg daily
Pantoprazole	40 mg daily	40 mg daily
Rabeprazole	20 mg daily	20 mg daily

DU, duodenal ulcer; GU, gastric ulcer.

Misoprostol A synthetic prostaglandin E1 (PGE_1) analog that exogenously replaces PG stores, misoprostol is indicated for reducing the risk of NSAID-induced GUs in patients at high risk of complications from ulcers (eg, the elderly and patients with concomitant debilitating disease), as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcers. Misoprostol 200 mcg four times a day reduces ulcer complications by inhibiting acid secretion and promoting mucosal defense. It is superior to H_2RAs for prevention of NSAID-induced ulcers.[28] Misoprostol use is limited by a high frequency of bothersome GI effects such as abdominal pain, flatulence, and diarrhea, and it is contraindicated in pregnancy due to potential abortifacient effects. Arthrotec is a combination product that contains diclofenac (either 50 or 75 mg) and misoprostol 200 mcg in a single tablet.

H_2-Receptor Antagonists The efficacy of H_2RAs (eg, famotidine 40 mg daily) in preventing NSAID-related ulcers varies. DUs appear to respond better than GUs (the most frequent type of ulcer associated with NSAIDs). Higher doses of H_2RAs (eg, famotidine 40 mg twice daily) may reduce the risk of NSAID-induced gastric and DUs, but results from clinical trials are variable.

Duexis™, a prescription combination product containing ibuprofen 800 mg and famotidine 26.6 mg, is indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper GI ulcers. The recommended dosage is one tablet orally three times daily. Clinical trials evaluating this agent are 6 months or less in duration and primarily evaluated patients younger than 65 years with no ulcer history.

Proton Pump Inhibitors PPI therapy is more effective than H_2RAs in reducing the risk of nonselective NSAID-related gastric and DUs.[28] PPIs are as effective as misoprostol but better tolerated. All PPIs are effective when used in standard doses. In patients who experience a PUD-related bleeding event while taking aspirin but who require continued aspirin therapy, the addition of a PPI reduces the incidence of recurrent GI bleeding.[29] Prevacid NapraPAC™ provides naproxen (either 250, 375, or 500 mg) and lansoprazole 15 mg in individual blister packages. Vimovo™ provides naproxen (either 375 or 500 mg) and esomeprazole 20 mg in each tablet.

COX-2 Selective Inhibitors NSAIDs with COX-2 selectivity were developed in an attempt to reduce the incidence of PUD and its complications. KEY CONCEPT However, selective COX-2 inhibitors are no more effective than the combination of a PPI and a nonselective NSAID in reducing the incidence of ulcers. Celecoxib is the only agent in this class available in the United States. There was no difference in cardiovascular outcomes when celecoxib was compared to ibuprofen and naproxen.[30,31]

Sucralfate This drug is a negatively charged, nonabsorbable agent that forms a complex by binding with positively charged proteins in exudates, forming a viscous, paste-like adhesive substance that protects the ulcerated area of the gastric mucosa against gastric acid, pepsin, and bile salts.[16] Limitations of sucralfate include the need for multiple daily dosing, large tablet size, and interaction with a number of other medications (eg, digoxin and fluoroquinolones).

Adverse effects of sucralfate include constipation, nausea, metallic taste, and the possibility for aluminum toxicity in patients with renal failure. Sucralfate is effective in the treatment of NSAID-related ulcers when the NSAID will be stopped, but it is not recommended for NSAID-related ulcer prophylaxis.

▶ *Prevention of Stress-Related Mucosal Damage*

Prevention of stress ulcers involves maintaining hemodynamic stability to maximize mesenteric perfusion and pharmacologic suppression of gastric acid production. Stress ulcer prophylaxis (SUP) is only indicated in intensive care unit (ICU) patients with certain risk factors (see Table 18–4).[9,32] The clinician must weigh the risks and benefits of using acid suppression, especially PPIs, in low-risk patients. PPIs and H_2RAs are the drugs of choice for SUP; however, antacids and sucralfate may be acceptable options in some patients.

▶ *Long-Term Maintenance of Ulcer Healing*

KEY CONCEPT Low-dose maintenance therapy with a PPI or H_2RA is only indicated in patients with severe complications secondary to PUD such as gastric outlet obstruction or patients who need to be on long-term NSAIDs or high-dose corticosteroids and are at high risk for bleeding. Drug regimens and doses for PUD treatment and maintenance are presented in Table 18–3.

▶ *Treatment of GI Bleeding*

The immediate priorities in treating patients with a bleeding peptic ulcer are to achieve IV access, correct fluid losses, and restore hemodynamic stability. Insertion of a nasogastric tube is helpful in initial patient assessment, but the absence of bloody or coffee-ground material does not definitively rule out ongoing or recurrent bleeding; about 15% of patients without bloody nasogastric tube output have a high-risk lesion at endoscopy.[21]

Patients should be started on IV PPI therapy because optimal platelet aggregation, partially inhibited fibrinolysis, and better

Table 18–4

Appropriate Indications for Stress Ulcer Prophylaxis in Intensive Care Unit Patients

- Mechanical ventilation for longer than 48 hours
- Coagulopathy or hepatic failure (platelet count < 50 × 10^3/mm^3 [50 × 10^9/L], INR > 1.5, or aPTT > two times control)
- History of GI ulceration or bleeding within 1 year of admission
- Head trauma or Glasgow Coma Score of 10 or less (or inability to obey simple commands)
- Thermal injuries to more than 35% of body surface area
- Multiple traumas (injury severity score of 16 or greater)
- Partial hepatectomy
- Transplant patients in the ICU perioperatively
- Spinal cord injuries
- Two of the following risk factors: sepsis, ICU stay for more than 1 week, occult bleeding lasting 6 or more days, and use of high-dose corticosteroids (> 250 mg/day of hydrocortisone or equivalent)

GI, gastrointestinal; ICU, intensive care unit; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

Data from Quenot JP, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU? Curr Opin Crit Care. 2009;15:139–143 and Nissen SE, Yeomans ND, Solomon DH. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375:2519–2529.

clot stabilization on the ulcer are achieved when the gastric pH is greater than 6.[33] IV PPI therapy should be continued for 72 hours (because most rebleeding occurs during this time) followed by oral PPI therapy. Three-day PPI infusion therapy has been shown to be as effective as twice-daily IV PPI therapy.[33]

▶ *Treatment of Refractory Ulcers*

Refractory ulcers are defined as ulcers that fail to heal despite 8 to 12 weeks of acid suppressive therapy.[1] The presence of refractory ulcers requires a thorough assessment, including evaluation of medication adherence, extensive counseling and questioning regarding recent over-the-counter and prescription medication use, and testing for *H. pylori* using a different method than previously done if testing was negative. Changing from H_2RA therapy to a PPI should be considered.[16] Other considerations include esophagogastroduodenoscopy (EGD) with biopsy of the ulcer to exclude malignancy, *H. pylori* testing (if not done initially), serum gastrin measurement to exclude ZES, and gastric acid studies.

OUTCOME EVALUATION

- Obtain a baseline complete blood count (CBC). Recheck the CBC if the patient exhibits alarm signs or symptoms.
- Obtain a baseline serum creatinine measurement. Calculate the estimated creatinine clearance and adjust the dose of H_2RAs and sucralfate if needed.
- Obtain a history of symptoms from the patient. Monitor for improvements in pain symptoms (eg, epigastric or abdominal pain) daily.
- Monitor the patient for the development of any alarm signs and symptoms.
- Recommend a follow-up visit if signs and symptoms worsen at any time or do not improve within the defined treatment period.
- Assess for potential drug interactions whenever there is a change in the patient's medications.

Patient Encounter 3

A 68-year-old woman presents with reports of dark, tarry stools for 3 days. She denies coffee-ground emesis or recent weight loss but reports occasional abdominal pain.

PMH: Hypertension × 10 years, type 2 diabetes × 5 years, dyslipidemia × 5 years, osteoarthritis × 3 years

FH: Parents deceased; mother with stroke at age 82, father with MI at age 74; one sister alive at 74 with hypertension, type 2 diabetes, and dyslipidemia

SH: Smokes one pack per day, denies alcohol or illicit drug use

Allergies: NKDA

Meds: Lisinopril 40 mg daily, amlodipine 5 mg daily, metformin 1000 mg twice daily, glipizide 10 mg twice daily, simvastatin 40 mg daily, ibuprofen 800 mg three times daily, aspirin 81 mg daily, Tums™ Extra Strength as needed for dyspeptic symptoms

Other: An endoscopy reveals a duodenal ulcer that is negative for *H. pylori*

What risk factors does this patient have for GI complications related to NSAID use?

Make a recommendation for treatment of this patient's ulcer.

Discuss the use of prophylactic therapy in this patient after the treatment course is completed.

Patient Encounter 4

A 55-year-old man is brought to the surgical ICU after emergency surgery following a motor vehicle accident. The physician would like him to remain NPO (nothing by mouth except for medications) for at least several days until he improves clinically and can sit up in bed.

PMH: Type 2 diabetes × 5 years, dyslipidemia × 5 years, hypothyroidism × 2 years

FH: Father with type 2 diabetes

SH: Nonsmoker; 1 drink 1–2 times weekly; no illicit drug use

Allergies: NKDA

Meds: Atorvastatin 20 mg daily, metformin 500 mg twice daily, levothyroxine 75 mcg daily, aspirin 81 mg daily, ibuprofen 800 mg alternating with oxycodone 5 mg/acetaminophen 325 mg two tablets every 8 hours for surgical site pain

Based on this patient's clinical presentation, is he a candidate for stress ulcer prophylaxis?

What pharmacologic therapy would you recommend for this patient?

Two days later, the patient is transferred to a general medicine floor and begins a regular diet that is well tolerated. Ibuprofen has been discontinued, and he is alternating between oxycodone/acetaminophen and acetaminophen alone to relieve incision site pain. He is sitting up in bed and feeling much better. Is this patient still a candidate for stress ulcer prophylaxis?

Patient Care Process: Peptic Ulcer Disease

Collect Information:

- Obtain a history of prescription and over-the-counter medications and dietary supplements.
- Verify patient allergies and intolerances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on review of signs and symptoms and assessment of risk factors (Table 18–1), determine whether the patient is experiencing signs or symptoms of PUD.
- Review available diagnostic tests (eg, serologic testing, urea breath test, stool antigen assay, endoscopy) to determine etiology of peptic ulcer.
- If patient is already receiving pharmacotherapy, assess its efficacy, safety, and patient adherence.

Assess the potential for drug interactions, particularly in patients taking regimens containing metronidazole, clarithromycin, or cimetidine.

Develop a Care Plan:

- If patient has been diagnosed with a peptic ulcer, determine which course of therapy is indicated.
- Recommend an appropriate regimen (Tables 18–2 and 18–3) that will eradicate *H. pylori* and/or heal the peptic ulcer.
- Avoid drug classes to which the patient is allergic.
- If the patient has been treated for *H. pylori* previously, recommend different antibiotics if this episode is a result of treatment failure.
- Evaluate patient accessibility to medication (eg, formulary status, insurance coverage).

Implement the Care Plan:

- Inform patient about potential adverse drug effects and drug interactions.
- Educate the patient on the importance of adherence to eradication and ulcer-healing therapy.
- Identify appropriate lifestyle modifications.

Follow-up: Monitor and Evaluate:

- Assess patient adherence and progress toward efficacy and safety goals.
- Monitor annually for signs and symptoms of complications such as unintentional weight loss or bleeding.
- Evaluate the need for a prophylactic acid suppressive regimen in patients requiring chronic NSAID therapy.

- Educate the patient on the importance of adhering to the *H. pylori* eradication regimen.
- Monitor the patient for complications related to antibiotic therapy (eg, diarrhea or oral thrush) during and after completion of *H. pylori* eradication therapy.
- Recommend follow-up care if the patient's signs and symptoms do not improve after completion of *H. pylori* eradication therapy.

Abbreviations Introduced in This Chapter

COX	Cyclooxygenase
DU	Duodenal ulcer
EGD	Esophagogastroduodenoscopy
GI	Gastrointestinal
GU	Gastric ulcer
H_2RA	Histamine-2 receptor antagonist
INR	International normalized ratio
MALT	Mucosa-associated lymphoid tissue
NSAID	Nonsteroidal anti-inflammatory drug
NUD	Nonulcer dyspepsia
PG	Prostaglandin
PGE_1	Prostaglandin E1
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease
SRMD	Stress-related mucosal damage
SUP	Stress ulcer prophylaxis
ZES	Zollinger–Ellison syndrome

REFERENCES

1. Banerjee S, Cash BD, Dominitz JA, et al. The role of endoscopy in the management of patients with peptic ulcer disease. Gastrointest Endosc. 2010;71:663–668.
2. Vakil N. Peptic ulcer disease. In: Feldman M, Friedman LW, Brandt L, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th ed. Philadelphia, PA: Saunders; 2010: 861–868.
3. Hunt RH, Xiao SD, Megraud F, et al. World Gastroenterology Organisation Global Guideline: *Helicobacter pylori* in developing countries. J Clin Gastroenterol. 2011;45:383–388.
4. Del Valle J. Peptic ulcer disease and related disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 19th ed. New York, NY: McGraw-Hill; 2014.
5. Joish VN, Donaldson G, Stockdale W, et al. The economic impact of GERD and PUD: examination of direct and indirect costs using a large integrated employer claims database. Curr Med Res Opin. 2005;21:535–544.
6. Chan FK, Graham DY. Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications—review and recommendations based on risk assessment. Aliment Pharmacol Ther. 2004;19:1051–1061.
7. Lanas A, Chan FKL. Peptic ulcer disease. Lancet. 2017;390:613–624.
8. Fashner J, Gitu AC. Diagnosis and treatment of peptic ulcer disease and *H. pylori* infection. Am Fam Physician. 2015;91(4):236–242.

9. Quenot JP, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU? Curr Opin Crit Care. 2009;15:139–143.
10. American Society of Health-System Pharmacists: ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. Am J Health Syst Pharm. 1999;56:347–379.
11. Malfertheiner P, Chan F, McColl K. Peptic ulcer disease. Lancet. 2009;374:1449–1461.
12. Zhang L, Ren JW, Wong CCW, et al. Effects of cigarette smoke and its active components on ulcer formation and healing in the gastrointestinal mucosa. Curr Med Chem. 2012;19:63–69.
13. Schubert ML, Kaunitz JD. Gastric secretion. In: Feldman M, Friedman LW, Brandt L, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th ed. Philadelphia, PA: Saunders; 2010:817–832.
14. Semrin MG, Russo MA. Anatomy, histology, embryology, and developmental anomalies of the stomach and duodenum. In: Feldman M, Friedman LW, Brandt L, eds. Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th ed. Philadelphia, PA: Saunders; 2010:773–788.
15. McColl KE. *Helicobacter pylori* infection. N Engl J Med. 2010;362:1597–1604.
16. Berardi R, Fugit R. Peptic ulcer disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014:471–495.
17. Moayyedi PM, Lacey BE, Andrews CN, et al. ACG and CAG clinical guideline: management of dyspepsia. Am J Gastroenterol. 2017;112:988–1013.
18. Chey WD, Leontiadis GI, Howden CW, et al. ACG Clinical Guideline: treatment of *Helicobacter pylori* infection. Am J Gastroenterol. 2017;112:212–238.
19. Garza Gonzalez E, Perez-Perez GI, Maldonado-Garza HJ, Bosque-Padilla FJ. A review of Helicobacter pylori diagnosis, treatment, and methods to detect eradication. World J Gastroenterol. 2014;20(6):1438–1449.
20. Bertleff MJ, Lange JF. Perforated peptic ulcer disease: a review of history and treatment. Dig Surg. 2010;27:161–169.
21. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. N Engl J Med. 2008;359:928–937.
22. Wong TCI, Wong KT, Chiu PWY, et al. A comparison of angiographic embolization with surgery after failed endoscopic hemostasis to bleeding peptic ulcers. Gastrointest Endosc. 2011;73:900–908.
23. Ikenberry SO, Harrison ME, Lichtenstein D, et al. The role of endoscopy in dyspepsia. Gastrointest Endosc. 2007;66:1071–1075.
24. Fuccio L, Minardi ME, Zagari RM, et al. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for *Helicobacter pylori* eradication. Ann Intern Med. 2007;147:553–562.
25. Venerito M, Krieger T, Ecker T, et al. Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of Helicobacter pylori infection. Digestion. 2013;88:33–45.
26. Malfertheiner P, Megraud F, O'Morain CA, et al. Management of Helicobacter pylori infection—the Maastricht IV/Florence Consensus Report. Gut. 2012;61:646–664.
27. Targownik LE, Metge CJ, Leung S, Chateau DG. The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. Gastroenterology. 2008;134:937–944.
28. Lanza FL, Chan FKL, Quigley EMM, et al. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728–738.
29. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 Expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Am J Gastroenterol. 2008;103:2890–2907.
30. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ. 2017;357:j1909.
31. Nissen SE, Yeomans ND, Solomon DH. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375:2519–2529.
32. Grube RA, May B. Stress ulcer prophylaxis in hospitalized patients not in intensive care units. Am J Health Syst Pharm. 2007;64:1396–1400.
33. Songür Y, Balkarli A, Acartürk G, Senol A. Comparison of infusion or low-dose proton pump inhibitor treatments in upper gastrointestinal system bleeding. Eur J Intern Med. 2011;22:200–204.

19 Inflammatory Bowel Disease

Brian A. Hemstreet

LEARNING OBJECTIVES

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

LO

1. Characterize the pathophysiologic mechanisms underlying inflammatory bowel disease (IBD).
2. Recognize the signs and symptoms of IBD, including major differences between ulcerative colitis (UC) and Crohn disease (CD).
3. Identify appropriate therapeutic outcomes for patients with IBD.
4. Describe pharmacologic treatment options for patients with acute or chronic symptoms of UC and CD.
5. Create a patient-specific drug treatment plan based on symptoms, severity, and location of UC or CD.
6. Recommend appropriate monitoring parameters and patient education for drug treatments for IBD.

INTRODUCTION

KEY CONCEPT The term inflammatory bowel disease (IBD) encompasses ulcerative colitis (UC) and Crohn disease (CD). Both disorders are associated with acute and chronic inflammation of the gastrointestinal (GI) tract. Differences exist between UC and CD with regard to regions of the GI tract that may be affected and the distribution and depth of intestinal inflammation. Patients with IBD may also develop inflammation involving organs other than the GI tract, known as extraintestinal manifestations. Symptoms of IBD are associated with significant morbidity, reduction in quality of life, and costs to the health care system.[1–6]

EPIDEMIOLOGY AND ETIOLOGY

IBD is most common in Western countries such as the United States and Northern Europe. The age of initial presentation is bimodal, with patients typically diagnosed between the ages of 20 and 40 or 60 and 80 years. Approximately 1.6 million Americans have UC or CD. Up to 70,000 new cases of IBD are diagnosed in the United States each year.[3]

Men and women are approximately equally affected by IBD in Western countries.[6] In general, whites are affected more often than blacks, and persons of Jewish descent are also at higher risk. The incidence of IBD is 10 to 40 times greater in individuals with a first-degree relative who has IBD compared with the general population.[4,5,7] A positive family history may be more of a contributing factor for development of CD than UC.[7–9]

The cause of IBD is not fully understood. Dysregulation of the inflammatory response within the GI tract in response to environmental or microbiologic factors is thought to be the prevailing mechanism.[3,4] The fact that a positive family history is a strong predictor of IBD supports the theory that genetic predisposition is involved in many cases. Many potential candidate genes have been identified.

An alteration in the inflammatory response regulated by intestinal epithelial cells may also contribute to development of IBD. This may involve inappropriate processing of antigens presented to the GI epithelial cells.[3-5,10,11] The inflammatory response in IBD may be directed at bacteria that normally colonize the GI tract. Products derived from these bacteria may translocate across the mucosal layer of the GI tract and interact with various cells involved in immunologic recognition. The result is T-cell stimulation, excess production of proinflammatory cytokines, and persistent inflammation within the GI tract. Drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) that disrupt the integrity of the GI mucosa may facilitate mucosal entry of intestinal antigens and lead to IBD flares.[12]

Use of oral contraceptives has been associated with increased development of CD in white patients in some cohort studies, but a strong causal relationship has not been proven.[5] Use of antibiotics in childhood and low levels of vitamin D have also been reported to increase risk of UC and CD.[5]

Smoking has protective effects in UC, leading to reductions in disease severity.[5] The opposite is true in CD because smoking may lead to increases in symptoms or worsening of the disease in Caucasian and Middle Eastern migrants.[5] Tea or coffee consumption is protective in Asian patients.[5]

PATHOPHYSIOLOGY

Ulcerative Colitis

LO 1

The inflammatory response in UC is propagated by atypical type 2 helper T cells that produce proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α).[3,4,9] The potential role of environmental factors in development of UC implies that the immune response is directed against an unknown antigen. The findings that development and severity of UC are reduced in patients who smoke, those who have had appendectomies, and patients who were breastfed may support the theory that these factors may somehow modify either the genetic component or phenotypic response to immunologic stimuli.[3,4,5]

The inflammatory process within the GI tract is limited to the colon and rectum in patients with UC (Figure 19–1). Most

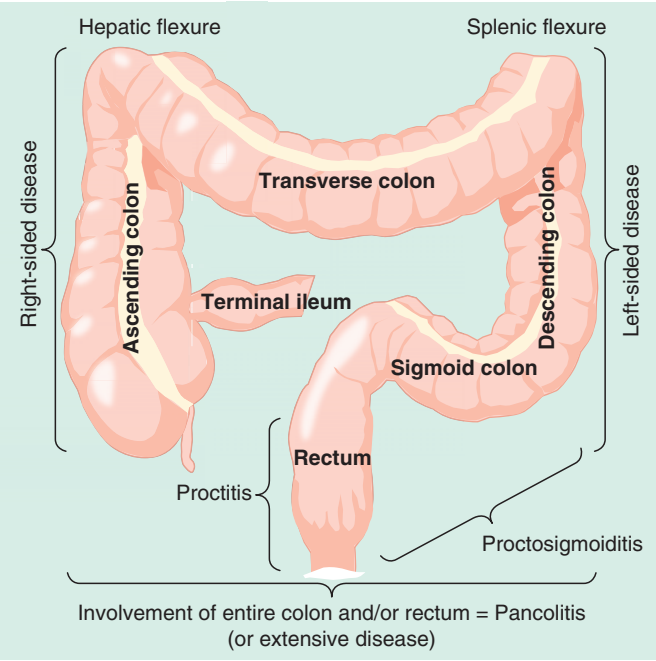


FIGURE 19–1. Major GI landmarks and disease distribution in inflammatory bowel disease.

patients with UC have involvement of the rectum (**proctitis**) or both the rectum and the sigmoid colon (**proctosigmoiditis**). Inflammation involving the entire colon is referred to as extensive disease or **pancolitis**. Left-sided (distal) disease, defined as inflammation extending from the rectum to the splenic flexure, occurs in 30% to 40% of patients.[12] A small number of cases of UC involve mild inflammation of the terminal ileum, referred to as "backwash ileitis."

The pattern of inflammation in UC is continuous and confluent throughout the affected areas of the GI tract. The inflammation is superficial and does not typically extend below the submucosal layer of the GI tract (Figure 19–2). Ulceration or erosion of the GI mucosa may be present and varies with disease severity. Formation of **crypt abscesses** within the mucosal layers of the GI tract is characteristic of UC and may help to distinguish it from CD. Severe inflammation may also result in areas of hypertrophied GI mucosa, which may manifest as **pseudopolyps** within the colon.[13] The inflammatory response may progress in severity, leading to mucosal friability and significant GI bleeding.

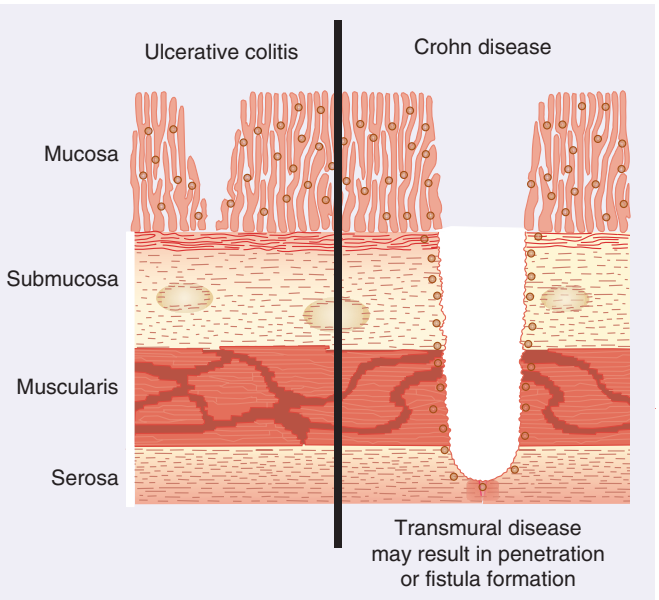


FIGURE 19–2. Depth of disease penetration in ulcerative colitis and Crohn disease.

Crohn Disease

LO 1

As with UC, the immune activation seen in CD involves the release of many proinflammatory cytokines. Cytokines thought to play major roles in CD are derived from T-helper type 1 cells and include interferon-γ, transforming growth factor-β, TNF-α, and IL-1, IL-6, IL-8, IL-12, and IL-23. TNF-α, IL-12, and IL-23 are major contributors to the inflammatory process and development of fibrosis in CD.[3-5,11,15] TNF-α effects include activation of macrophages, procoagulant effects in the vascular endothelium, and increased production of matrix metalloproteinases in mucosal cells.[10–15] TNF-α is also thought to induce production of nuclear factor κβ, which stimulates further production of TNF-α and other proinflammatory cytokines.[3,11,15] Alterations in Paneth cell function may also dictate the phenotypes of CD that are observed.[10] IL-12 and IL-23 are involved in T-cell and lymphocyte differentiation and expansion as part of the inflammatory process.

In contrast to UC, the inflammation in CD may affect any part of the entire GI tract from the mouth to the anus. The small intestine is most commonly involved, and the terminal ileum and cecum are almost always affected. Approximately 20% of patients have isolated colonic involvement, whereas inflammation proximal to the small intestine is almost never seen without the presence of small or large intestinal disease.[13]

The pattern of inflammation in CD is discontinuous; areas of inflammation are intermixed with areas of normal GI mucosa, resulting in characteristic "skip lesions." Superficial **aphthous ulcers** may also develop in the GI mucosa. These ulcers may coalesce into larger linear ulcers, resulting in fissure formation as they increase in depth, giving rise to the characteristic "cobblestone" pattern observed upon examination of the mucosa.

The inflammation may be **transmural**, penetrating to the muscularis or serosal layers of the GI tract (Figure 19–2). This propensity for transmural involvement may lead to serious complications such as **strictures**, **fistulae**, abscesses, and perforation.[13] Although rectal inflammation is typically less common in CD than UC, several types of perianal lesions may be observed including skin tags, hemorrhoids, fissures, anal ulcers, abscesses, and fistulae.[14]

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Differentiation between UC and CD is based on signs and symptoms as well as characteristic endoscopic findings, including the extent, pattern, and depth of inflammation. See accompanying box for the clinical presentation of IBD.

Extraintestinal Manifestations and Complications of IBD

KEY CONCEPT Patients may manifest signs and symptoms of disease in areas outside the GI tract (extraintestinal manifestations).[13] Painful joint complications associated with IBD include sacroiliitis and ankylosing spondylitis. Ocular involvement with episcleritis, uveitis, or iritis may manifest as blurred vision, eye pain, and photophobia. Associated skin findings include pyoderma

Clinical Presentation of IBD

LO 2

General

- Patients with UC or CD may present with similar symptoms.
- The onset may be insidious and subacute.
- Some patients present with extraintestinal manifestations before GI symptoms occur.
- It may be impossible to distinguish between UC and CD in approximately 10% of cases. These patients are described as having "indeterminate colitis."

Symptoms

- *Ulcerative colitis*: Diarrhea (bloody, watery, or mucopurulent), rectal bleeding, abdominal pain/cramping, weight loss and malnutrition, tenesmus, constipation (with proctitis)
- *Crohn disease*: Diarrhea (less bloody than UC), rectal bleeding (less than UC), abdominal pain/cramping, weight loss and malnutrition (more common than UC), fatigue/malaise

Signs

- *Ulcerative colitis*: Fever, tachycardia (with severe disease), dehydration, arthritis, hemorrhoids, anal fissures, perirectal abscesses
- *Crohn disease*: Fever, tachycardia (with severe disease), dehydration, arthritis, abdominal mass and tenderness, perianal fissure or fistula

Laboratory Tests

- *Ulcerative colitis*: Leukocytosis, decreased hematocrit/hemoglobin, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), positive test for fecal occult blood, (+) perinuclear antineutrophil cytoplasmic antibodies (pANCA; up to 70% of patients), and elevated fecal calprotectin
- *Crohn disease*: Leukocytosis, decreased hematocrit/hemoglobin, elevated ESR or CRP, positive test for fecal occult blood, (+) anti–*Saccharomyces cerevisiae* antibodies (up to 50% of patients), hypoalbuminemia with severe disease, and elevated fecal calprotectin

gangrenosum (papules and vesicles that develop into painful ulcerations) and erythema nodosum (red nodules of varying size typically found on the lower extremities). Nephrolithiasis may also develop at a higher rate in patients with IBD. Oxalate stones are more common in CD, and uric acid-containing stones are more common in UC.[13]

Liver and biliary manifestations of IBD include increased incidence of gallstone formation in patients with CD and development of sclerosing cholangitis or cholangiocarcinoma in patients with UC. Patients with UC are at increased risk for developing colorectal cancer and should undergo periodic cancer screening. Ongoing inflammation due to active IBD may induce a hypercoagulable state, resulting in higher rates of both arterial and venous thromboembolism, including deep vein thrombosis and pulmonary embolism. Likewise, inflammation and recurrent blood loss may result in chronic anemia. Patients with IBD also have higher rates of osteopenia, osteoporosis, and fractures, which are most strongly associated with use of corticosteroids.[16]

A serious complication of UC is toxic megacolon, defined as dilation of the transverse colon greater than 6 cm (2.4 in). Patients with toxic megacolon typically manifest systemic signs of severe inflammation such as fever, tachycardia, and abdominal distention.[3,9,13] Surgical intervention, including colonic resection, may be necessary to acutely manage toxic megacolon.

Patients with CD may develop significant weight loss or nutritional deficiencies secondary to malabsorption of nutrients in the small intestine, or as a consequence of multiple small- or large-bowel resections. Common nutritional deficiencies in IBD include vitamin B_{12}, fat-soluble vitamins, zinc, folate, and iron. Malabsorption in children with CD may contribute to significant reductions in growth and development.

Diagnosis

Because patients often present with nonspecific GI symptoms, initial diagnostic evaluation includes methods to characterize the disease and rule out other potential etiologies. This may include stool cultures to examine for infectious causes of diarrhea.[9] Use of fecal calprotectin, a protein found in neutrophil granulocytes and released during leukocyte trafficking, is measured in the stool and may help to differentiate IBD from nonorganic disease (intestinal damage due to external causes such as drugs or mechanical intervention).[9] Levels greater than 120 mcg/g are considered abnormal.

Endoscopic approaches are typically used and may include colonoscopy, proctosigmoidoscopy, or possibly upper GI endoscopy in patients with suspected CD. Endoscopy is useful for determining the disease distribution, pattern and depth of inflammation, and to obtain mucosal biopsy specimens. Supplemental information from imaging procedures, such as computed tomography, abdominal x-ray, abdominal ultrasound, or intestinal barium studies may provide evidence of complications such as obstruction, abscess, perforation, or colonic dilation.[9]

The information derived from diagnostic testing and the patient's medical history and symptoms are used to gauge disease severity. Traditionally, the severity of active IBD is classified as mild, moderate, severe, or fulminant.[1,2] These categories are determined using a mix of signs, symptoms, and laboratory markers such as daily stool count, hydration status, presence of tachycardia, and elevated ESR or CRP.

A clinical care pathway developed by the American Gastroenterological Association (AGA) provides guidance on assessing severity of UC based on risk for colectomy.[35] After a diagnosis is made, inflammatory status (based on signs/symptoms, lab markers, and endoscopic findings), comorbidities, and therapy-related complications (if the patient is already receiving treatment) are assessed. Patients are then stratified according to low risk for colectomy (limited anatomic extent and mild endoscopic disease) or high risk for colectomy (extensive colitis, age less than 40 years, deep ulcers, high ESR/CRP, steroid dependence, history of hospitalization, and *Clostridium difficile* or cytomegalovirus infection).

The AGA also developed a similar clinical decision support tool for managing CD.[39] Initially, the patient's inflammatory status, comorbidities, and disease and therapy-related complications are assessed. Categorization is slightly different from UC, and patients considered low risk (age at initial

diagnosis over 30 years, limited anatomic involvement, no perianal and/or severe rectal disease, superficial ulcers, no prior surgical resection, and no stricturing and/or penetrating disease) or moderate–high risk (age at initial diagnosis less than 30 years, extensive anatomic involvement, perianal and/or severe rectal disease, deep ulcers, prior surgical resection, stricturing and/or penetrating disease).

TREATMENT

Desired Outcomes

LO 3

Treatment goals for IBD involve both management of active disease and prevention of disease relapse. KEY CONCEPT Major treatment goals include alleviation of signs and symptoms and suppression of inflammation during acute episodes and maintenance of remission thereafter. Addressing active IBD in a timely and appropriate manner may prevent major complications and reduce the need for hospitalization or surgical intervention.

Once control of active disease is obtained, treatment regimens are designed to achieve these long-term goals: (a) maintain remission and prevent disease relapse, (b) improve the patient's quality of life, (c) prevent the need for surgical intervention or hospitalization, (d) manage extraintestinal manifestations, (e) prevent malnutrition, and (f) prevent treatment-associated adverse effects.

General Approach to Treatment

Pharmacologic interventions for IBD are designed to target the underlying inflammatory response. KEY CONCEPT When designing a drug regimen for treatment of IBD, several factors should be considered, including the patient's symptoms; medical history; current medication use; drug allergies; and extent, location, and severity of disease. The history may also help identify a family history of IBD or potential exacerbating factors, such as tobacco or NSAID use.

Nonpharmacologic Therapy

No specific dietary restrictions are recommended for patients with IBD, but avoidance of high-residue foods in patients with strictures may help prevent obstruction. Avoidance of excess dietary fat and foods containing emulsifying agents (eg, mayonnaise, salad dressing, ice cream) may also be preferred.[8] Nutritional strategies in patients with longstanding IBD may include vitamin and mineral supplementation and intake of soluble fiber.[8] Administration of vitamin B_{12}, folic acid, fat-soluble vitamins, and iron may be needed to prevent or treat deficiencies. In severe cases, enteral or parenteral nutrition may be needed to achieve adequate caloric intake.[8]

Patients with IBD, particularly those with CD, are also at risk for bone loss. This may be a function of malabsorption of vitamin D or repeated courses of corticosteroids.[16] Risk factors for osteoporosis should be determined, and baseline bone density measurement may be considered.[16] Vitamin D and calcium supplementation should be used in all patients receiving long-term corticosteroids. Oral bisphosphonate therapy may also be considered in patients receiving prolonged courses of corticosteroids or in those with osteopenia or osteoporosis.

Surgical intervention is an option in patients with complications such as fistulae or abscesses, or in patients with medically refractory disease. UC is curable with performance of a total colectomy; patients with UC may opt to have a colectomy to reduce the chance of developing colorectal cancer. Patients with CD may have affected areas of intestine resected. Unfortunately, CD may recur following surgical resection. Repeated surgeries in CD may lead to significant malabsorption of nutrients and drugs consistent with development of short-bowel syndrome.

Pharmacologic Therapy

Several pharmacologic classes are available for acute treatment and maintenance therapy of IBD. Selection of an initial agent for patients with active IBD should be designed to deliver maximum efficacy while minimizing toxicity. Response rates to individual classes of medications for both UC and CD are discussed within the specific treatment section for each disease.

▶ *Symptomatic Interventions*

LO 4

Patients with active IBD often have severe abdominal pain and diarrhea. Medications used to manage these symptoms may have adverse consequences. KEY CONCEPT Antidiarrheal medications that reduce GI motility such as loperamide, diphenoxylate/atropine, and codeine should be avoided in patients with active IBD due to the risk of precipitating acute colonic dilation (toxic megacolon).[13] Drugs with anticholinergic properties, such as hyoscyamine and dicyclomine, are often used to treat intestinal spasm and pain, but these drugs may also reduce GI motility and should generally be avoided in active IBD.

Patients who have had multiple intestinal resections due to CD may have diarrhea related to the inability to reabsorb bile salts. Cholestyramine may improve diarrheal symptoms in this population.[14] NSAIDs should be avoided for pain management because they can worsen IBD symptoms. Opioid analgesics should be used with caution because they may significantly reduce GI motility.

▶ *Aminosalicylates*

LO 4

The aminosalicylates are among the most commonly used drugs for inducing and maintaining remission in patients with mild to moderate IBD (Table 19–1). These drugs are designed to deliver 5-aminosalicylate (5-ASA, mesalamine) to areas of inflammation within the GI tract. The mechanism of mesalamine is not fully understood, but it appears to have favorable anti-inflammatory effects. The delivery of mesalamine to the affected sites is

Patient Encounter 1

A 28-year-old man presents to the clinic for initial treatment of UC. A colonoscopy revealed extensive disease in the colon and rectum. He reports two to three loose stools per day 5 to 6 days per week with intermittent blood and abdominal pain. This has caused a significant impact on his daily activities and quality of life. His medical history is significant for gastroesophageal reflux disease, and he takes nonprescription ranitidine as needed. He reports no tobacco use and social intake of alcohol. He has an allergy to peanuts (hives). His medical provider has determined this episode to be of moderate severity and would like to initiate adalimumab.

How does adalimumab differ from infliximab with regard to chemical structure and route of administration?

How would you educate this patient on the appropriate storage of adalimumab?

Table 19–1

Aminosalicylates for Treatment of IBD

Drug	Trade Names	Formulation	Strengths	Daily Dosage Range (g)	Site of Action
Sulfasalazine	Azulfidine	Immediate-release or enteric-coated tablets	500 mg	1.6–4.8	Distal ileum and colon
	Azulfidine En-tabs	Suspension	250 mg/5 mL		
Mesalamine	Rowasa	Enema	4 g/60 mL	4	Distal left colon and rectum
Mesalamine	Asacol Asacol-HD	Delayed-release resin tablet	400 mg, 800 mg	1.6–4.8	Distal ileum and colon
	Delzicol	Delayed-release capsule	400 mg	1.6–4.8	Distal ileum and colon
	Canasa	Rectal suppository	1000 mg	1	Rectum
	Pentasa	Delayed-release capsule	250 mg 500 mg	2–4	Small bowel and colon
	Lialda	MMX formulated pH-dependent polymer film coated tablet	1.2 g	1.2–4.8	Terminal ileum and colon
	Apriso	Enteric-coated granules in polymer matrix	375 mg	1.5	Colon
Olsalazine	Dipentum	Delayed-release capsule	250 mg	1–3	Colon
Balsalazide	Colazal	Delayed-release capsule	750 mg	2–6.75	Colon
	Giazo	Tablet	1.1 g	2.2–6.6	Colon

accomplished by either linking mesalamine to a carrier molecule or altering the formulation to release drug in response to changes in intestinal pH. Topical suppositories and enemas are designed to deliver mesalamine directly to the distal colon and rectum.[7,17–20]

The prototypical aminosalicylate is sulfasalazine, which chemically is mesalamine linked by a diazo bond to the carrier molecule sulfapyridine. This linkage prevents premature absorption of mesalamine in the small intestine. Once sulfasalazine is delivered to the colon, bacterial degradation of the diazo bond frees mesalamine from sulfapyridine. Sulfapyridine is then absorbed and excreted renally while mesalamine acts locally within the GI tract.

Newer mesalamine products utilize nonsulfapyridine methods for drug delivery. Olsalazine consists of two mesalamine molecules linked together, whereas balsalazide uses the inert carrier molecule 4-aminobenzoyl-β-alanine. Both drugs use a diazo bond similar to sulfasalazine. Lialda is a proprietary multimatrix (MMX) mesalamine formulation with a pH-sensitive coat that releases in the terminal ileum, allowing for once-daily dosing.[17,18] Apriso contains enteric-coated mesalamine granules also with a polymer matrix for extended release that can be given once daily.

Sulfasalazine is associated with various adverse effects, most of which are thought to be due to the sulfapyridine component. Common dose-related adverse effects include headache, dyspepsia, nausea, vomiting, and fatigue.[20–22] Idiosyncratic effects include bone marrow suppression, reduction in sperm counts in males, hepatitis, and pulmonitis. Hypersensitivity reactions may occur in patients allergic to sulfonamide-containing medications.

Nonsulfapyridine-based aminosalicylates are better tolerated than sulfasalazine. Although the types of adverse effects are similar, they occur much less frequently. However, olsalazine is associated with a higher incidence of secretory diarrhea than other aminosalicylates. These agents can be used safely in patients with a reported sulfonamide allergy, but they are more expensive than generic sulfasalazine.

▶ *Corticosteroids*

LO 4

Corticosteroids have potent anti-inflammatory properties and are used in active IBD to suppress inflammation rapidly. They may be administered systemically or delivered locally to the site of action (Table 19–2). Corticosteroids usually improve symptoms and disease severity rapidly, but use should be restricted to short-term management of active disease. Long-term systemic corticosteroid use is associated with significant adverse effects, including cataracts, skin atrophy, hypertension, hyperglycemia, adrenal suppression, osteoporosis, increased risk of infection, and delayed growth in children, among others.[20–22]

Table 19–2

Corticosteroids for Treatment of IBD

Drug	Trade Names	Daily Dose
Prednisone	Generic	20–60 mg orally
Prednisolone	Generic	20–60 mg orally
Methylprednisolone	Medrol (orally) Solu-Medrol (IV)	15–60 mg orally or IV
Hydrocortisone	Solu-Cortef	300 mg IV in three divided doses
	Cortenema	100 mg rectally at bedtime
	Cortifoam	90 mg rectally once or twice daily
	Anusol-HC	25–50 mg rectally twice daily
	Proctocort	30 mg rectally twice daily
Budesonide	Uceris 9-mg tablet	9 mg orally once daily
	Entocort 3-mg capsule	9 mg orally once daily
	Uceris rectal foam	2 mg twice daily, then once daily

Budesonide is a high-potency glucocorticoid used in IBD that has low systemic bioavailability when administered orally or rectally.[23,24] Oral formulations may release in either the terminal ileum or colon. Rectal foam formulations reach up to 40 cm from the anal verge. Compared to traditional corticosteroids, budesonide may reduce long-term adverse effects and can be used for induction therapy.[21–23]

▶ *Immunomodulators and Immunosuppressants*

LO 4 Agents targeting the immune response or cytokines involved in IBD are potential treatment options (Table 19–3). Azathioprine and 6-mercaptopurine (6-MP) are immunomodulators that inhibit purine biosynthesis and reduce IBD-associated GI inflammation. They are most useful for maintaining remission of IBD or reducing the need for long-term use of corticosteroids.[22,2,25–27] Use in active disease is limited by their slow onset of action, which may be as long as 3 to 12 months. Azathioprine is metabolized to 6-MP, which is further metabolized to the active 6-thioguanine (6-TGN) nucleotide, which functions as a purine antagonist. Evaluation of 6-TGN concentrations can be performed in patients who may not be responding to therapy or may be experiencing toxicity. Adverse effects associated with azathioprine and 6-MP include hypersensitivity reactions resulting in pancreatitis, fever, rash, hepatitis, and leukopenia.[21,22,25,26] Patients should be tested for activity of thiopurine methyltransferase (TPMT), the major enzyme responsible for metabolism of azathioprine prior to use. Deficiency or reduced activity of TPMT may result in toxicity from azathioprine and 6-MP and may require dose reductions.

LO 4 Methotrexate, also an immunomodulator, is a folate antagonist used primarily for maintaining remission of CD. It may be administered orally, subcutaneously, or IV and may have a steroid-sparing effect in patients with steroid-dependent disease.[6,25,26] Long-term methotrexate use may result in serious adverse effects, including hepatotoxicity, pulmonary fibrosis, and bone marrow suppression.

LO 4 Cyclosporine is a cyclic polypeptide immunosuppressant typically used to prevent organ rejection in transplant patients. Its use in IBD is restricted to patients with fulminant or refractory symptoms in patients with active disease. Significant toxicities associated with cyclosporine are nephrotoxicity, risk of infection, seizures, hypertension, and liver function test abnormalities.[1,20]

▶ *Biologic Agents*

LO 4 Several biologic agents targeting TNF-α are used for treatment of IBD (Table 19–3). Reduction in TNF-α activity is associated with improvement in the underlying inflammatory process. Infliximab is a chimeric anti-TNF-α agent (ie, 75% human, 25% mouse), certolizumab is a pegylated antibody fragment, and both adalimumab and golimumab are humanized anti-TNF-α antibodies.

"Biosimilars" are highly similar to an FDA-approved biologic agent (called the reference product) and have been shown to have no clinically meaningful differences in efficacy or adverse effects from the reference product. They are not identical in structure or considered generically equivalent to the originator compound because of molecular complexity and production using recombinant DNA techniques in living organ systems. However, some biosimilars may be considered to be interchangeable with the reference product. The FDA will approve a biosimilar product only if it has the same mechanism of action, route of administration, dosage form, and strength as the reference product. Also, a biosimilar can only be approved for the indications that were previously approved for the reference product. Biosimilars have a nonproprietary name plus an FDA-designated suffix consisting of four lowercase letters that have no intended meaning. Five biosimilar agents are now approved for use in UC and CD: Infliximab-dyyb, infliximab-abda, infliximab-qbtx, adalimumab-adbm, and adalimumab-atto.

Disadvantages of anti-TNF biologic therapy include the need for parenteral administration, significant drug cost, and the

Table 19–3

Immunodulators and Biologic Agents for Treatment of IBD

Drug	Trade Name(s)	Dose
Azathioprine	Imuran, Azasan	1.5–2.5 mg/kg/day orally
Mercaptopurine	Purinethol, Purixan	1.5–2.5 mg/kg/day orally
Methotrexate	Trexall	15–25 mg weekly (IM/SC/orally)
Cyclosporine	Sandimmune	4 mg/kg/day IV continuous infusion
Infliximab	Remicade	Induction: 5 mg/kg IV at 0, 2, and 6 weeks; 10 mg/kg per dose IV for nonresponders Maintenance: 5 mg/kg IV every 8 weeks
Infliximab-dyyb	Inflectra	
Infliximab-abda	Renflexis	
Inflixmab-qbtx	IXIFI	
Adalimumab	Humira	Induction: 160 mg SC day 1 (given as four 40-mg injections in 1 day or as two 40-mg injections per day for 2 consecutive days), then 80 mg SC 2 weeks later (day 15) Maintenance: 40 mg SC every other week, starting on day 29 of therapy
Adalimumab-atto	Amjevita	
Adalimumab-adbm	Cyltezo	
Certolizumab	Cimzia	Induction: 400 mg SC initially, then 400 mg SC at 2 and 4 weeks Maintenance: 400 mg SC every 4 weeks if initial response
Golimumab	Simponi	200 mg SC at week 0 and 2; then every 4 weeks
Natalizumab	Tysabri	Induction/maintenance: 300 mg IV every 4 weeks; discontinue by 12 weeks if no response or if unable to withdraw steroids within 6 months
Vedolizumab	Entyvio	300 mg IV at weeks 0, 2, and 6; then every 8 weeks; discontinue if no response at 14 weeks
Ustekinumab	Stelara	Weight-based initial IV dose < 55 kg (260 mg), 55–85 kg (390 mg), > 85 kg (520 mg); then 90 mg SC every 8 weeks

IM, intramuscular; IV, intravenously; SC, subcutaneously.

potential for serious adverse effects. Adalimumab, golimumab, and certolizumab are administered subcutaneously, whereas infliximab requires intravenous (IV) infusion. Adverse effects of IV infliximab may include infusion-related reactions such as fever, chest pain, hypotension, and dyspnea. Antibodies may develop to infliximab over time that may reduce its efficacy and predispose patients to development of infusion-related adverse effects.

All TNF-α inhibitors have been associated with reactivation of serious infections, particularly intracellular pathogens such as tuberculosis, as well as hepatitis B.[15,20,25,26] Biologic agents should not be used in patients with existing infections, and patients should be screened for latent tuberculosis and viral hepatitis prior to initiating therapy. Exacerbation of heart failure is also a potential adverse effect, so these agents should be avoided in patients with advanced or decompensated heart failure.[15,20] Anti-TNF-α agents also carry a risk of developing lymphoma, including a rare form known as hepatosplenic T-cell lymphoma. The risk appears to be highest in younger male patients and those using concomitant azathioprine or 6-MP.[20,23-28]

LO 4 Natalizumab and vedolizumab are humanized monoclonal antibodies that antagonize integrin heterodimers, prevent α_4-mediated leukocyte adhesion to adhesion molecules, and prevent migration across the endothelium.[28-31] Natalizumab is associated with development of progressive multifocal leukoencephalopathy (PML). Vedolizumab carries a theoretical risk of PML, but this has not been reported to date. Use of natalizumab is restricted to patients who have failed all other therapies, including anti TNF-α agents. Vedolizumab can be used as alternative to anti-TNF therapy or reserved for patients who fail these agents.[30]

LO 4 Ustekinumab is a biologic therapy that blocks IL-21 and IL-23 action by binding to the p40 protein subunit used by these cytokines.[31] It is approved for use in moderate to severe CD in patients who failed immunomodulators or corticosteroids but have not received anti-TNF therapy. It can also be used for patients who have failed anti-TNF therapy.

► *Other Agents*

Antibiotics have been used in IBD based on the rationale that they may interrupt the inflammatory response directed against endogenous bacterial flora. Metronidazole and ciprofloxacin have been the two most widely studied agents.[1,2,32] Metronidazole LO 4 may benefit some patients with pouchitis (inflammation of surgically created intestinal pouches) and patients with CD who have had ileal resection or have perianal fistulas. Ciprofloxacin has shown some efficacy in refractory active CD and may be used in combination with metronidazole. Long-term metronidazole use is associated with development of peripheral neuropathy.

Because smoking is associated with reduced UC symptoms, transdermal nicotine has been studied as a potential treatment option. Improvement in mild to moderate UC symptoms may be seen and may be more evident in patients who are ex-smokers.[1,33] Daily doses between 15 and 25 mg appear to be most effective.

Probiotics such as *Lactobacillus acidophilus* or *Bifidobacterium* have been used with the rationale that modification of host flora may alter the inflammatory response. There are minimal data to support use of probiotics in CD.[2] In patients with UC, the probiotic preparation VSL#3 demonstrated efficacy in reducing recurrence of pouchitis in patients with ileal pouch anal anastomosis and may prevent relapse in mild to moderate disease.[1,34]

Treatment of UC

LO 4 As described previously, patients may be stratified for treatment based on risk level for colectomy. See Table 19–4 for the AGA recommendations for induction and maintenance therapy of UC based on risk level.

Table 19–4

Ulcerative Colitis Initial Inductive and Maintenance Therapy Based on Colectomy Risk

Risk Level	Inductive Therapy	Maintenance Therapy (Remission)
Low risk	• Oral mesalamine and/or • Rectal mesalamine and/or • Oral budesonide or prednisone and/or • Rectal corticosteroids	• Oral and/or rectal mesalamine • Taper oral corticosteroids over 60 days
High-risk outpatients	1. Short course of systemic corticosteroids (eg, prednisone) with initiation of thiopurine	1. Options: • Thiopurine and taper corticosteroids over 60 days • Anti-TNF agent, with or without thiopurine • Vedolizumab, with or without thiopurine or methotrexate
	2. Anti-TNF agent with or without thiopurine	2. Continue anti-TNF agent, with or without thiopurine
	3. Vedolizumab, with or without thiopurine or methotrexate	3. Continue vedolizumab, with or without thiopurine or methotrexate
High-risk inpatients	1. IV corticosteroids	1. Options: • Thiopurine • Anti-TNF agent with or without thiopurine • Vedolizumab with or without thiopurine or methotrexate
	2. Infliximab	2. Infliximab with or without thiopurine
	3. IV cyclosporine	3. Options: • Start thiopurine • Anti-TNF agent with or without thiopurine • Vedolizumab with or without thiopurine or methotrexate

Thiopurine = azathioprine or mercaptopurine.

Anti-TNF agent = adalimumab, certolizumab, golimumab, infliximab.

Adapted from: American Gastroenterological Association. Identification, assessment and initial medical treatment of ulcerative colitis clinical care pathway. http://campaigns.gastro.org/algorithms/UlcerativeColitis/pdf/Ulcerative_Colitis_Care_Pathway.pdf.

▶ Low-Risk Active UC in Outpatients

LOS KEY CONCEPT Treatment of acute episodes of UC is dictated by the severity and extent of disease. First-line therapy of mild to moderate disease or low-risk patients involves oral or topical aminosalicylate derivatives, oral or topical budesonide, or oral prednisone and/or rectal steroids. Topical mesalamine is superior to both topical corticosteroids and oral aminosalicylates for inducing remission in active mild to moderate UC.[1,35–37] Enemas are appropriate for patients with left-sided disease because the medication will reach the splenic flexure. Suppositories deliver mesalamine up to approximately 20 cm and are most appropriate for treating proctitis.[6,7,35] Oral and topical mesalamine preparations may be used together for maximal effect. Oral mesalamine may also be used for patients who are unwilling or unable to use topical preparations.[35–37]

Topical corticosteroids are usually reserved for patients who do not respond to topical mesalamine.[1,22] Patients should be properly educated regarding appropriate use of topical products, including proper administration and adequate retention in order to maximize efficacy. Oral or rectal budesonide may be used as either an alternative first-line therapy or as add-on to aminosalicylates in patients with active UC.[2,23,24] Oral prednisone is also an option; however, its effects are systemic, and oral formations targeting specific areas of the colon are not available. Patients requiring corticosteroids should have them tapered over 60 days.

For patients with disease extending proximal to the splenic flexure, oral sulfasalazine, any oral mesalamine product, or oral budesonide are considered first-line therapy.[1,6,23,24] Doses should provide 4 to 6 g of sulfasalazine or 2.4 g of mesalamine or equivalent.[6,17-19] Use of once-daily formulations may improve patient adherence.[17-19] Induction of remission may require 4 to 8 weeks of therapy at appropriate treatment doses.

▶ High-Risk Active UC in Outpatients

LOS In moderate to severe UC or high-risk outpatients, oral corticosteroids may be used for short-term treatment of patients who are unresponsive to sulfasalazine or mesalamine. Prednisone doses of 40 to 60 mg/day (or equivalent) are recommended.[1,22] Azathioprine or 6-MP should be started when corticosteroids are initiated and can be continued with an anti-TNF agent as maintenance therapy.[35,37] Infliximab, adalimumab, and golimumab are effective for patients with moderate disease who are unresponsive to oral therapies.[38] Vedolizumab is an alternative to anti-TNF therapy or can be reserved for patients who fail oral therapies and anti-TNF-α agents.[30] Vedolizumab can also be combined with an immunomodulator and continued as maintenance therapy once remission is achieved.

Patient Encounter 2, Part 1

A 21-year-old African-American woman presents to the gastroenterology clinic because of a 1-month history of crampy abdominal pain and two to three loose stools 3 to 4 days per week. She denies vomiting, fever, or chills, and has missed several days of school and work in the past 2 weeks.

What other pertinent information from the history would be beneficial to help determine the cause of her symptoms?

What additional information would you obtain prior to recommending drug therapy?

▶ High-Risk UC in Inpatients

LOS Patients with severe or high-risk UC symptoms generally require hospitalization. If the patient is unresponsive to mesalamine and oral corticosteroids, a course of IV corticosteroids should be initiated.[1] Hydrocortisone 300 mg/day IV given in three divided doses or methylprednisolone 60 mg IV once daily for 7 to 10 days are recommended.[1,22,35] Infliximab is also an option for severe UC in high-risk inpatients. If remission with steroids is achieved, then a thiopurine with or without an anti-TNF agent, or vedodlizumab with or without an immunomodulator are maintenance options. Cyclosporine 2 to 4 mg/kg/day given as a continuous IV infusion can be used as inductive therapy but is often reserved for patients unresponsive to 7 to 10 days of IV corticosteroid therapy.

▶ Maintenance of Remission in UC

Unfortunately, up to 50% of patients receiving oral therapies and up to 70% of untreated patients relapse within 1 year after achieving remission.[37] For this reason, patients may require maintenance drug therapy indefinitely to preserve remission.

LOS KEY CONCEPT Maintenance of remission of UC may be achieved with oral or topical aminosalicylates. In low-risk patients with proctitis, mesalamine suppositories 1 g daily may prevent relapse in up to 90% of patients.[1,7,35] Mesalamine enemas are appropriate for left-sided disease and may often be dosed two to three times weekly. Oral mesalamine at lower doses (eg, 1.2–1.6 g/day) may be combined with topical therapies to maintain remission.

Oral sulfasalazine or mesalamine is effective in maintaining remission in low-risk patients with more extensive disease.[1,6] Lower daily doses (eg, 2–4 g sulfasalazine or 2–2.4 g mesalamine) may be used for disease maintenance. Oral or topical corticosteroids are not effective for maintaining remission and should be avoided due to the high incidence of adverse effects. Systemic corticosteroids and budesonide should be tapered over 60 days in low-risk patients achieving remission.[37]

LOS KEY CONCEPT Immunomodulators (eg, azathioprine, 6-MP), anti-TNF agents (eg, infliximab, adalimumab, golimumab), or vedolizumab can be used to maintain UC remission in unresponsive patients or those who develop corticosteroid dependency. Intermittent anti-TNF agent dosing may be used to maintain remission and reduce the need for corticosteroids in patients with moderate to severe UC. Combining a thiopurine and anti-TNF agent may be more effective initially, and patients may be able to be transitioned to azathioprine monotherapy. Vedolizumab may be used as an alternate maintenance option if patients had a favorable response to induction therapy and may be combined with azathioprine or methotrexate.[30,35] Colectomy is an option for patients with progressive disease who cannot be maintained on drug therapy alone.

▶ Treatment of CD

LOS See Table 19–5 for a summary of the AGA treatment recommendations for CD based on risk level.

▶ Low-Risk Active CD

LOS KEY CONCEPT Induction of remission in low-risk patients with mild to moderate active CD may be accomplished with oral budesonide, with or without azathioprine, in patients with ileal and/or proximal colonic involvement and no to minimal systemic symptoms, or a tapering course of prednisone with or without azathioprine in patients with diffuse or left colonic involvement. Budesonide 9 mg orally once daily for up to 8 weeks

Table 19–5

Crohn Disease Initial Inductive and Maintenance Therapy Based on Risk

Risk Level	Inductive Therapy	Maintenance Therapy (Remission)
Low risk	1. Ileum and/or proximal colon with none to minimal systemic symptoms. Options: • Oral budesonide 9 mg/day without or without azathioprine • Tapering course of prednisone with or without azathioprine 2. Diffuse or left colon with none to minimal systemic symptoms. Options: • Tapering course of prednisone with or without azathioprine	Options: • Stop therapy and observe (high chance of relapse over 1 year) • Oral budesonide 6 mg/day (prolongs median time to relapse by about 114 days, but no difference in remission rates vs. placebo at 1 year) • Immunosuppressive therapy (azathioprine, mercaptopurine, and methotrexate are effective in maintaining prednisone- or prednisolone-induced remissions but are associated with rare risk of infection and lymphoma)
Moderate to high risk	Moderately severe Crohn disease. Options: • Systemic corticosteroids • Use anti-TNF monotherapy over no therapy or thiopurine monotherapy • Use anti-TNF agent plus thiopurine over monotherapy with either thiopurine or anti-TNF agent • Use methotrexate for patients who do not tolerate thiopurine plus anti-TNF agent	Options: • Steroid-induced remission: Use thiopurine or methotrexate over no immunomodulator; **or** use anti-TNF agent with or without thiopurine over no anti-TNF agent • Anti-TNF alone or anti-TNF plus thiopurine-induced remission: Use anti-TNF agent with or without thiopurine over no anti-TNF agent

Thiopurine = azathioprine or mercaptopurine.

Anti-TNF agent = adalimumab, certolizumab, golimumab, infliximab.

Adapted from: Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. Gastroenterology. 2014;147:702–705.

is effective for low-risk, active CD in patients with involvement of the terminal ileum or ascending colon, with success expected in 50% to 69% of patients.[3,22,37,39] Because the formulation releases budesonide in the terminal ileum, it is not effective in reaching sites distal to the ascending colon.[39] Conventional oral corticosteroids (eg, prednisone, methylprednisolone) may also be used with or without an immunomodulator and are preferred if there is diffuse or left-sided disease.[39] However, other oral corticosteroids carry a higher risk of adverse effects than budesonide.[6]

Sulfasalazine or mesalamine products have demonstrated minimal efficacy in patients with ileal, ileocolonic, or colonic CD due to their more favorable adverse effect profile when compared to corticosteroids.[2,3,40]

Metronidazole or ciprofloxacin can be used in patients who do not respond to budesonide or oral aminosalicylates. Response rates of up to 50% are reported, but data are conflicting, and these agents should generally not be considered first-line therapy.[2,3,32,39]

▶ *Moderate- to High-Risk Active CD*

LO 5

Patients with moderate- to high-risk CD may be treated with oral corticosteroids (eg, prednisone 40–60 mg daily). Per the AGA recommendations (Table 19–5), moderately severe patients can be treated with anti-TNF monotherapy or anti-TNF therapy combined with a thiopurine. Methotrexate can be used in patients who do not tolerate purine therapy.

For patients with perianal fistulae, antibiotics (metronidazole or ciprofloxacin), infliximab, adalimumab, and certolizumab are appropriate treatment options. Complex perianal fistulae may require surgical intervention but may also be amenable to treatment with antibiotics, azathioprine, 6-MP, or anti-TNF-α agents.[15,22,26,27]

Many patients with severe CD require hospitalization for appropriate treatment. Patients should be assessed for possible surgical intervention if abdominal distention, masses, abscess, or obstruction are present. Daily IV doses of corticosteroids equivalent to prednisone 40 to 60 mg may be tried as initial therapy to rapidly suppress severe inflammation.

LO 5

Anti-TNF agents or vedolizumab may be used in severe active CD. Anti-TNF therapy can be combined with a thiopurine for increased effectiveness. Patients failing to respond should have drug trough concentrations and anti-drug antibodies assessed if anti-TNF agents are being used. Depending on the outcome this may necessitate a dose increase or a switch to another drug within the class. Ustekinumab is generally reserved for outpatients with severe disease who have failed other traditional therapies.

Adjunctive therapy with fluid and electrolyte replacement should be initiated. Nutritional support with enteral or parenteral nutrition may be indicated for patients unable to eat for more than 5 to 7 days.[2] Limited evidence indicates that cyclosporine, or possibly tacrolimus, may be effective as salvage therapy for patients who fail IV corticosteroid therapy.[2,3,26] Surgical intervention may ultimately be necessary for medically refractory disease.

▶ *Maintenance of Remission in CD*

Patients with CD are at high risk for disease relapse after induction of remission. Within 2 years, up to 80% of patients experience a relapse; therefore, many patients require indefinite maintenance therapy. KEY CONCEPT Maintenance of remission of CD may be achieved with immunosuppressants (azathioprine, 6-MP, or methotrexate), biologic agents (infliximab, adalimumab, certolizumab pegol, or vedolizumab), and less frequently with oral or topical aminosalicylate derivatives.

LO 5

In contrast to their use in UC, sulfasalazine and the newer aminosalicylates are marginally effective in preventing CD relapse in patients with medically induced remission, with success rates of only 10% to 20% at 1 year.[3,37,39,40] Despite not being

recommended as first-line therapy, aminosalicylates are routinely used to attempt maintenance of remission of CD.

The anti-TNF agents are effective in maintaining remission in CD.[26,27] Azathioprine and 6-MP in oral doses up to 2.5 mg/kg/day have been shown to maintain remission in 45% of patients for up to 5 years.[22,25–27] The immunomodulators azathioprine and 6-MP may be preferred for maintenance following a steroid-induced remission. There is evidence to support use of combination therapy with an anti-TNF agent plus azathioprine or methotrexate to maintain remission in CD in patients achieving steroid-induced remission.[26,27,39] Anti-TNF agents are preferred for patients with surgically induced remission and may also be combined with azathioprine in this situation.[42] Vedolizumab or ustekinumab may be used for maintenance in patients unresponsive to anti-TNF-α agents.[29–31]

Patients not responding to anti-TNF agents should have drug trough levels obtained and be assessed for presence of antibodies.[43] Dose escalation or switching to another anti-TNF agent may be required. Similarly, evaluation of azathioprine metabolites, particularly 6-thioguanine, should be performed to evaluate the need for dose escalation if there is lack of response or in the setting of potential thiopurine toxicity.[35,44]

Systemic or topical corticosteroids should not be used for maintaining remission in patients with CD. Unfortunately, up to 50% of patients treated acutely with corticosteroids become dependent on them to prevent symptoms.[2] Budesonide 6 mg (2 × 3-mg Entocort capsules) orally once daily may be used in place of conventional corticosteroids for up to 3 months after remission induction in mild to moderate CD or in patients dependent on corticosteroids.[3,22,23]

Treatment of IBD in Special Populations (Table 19–6)

▶ *Older Persons*

Approximately 10% to 30% of patients with IBD initially develop symptoms after age 60.[45] In general, IBD presents similarly in older patients and younger individuals. Elderly patients may have more comorbid diseases, some of which may make the diagnosis of IBD more difficult. Such conditions include ischemic colitis, diverticular disease, and microscopic colitis. Increased age is also associated with a higher incidence of adenomatous polyps, but the onset of IBD at an advanced age does not appear to increase the risk of developing colorectal cancer. Older patients may also use more medications, particularly NSAIDs, which may induce or exacerbate colitis. Adherence may be more challenging for older patients, especially for injectable products, and costs of some agents may be problematic depending on the patient's financial or insurance situation.

LOS

Treatment of older patients with IBD is similar to that for younger patients, but special consideration should be given to some of the medications used. Corticosteroids may worsen diabetes, hypertension, heart failure, or osteoporosis. The TNF-α inhibitors should be used cautiously in patients with heart failure and should be avoided in New York Heart Association class III or IV disease. Older patients requiring major surgical interventions

Patient Encounter 2, Part 2: Medical History and Physical Examination

PMH: Migraine headaches, UTI

FH: Both parents alive; father has a history of hypertension; mother has a history of migraines

SH: College student (majoring in elementary education); social alcohol use; no tobacco use

Allergies: Sulfa (rash)

Meds: Sumatriptan subcutaneous as needed, ibuprofen as needed

ROS: (+) Diarrhea, abdominal pain

PE:

VS: BP 121/72 mm Hg, P 101 beats/min, RR 17/min, T 37.7°C (99.8°F)

CV: Tachycardia with normal rhythm. No murmurs, rubs, or gallops

HEENT: Slightly dry mucous membranes

Skin: No evidence of tenting

Abd: Soft, nondistended, mild diffuse tenderness, (+) bowel sounds, (–) hepatosplenomegaly, (–) masses, heme (+) stool

MS: 5/5 strength in upper and lower extremities; normal ROM

Labs:

Sodium 135 mEq/L (mmol/L)
Potassium 3.3 mEq/L (mmol/L)
Chloride 98 mEq/L (mmol/L)
AST 22 IU/L (0.36 µkat/L)
ALT 22 IU/L (0.36 µkat/L)
Albumin 4.0 g/dL (40 g/L)
Bicarbonate 26 mEq/L (mmol/L)
BUN 15 mg/dL (5.4 mmol/L)
Serum creatinine 1 mg/dL (88 µmol/L)
Glucose 100 mg/dL (5.6 mmol/L)
Hemoglobin 10 g/dL (100 g/L; 6.21 mmol/L)
Hematocrit 34% (0.34)
WBC 18.0 × 10^3/mm^3 (10^9/L)
Platelets 490 × 10^3/mm^3 (10^9/L)
CRP 3.5 mg/dL (35 mg/L)
A1C 5% (0.05; 31 mmol/mol Hb)
ESR 115 mm/hour

Abdominal x-ray: (–) obstruction, free-air, or colonic dilation

Colonoscopy: Patchy inflammation involving the terminal ileum with evidence of recent bleeding, (–) polyps or strictures, biopsy taken

Pathology: Evidence of granuloma and PMN infiltration

How is this additional information helpful in determining disease extent and location?

What factors should you consider in choosing appropriate therapy for this patient?

What treatment options would you consider at this time?

What are some important educational points you would provide to this patient regarding appropriate use of her medication?

Table 19–6

Dosing Considerations of IBD Therapies in Special Populations

Therapy	Pediatric Patients	Elderly Patients	Pregnancy[44–46]
Sulfasalazine	Age > 2 years: 40–60 mg/kg/day in 3–6 divided doses; 30 mg/kg/day in 3–6 divided doses for maintenance	No specific changes	Category B[a] Administer folic acid 2 mg daily during prenatal period and pregnancy
Mesalamine	No specific changes; Balsalazide indicated for age > 5 years	No specific changes	Category B (Olsalazine Category C) Generally considered safe and effective
Corticosteroids	No specific changes	No specific changes Elderly patients at high risk for osteoporosis	Older agents not rated Budesonide category C Generally considered safe and effective
TNF-α inhibitors	Infliximab indicated for pediatric patients: 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks Adalimumab indicated for patients age ≥ 6 or greater: 80 mg (< 40 kg), 40 mg week 2, then 20 mg every other week or 160 mg (> 40 kg) initial followed by 80 mg week 2, then 40 mg every other week	Avoid in patients with heart failure Elderly patients at higher risk for infections	Category B Pregnancy registry for adalimumab via manufacturer
Natalizumab	Dose of 3 mg/kg IV at 0, 4, and 8 weeks reported; data are lacking in children	No specific changes	Category C Report pregnancy to manufacturer's pregnancy registry
Vedolizumab	Not indicated	No specific changes	Category B Manufacturer pregnancy exposure registry
Ustekinumab	Not indicated	No specific changes	Manufacturer pregnancy exposure registry
Azathioprine 6-Mercaptopurine	1.5–2 mg/kg/day to start	No specific changes	Category D Accepted as safe Avoid initiating during pregnancy, but continue if patient is already receiving when pregnant
Methotrexate	17 mg/m^2 orally/SC/IM	No specific changes	Category X Contraindicated
Cyclosporine	No specific changes	No specific changes	Category C Use only in refractory patients
Metronidazole	30–50 mg/kg/day divided every 6 hours	No specific changes	Category B Use short courses if possible
Ciprofloxacin	Avoid use	Adjust dose for CrCl < 50 mL/min (0.83 mL/s)	Category C Consider other alternatives

[a]In 2015, the FDA recommended that the pregnancy categories be replaced with narrative recommendations to better inform clinical decision making. Drugs submitted for approval after June 30, 2015 will use this new designation immediately, whereas those approved after June 30, 2001 will be gradually phased in (https://www.drugs.com/pregnancy-categories.html).

CrCl, creatinine clearance; IM, intramuscular; SC, subcutaneously.

may be at higher risk for surgical complications or may not meet eligibility criteria for surgery because of comorbid conditions, age-related organ dysfunction, or reduced functional status.[45]

► *Children and Adolescents*

Approximately 50,000 individuals younger than 20 years of age in the United States have IBD, which represents 5% of all IBD patients. CD occurs twice as frequently as UC in children.[46,47] A major issue in children with IBD is the risk of growth failure secondary to inadequate nutritional intake and corticosteroid therapy. Failure to thrive may be an initial presentation of IBD in this population. Aggressive nutritional interventions may be required to facilitate adequate caloric intake. Chronic corticosteroid therapy may also be associated with reductions in growth and bone demineralization. Using lower doses in patients who are corticosteroid dependent may reduce altered height velocity.[46] Guidelines for management of acute severe UC in children favor methylprednisolone as first-line therapy, with calcineurin inhibitors or infliximab used for unresponsive patients.[47]

LO 5

The aminosalicylates, azathioprine, 6-MP, and infliximab are all viable options for treatment and maintenance of IBD in pediatric patients. Infliximab is approved for use in the United States for patients 6 to 17 years of age with moderate to severe active CD. Use of immunosuppressive therapy or infliximab may help reduce overall corticosteroid exposure. Adalimumab is also approved for use in patients 6 years of age or older with CD. Certolizumab, natalizumab, vedolizumab, and ustekinumab are only FDA approved for use in adults with IBD; data in children are limited.[49]

► *Pregnant Women*

Inducing and maintaining remission of IBD prior to conception is the optimal approach in women planning to become

pregnant. Pregnant women with IBD are at higher risk of spontaneous abortion, preterm birth, low birth weight infants, and complications of delivery such as preeclampsia and liver and platelet disorders.[48,49] Given these implications, preconception counseling should be provided, and good communication among medical providers is necessary. Vaccination schedules should be updated and disease severity assessed.

LO 5 Patients do not need to discontinue drug therapy for IBD once they become pregnant. Maintenance medications may generally be continued, but certain adjustments may be required.[4] The aminosalicylates are considered safe in pregnancy, but sulfasalazine is associated with folate malabsorption. Because pregnancy results in a higher folate requirement, pregnant patients treated with sulfasalazine should be supplemented with folic acid 1 mg orally twice daily. Asacol-HD contains dibutyl phthalate, which has been implicated in fetal defects; therefore, this product should be switched to an alternate mesalamine formulation.[48] Methotrexate is a known abortifacient and should be discontinued prior to patients becoming pregnant and an alternate medication initiated.

As pregnancy progresses, there is a potential risk of increased placental transfer of biologic drugs. Recommendations are to modify the dosing schedule in the third trimester to allow for the last dose to be given as far in advance of delivery as possible to reduce placental transfer.[48] This may require evaluation of trough concentrations of the anti-TNF agents.[44] Metronidazole carries a theoretical risk of mutagenicity in humans, but short courses are safe during pregnancy. Prolonged use of metronidazole should be avoided in pregnant patients due to lack of safety data supporting its use. Ciprofloxacin should be avoided in pregnant women. Lastly, the safety of continuing current therapies for IBD should be evaluated if the patient is considering breastfeeding to assess potential risk if the drugs are transferred into breastmilk.

OUTCOME EVALUATION

LO 6

- Monitor for improvement of symptoms in patients with active IBD, such as reduction in the number of daily stools, abdominal pain, fever, and heart rate.
- For patients in remission, assure that proper maintenance doses are used and inform the patient to seek medical attention if symptoms recur or worsen.
- Evaluate patients receiving systemic corticosteroid therapy for improvement in symptoms and opportunities to taper or discontinue therapy. For patients using more than 5 mg daily of prednisone for more than 2 months or for steroid-dependent patients consider the following:
  - Central bone mineral density testing to evaluate need for calcium, vitamin D, or bisphosphonate therapy
  - Periodic monitoring of blood glucose, lipids, and blood pressure
  - Evaluation for evidence of Cushingoid features or signs or symptoms of infection
- When considering treatment with azathioprine or 6-MP, obtain baseline complete blood count (CBC), liver function tests, and TPMT activity. These tests, except TPMT, should be monitored closely (every 2–4 weeks) at the start of therapy and then approximately every 3 months during maintenance therapy.

Patient Care Process

Collect the Information:

- Evaluate the medical record to determine the extent and location of IBD.
- Assess for evidence of extraintestinal manifestations or GI complications related to IBD.
- Interview the patient to evaluate the impact on quality of life and to identify psychosocial problems related to the presence of IBD.

Assess the Information:

- Assess inflammatory status, severity, and classify as high vs. low risk for colectomy.
- Determine if the patient is treatment-naive or if they are currently receiving pharmacotherapy.
- Evaluate the patient's current medication doses and adherence to therapy. Identify potential barriers to adherence, such as cost or inability to properly use certain drug formulations.
- Identify adverse effects related to current therapy.

Develop a Care Plan:

- Based on the current therapy and disease severity and location, choose appropriate drug(s) and formulations to target the regions of intestinal inflammation.
- Process any prior authorizations for insurance providers that require this.

Implement the Care Plan:

- Remove or switch medications that may be exacerbating IBD symptoms.
- Educate the patient on proper use of drug therapy, including when to expect symptom improvement after initiation of treatment and which signs or symptoms to report that might be adverse drug effects.
- Provide a detailed description of the tapering schedule for corticosteroids if applicable.
- Refer patients to available support groups or IBD organizational resources if they are having difficulty coping with their disease.

Follow-up: Monitor and Evaluate:

- Depending on disease severity, follow up in 2 to 4 weeks. Earlier telephone follow-up may be required to determine whether the patient is achieving some relief of symptoms.
- Assess adherence to therapy and determine if drug concentrations should be evaluated if lack of response is present.
- Assess patient quality of life and impact of treatment on ability to perform daily activities.

- With azathioprine and 6-MP, monitor for hypersensitivity reactions including severe skin rashes and pancreatitis. Educate the patient regarding signs and symptoms of pancreatitis (nausea, vomiting, and abdominal pain).
- Prior to initiating methotrexate therapy, obtain CBC, serum creatinine, liver function tests, chest x-ray, and pregnancy test (if female). Monitor blood counts weekly for 1 month, then monthly thereafter.
- Prior to initiating anti-TNF therapy, ustekinumab, or vedolizimab, obtain a tuberculin skin test to rule out latent tuberculosis, monitor for signs and symptoms of tuberculosis, and measure viral hepatitis serologies. Also monitor patients with a prior history of hepatitis B virus infection for signs of liver disease, such as jaundice. Assure that patients do not have a clinically significant systemic infection or New York Heart Association class III or IV heart failure.
- In patients receiving infliximab, monitor for infusion-related reactions such as hypotension, dyspnea, fever, chills, or chest pain when administering IV doses.
- Recommended trough concentrations for anti-TNF biologic agents are infliximab ≥ 5 mcg/mL (mg/L), adalimumab ≥ 7.5 mcg/mL (mg/L), and certolizumab ≥ 20 mcg/mL (mg/L).[44]
- In patients with fistulae, monitor at every anti-TNF therapy dosing interval for evidence of fistula closure and overall reduction in the number of fistulae.
- If receiving natalizumab or vedolizumab therapy, monitor for signs of PML such as mental status changes, signs of liver disease (eg, jaundice), and hypersensitivity reactions following administration.

Abbreviations Introduced in This Chapter

5-ASA	5-Aminosalicylate
6-MP	6-Mercaptopurine
CD	Crohn disease
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IL	Interleukin
NSAID	Nonsteroidal anti-inflammatory drug
pANCA	Perinuclear antineutrophil cytoplasmic antibodies
PR	Per rectum
TNF-α	Tumor necrosis factor-α
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis

REFERENCES

1. Kornbluth A, Sachar DB. Ulcerative practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010;105:501–523.
2. Lichtenstein GR, Hanauer SB, Sandborn WJ. The Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104:465–483.
3. Colombel JF, Mahadevan U. Inflammatory bowel disease: innovations and changing paradigms. Gastroenterology 2017;152: 309–312.
4. Sartor RB, Wu GD. Role for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. Gastroenterology. 2017;152:327–339.
5. Kaplan GG, Ng Siew. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology. 2017;152:313–321.
6. Talley NJ, Abreu MT, Anchkar JP, et al. An evidenced based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol. 2011;106:S2–S25.
7. Lie MR, Kanis SL, Hansen BE, van der Woude CJ. Drug therapies for ulcerative proctitis: systematic review and meta-analysis. Inflamm Bowel Dis. 2014;20:2157–2178.
8. Lewis JD, Abreu MT. Diet as a trigger or therapy for inflammatory bowel disease. Gastroenterology. 2017;152:398–414.
9. Panes J, Jairath V, Levesque BG. Advances in use of endoscopy, radiology, and biomarkers to monitor inflammatory bowel diseases. Gastroenterology. 2017;152:362–373.
10. Stappenbeck TS, McGovern DP. Paneth cell alterations in the development and phenotype of Crohn's disease. Gastroenterology. 2017;152:322–326.
11. Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel disease. Gastroenterology. 2017;152:340–350.
12. Cipolla G, Crema F, Sacco S, et al. Nonsteroidal anti-inflammatory drugs and inflammatory bowel disease: current perspectives. Pharmacol Res. 2002;46:1–6.
13. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. Ann Med. 2010;42(2):97–114.
14. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014;63:1381–1392.
15. Abraham C, Dular OS, Vermeire S, Sandborn WJ. Lessons learned from trials targeting cytokine pathways in patients with inflammatory bowel disease. Gastroenterology. 2017; 152:374–388.
16. American Gastroenterological Association. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology. 2003;124:795–841.
17. Yang LP, McCormack PL. MMX mesalamine: a review of its use in the management of mild to moderate ulcerative colitis. Drugs. 2011;71(2):221–235.
18. Campregher C, Gasche C. Aminosalicylates. Best Pract Res Clin Gastroenterol. 2011;25:535–546.
19. Oliveira L, Cohen RD. Maintaining remission in ulcerative colitis—role of once daily extended-release mesalamine. Drug Des Dev Ther. 2011;5:111–116.
20. Biancone L, Annese V, Ardizzone S, et al. Safety of treatments for inflammatory bowel disease: clinical practice guidelines for the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Dig Liver Dis. 2017;49:338–358.
21. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:590–599.
22. Christophi GP, Rengarajan A, Ciorba MA. Rectal budesonide and mesalamine formulations in active ulcerative proctosigmoiditis: efficacy, tolerance, and treatment approach. Clin Exp Gastroenterol. 2016;9:125–130.
23. Gionchetti P, Pratico C, Rizzello F, et al. The role of Budesonide-MMX in active ulcerative colitis. Expert Rev Gastroenterol Hepatol. 2014:8(3):215–222.
24. Louis E, Irving P, Beaugerie L. Use of azathioprine in IBD: modern aspects of an old drug. Gut. 2014;63(11):1695–1699.
25. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs

for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145:1459–1463.
26. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013;145:1464–1478.
27. Akobeng AA, Sandborn WJ, Bickston SJ, et al. Tumor necrosis factor-alpha antagonists twenty years later: what do Cochrane reviews tell us? Inflamm Bowel Dis. 2014;20:2132–2141.
28. Beniwal-Patel P, Saha S. The role of integrin antagonists in the treatment of inflammatory bowel disease. Expert Opin Biol Ther. 2014;14:1815–1823.
29. Feagan BG, Rutgeerts P, Sands BE, et al; the GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699–710.
30. Sandborn WJ, Feagan BG, Rutgeerts, P, et al; the Gemini 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711–721.
31. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375:1946–1960.
32. Khan KJ, Ullman TA, Ford AC, et al. Antibiotic therapy in inflammatory bowel disease: a systematic review and meta-analysis. Am J Gastroenterol. 2011;106:661–673.
33. Nikfar S, Ehteshami-Ashar S, Rahimi R, Abdollahi M. Systematic review and meta-analysis of the efficacy and tolerability of nicotine preparations in active ulcerative colitis. Clin Ther. 2010;32:2304–2315.
34. Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. Drugs. 2012;72(6):803–823.
35. Ulcerative Colitis Clinical Care Pathway. American Gastroenterological Association. Available from: http://campaigns.gastro.org/algorithms/UlcerativeColitis/. Accessed September 28, 2017.
36. Ford AC, Ackhar AC, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:601–616.
37. Peyrin-Biroulet L, Lémann M. Remission rates achievable by current therapies for inflammatory bowel disease. Aliment Pharmacol Ther. 2011;33:870–879.
38. Panaccione R, Ghosh, S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146(2):392–400.
39. AGA Institute Guidelines for the Identification, Assessment and Initial Medical Treatment in Crohn's Disease Clinical Care Pathway. American Gastroenterological Association. Available from: http://campaigns.gastro.org/algorithms/IBDCarePathway/pdf/IBDCarePathway.pdf. Accessed September 28, 2017.
40. Moja L, Danese S, Fiorino C, et al. Systematic review with network meta-analysis: comparative efficacy and safety of budesonide and mesalazine (mesalamine) for Crohn's disease. Aliment Pharmacol Ther. 2015;41:1055–1065.
41. AGA Institute Guideline on the Use of Biologic Drugs for Inflammatory Crohn's Disease Clinical Decision Support Tool. American Gastroenterological Association. Available from: http://campaigns.gastro.org/algorithms/crohns/crohns_aga_branded_algorithm_web.pdf. Accessed September 28, 2017.
42. Nguyen GD, Loftus EV, Hirano I, et al. American Gastroenterological Association Institute Guideline on the management of Crohns disease after surgical resection. Gastroenterology. 2017;152:271–275.
43. Yarur AJ, Rubin DT. Therapeutic drug monitoring of anti-tumor necrosis factor agents in patients with inflammatory bowel disease. Inflamm Bowel Dis. 2015;21:1709–1718.
44. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology. 2017;153:827–834.
45. Robertson DJ, Grimm IS. Management of inflammatory bowel disease in the elderly patient: challenges and opportunities. Inflamm Bowel Dis. 2017;23:882–893.
46. vanMahade U, Cucchiara S, Hyams JS, et al. The London position statement of the World Congress of Gastroenterology on biological therapy for IBD with the European Crohn's and Colitis Organization: pregnancy and pediatrics. Am J Gastroenterol. 2011;106:214–223.
47. Turner D, Travis SP, Griffiths AM, et al. Consensus for managing acute severe ulcerative colitis in children: a systematic review and joint statement from ECCP, ESPGHAN, and the Porto IBD Working group of ASPGHAN. Am J Gastroenterol. 2011;106:574–588.
48. Mahadevan U, McConnell RA, Chambers CD. Drug safety and risk of adverse outcomes for pregnant patients with inflammatory bowel disease. Gastroenterology. 2017;152:451–462.
49. Boyd HA, Basit, S, Harpsoe, et al. Inflammatory bowel disease and risk of adverse pregnancy outcomes. PLoS One. 2015; 10(6):e0129567.

20 Nausea and Vomiting

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LEARNING OBJECTIVES

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

LO

1. Identify common causes of nausea and vomiting.
2. Describe the pathophysiologic mechanisms of nausea and vomiting.
3. Distinguish between simple and complex nausea and vomiting.
4. Create goals for treating nausea and vomiting.
5. Describe attributes of available antiemetic therapies.
6. Recommend treatment regimens for nausea and vomiting associated with cancer chemotherapy, surgery, pregnancy, or motion sickness.
7. Outline a monitoring plan to evaluate treatment outcomes for nausea and vomiting.

INTRODUCTION

Nausea and vomiting result from complex interactions of the gastrointestinal (GI) system, the vestibular system, and the brain and have a variety of causes. Preventing and treating nausea and vomiting requires pharmacologic and nonpharmacologic measures tailored to individual patients and situations.

EPIDEMIOLOGY AND ETIOLOGY

LO 1

KEY CONCEPT Nausea and vomiting are symptoms that can be due to many different causes such as GI, cardiac, neurologic, and endocrine disorders and various medications (Table 20–1).[1,2] Cancer chemotherapy agents are rated according to their emetogenic potential, and antiemetic therapy is prescribed based on these ratings. Radiation therapy can induce nausea and vomiting, especially when it is used to treat abdominal malignancies.[3]

Oral contraceptives, hormone therapy, and opioids can cause nausea and vomiting.[1] Some medications, such as digoxin, cause nausea and vomiting in a dose-related fashion, which may indicate excessive drug concentrations. Ethanol and other toxins also cause nausea and vomiting.

Postoperative nausea and vomiting (PONV) occurs in 30% of surgical patients overall and in up to 70% of high-risk patients.[4] Risk factors for PONV include female sex, history of motion sickness or PONV, nonsmoking status, and use of opioids postoperatively.[5] The choice of anesthetic agents and duration of surgery may also contribute to PONV.[4,5]

Nausea and vomiting of pregnancy (NVP) affects 70% to 85% of pregnant women, especially early in pregnancy.[6] In 0.3% to 3% of pregnancies, this can lead to **hyperemesis gravidarum**, a potentially life-threatening condition of prolonged nausea, vomiting, and resultant malnutrition.[6]

PATHOPHYSIOLOGY

Nausea is the unpleasant subjective feeling of the need to vomit.[1,2] Autonomic symptoms of pallor, tachycardia, diaphoresis, and salivation often accompany nausea. Vomiting (or emesis) is a forceful oral expulsion of upper GI contents due to sustained contractions in the abdominal and thoracic musculature.[1]

LO 2

Specific areas in the central nervous system (CNS) and GI tract are stimulated when the body is exposed to noxious stimuli or GI irritants: the **chemoreceptor trigger zone (CTZ)** in the area postrema of the fourth ventricle of the brain, the vestibular apparatus, visceral afferents from the GI tract, and the cerebral cortex.[1] These in turn stimulate regions of the reticular areas of the medulla within the brainstem. This area is the central vomiting center, which coordinates the impulses sent to the salivation and respiratory centers, and the pharyngeal, GI, and abdominal muscles that lead to vomiting (Figure 20–1).[7]

The CTZ, located outside the blood–brain barrier, is exposed to cerebrospinal fluid and blood.[1] Therefore, it is easily stimulated by uremia, acidosis, and circulating toxins such as chemotherapeutic agents. The CTZ has many 5-hydroxytryptamine (serotonin) type 3 (5-HT_3), neurokinin-1 (NK_1), and dopamine (D_2) receptors.[8] Visceral vagal nerve fibers are rich in 5-HT_3 receptors. They respond to GI distention, mucosal irritation, and infection.

Motion sickness is caused by stimulation of the vestibular system, rich in histaminic (H_1) and muscarinic cholinergic receptors.[9] The cerebral cortex is affected by sensory input such as sights, smells, or emotions that can lead to vomiting. This area is involved in anticipatory nausea and vomiting associated with chemotherapy.

LO 3

Nausea and vomiting can be classified as either simple or complex.[10] Simple nausea and vomiting occurs occasionally and is either self-limiting or relieved by minimal therapy. It does not detrimentally affect hydration status, electrolyte balance, or weight. Alternatively, complex nausea and vomiting requires more aggressive therapy because electrolyte imbalances, dehydration, and weight loss may occur.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to the accompanying box for the clinical presentation and diagnosis of nausea and vomiting.

Table 20–1

Causes of Nausea and Vomiting

GI or Intraperitoneal	Cardiac	Neurologic	Therapy or Toxin Induced	Endocrine/Metabolic
Mechanical obstruction	Cardiomyopathy	Vestibular disease	Antibiotics	Pregnancy (NVP or hyperemesis gravidarum)
Achalasia	Myocardial infarction	Motion sickness	Antiarrhythmics	Uremia
Enteric infections	Heart failure	Labyrinthitis	Aspirin	Diabetic ketoacidosis
Pancreatitis		Migraine headache	Cancer chemotherapy	Hyperthyroidism
Inflammatory bowel disease		Increased intracranial pressure	Digoxin	Parathyroid disease
Irritable bowel syndrome		Intracranial hemorrhage	Iron	Addison disease
Cholecystitis		Meningitis	Lead	
Hepatitis		Hydrocephalus	Marijuana	
Gastroparesis		Psychogenic causes	Oral antidiabetics	
Gastroesophageal reflux		Eating disorders	Oral contraceptives	
Peptic ulcer disease		Depression	Opioids	
Peritonitis		Anxiety disorders	Anticonvulsants	
			Radiation therapy	
			Ethanol	

TREATMENT

Desired Outcomes

LO 4

The primary goals of treatment are to relieve the symptoms of nausea and vomiting, increase quality of life, and prevent complications such as dehydration or malnutrition. Drug therapy for nausea and vomiting should be safe, effective, and economical.

General Approach to Treatment

KEY CONCEPT To treat nausea and vomiting most effectively, it is important to first identify and treat the underlying cause. Profuse or prolonged vomiting can lead to complications of dehydration and metabolic abnormalities. Patients must have adequate hydration and electrolyte replacement orally (if tolerated) or IV to prevent and correct these problems. Some pharmacologic treatments work locally in the GI tract, whereas others work in the CNS.[1]

Nonpharmacologic Therapy

KEY CONCEPT Nonpharmacologic approaches to nausea and vomiting include dietary, physical, and psychological measures. Dietary management is important when treating NVP due to concern for teratogenic effects with drug therapies.[11] Recommendations include eating frequent, small meals; avoiding spicy or fatty foods; eating high-protein snacks; avoiding iron-containing pills; and eating bland or dry foods the first thing in the morning.[6,11] The dietary supplement ginger (500–1000 mg daily given in three to four divided doses) was effective in NVP in some studies and is recommended in treatment guidelines.[6,11]

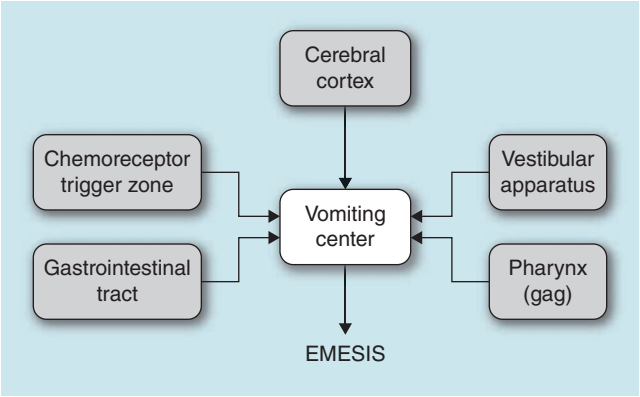

FIGURE 20–1. Primary afferent components to the vomiting center. (Reproduced, with permission, from Toy EC, Loose DS, Tischkau SA, Pillai AS, eds. Case Files: Pharmacology. 3rd ed. New York, NY: McGraw-Hill; 2014.)

Clinical Presentation and Diagnosis of Nausea and Vomiting

Symptoms

- Patients with nausea often complain of autonomic symptoms such as diaphoresis, disinterest in surroundings, pallor, faintness, and salivation.

Signs

- With complex and prolonged nausea and vomiting, patients may show signs of malnourishment, weight loss, and dehydration (dry mucous membranes, skin tenting, tachycardia, and lack of axillary moisture).

Laboratory Tests

- Dehydration, electrolyte imbalances, and acid–base disturbances may be evident in complex and prolonged nausea and vomiting.
- Dehydration is suggested by elevated blood urea nitrogen (BUN), serum creatinine (SCr), and BUN-to-SCr ratio (20:1 or greater using traditional units of measurement [100:1 or greater using SI units of mmol/L]).
- Calculated fractional excretion of sodium (FeNa) less than 1% (0.01) indicates dehydration and reduced renal perfusion.
- Low serum chloride and elevated serum bicarbonate levels indicate metabolic alkalosis.
- Hypokalemia may occur from GI potassium losses and intracellular potassium shifts to compensate for alkalosis.

Acupressure and electroacupoint stimulation of the P6 (Neiguan) point on the inside of the wrist seem safe and cost-effective; however, efficacy data for treatment of NVP, PONV, and motion sickness are conflicting.[6,12,13] Hypnosis and psychotherapy are also safe during pregnancy and in situations where adverse drug effects and interactions are a concern.

Pharmacologic Therapy

LO 5

Table 20–2 contains the names, usual dosages, and common adverse effects of the pharmacologic treatments for nausea and vomiting.[1,4,10,14]

▶ *Anticholinergics (Scopolamine)*

Scopolamine blocks muscarinic receptors in the vestibular system, thereby halting signaling to the CNS. It is effective for preventing and treating motion sickness and has some efficacy in preventing PONV.[15] Scopolamine is available as an adhesive transdermal patch that is effective for up to 72 hours after application. This may be beneficial for patients unable to tolerate oral medications or those requiring continuous prevention of motion sickness (eg, passengers on cruise ships). Transdermal scopolamine should be applied 4 hours prior to motion sickness triggers and the evening before surgery if used to prevent PONV. Scopolamine is associated with adverse anticholinergic effects such as sedation, visual disturbances, dry mouth, and dizziness. These adverse effects are worsened when a patient is taking concurrent anticholinergic agents, and these agents should be used with caution in older adults.

▶ *Antihistamines*

Antihistamines are used to prevent and treat nausea and vomiting due to motion sickness, vertigo, or migraine headache.[1,9,16] Their efficacy is presumably due to the high concentration of H_1 and muscarinic cholinergic receptors within the vestibular system. First-generation antihistamines cause undesired effects including drowsiness, blurred vision, and urinary retention. Although first-generation antihistamines are effective, the second-generation antihistamines cetirizine and fexofenadine were found to be ineffective for treating motion sickness, perhaps because they lack CNS depressant properties.[17]

Some first-generation antihistamines such as diphenhydramine, dimenhydrinate, doxylamine, and meclizine are available without a prescription, making self-treatment convenient. The combination of doxylamine and vitamin B6 (pyridoxine) has efficacy in NVP. Antihistamines are available in a variety of dosage forms, including oral capsules, tablets, and liquids. Liquid formulations are convenient for children or adults who are unable to swallow solid dosage forms.

▶ *Dopamine Antagonists*

Stimulation of D_2 receptors in the CTZ leads to nausea and vomiting (Figure 20–1). There are three main groups of dopamine antagonists: phenothiazines, butyrophenones, and prokinetic agents. Phenothiazine antiemetics act primarily via a central antidopaminergic mechanism in the CTZ.[1] Phenothiazines used to treat nausea and vomiting include promethazine, prochlorperazine, and chlorpromazine. Availability in multiple dosage forms (ie, oral, parenteral, rectal) permits use in a variety of settings including severe motion sickness or vertigo, gastritis or gastroenteritis, NVP, PONV, and chemotherapy-induced nausea and vomiting (CINV).[18,19]

Phenothiazines may cause sedation, orthostatic hypotension, and **extrapyramidal symptoms (EPS)** such as dystonia (involuntary muscle contractions), tardive dyskinesia (irreversible and permanent involuntary movements), and akathisia (motor restlessness or anxiety).[1,20] Chronic phenothiazine use has been associated with EPS, but single doses have also caused these effects.[21] Promethazine intravenous injection should not be administered in an undiluted bolus because this may lead to tissue necrosis requiring limb amputation.[20] The highest risk for this adverse event is when the medication is administered intraarterially.

Droperidol, a butyrophenone, is another centrally acting antidopaminergic agent effective for preventing PONV.[1,4] It may also be used for treating CINV for patients who are intolerant to serotonin receptor antagonists and corticosteroids.[14] Its adverse effects include sedation, agitation, and restlessness. Droperidol carries a US FDA black box warning regarding the potential for QT interval prolongation and cardiac arrhythmias that may result in torsades de pointes and sudden cardiac death.[22] Droperidol should not be used in patients with a prolonged QT interval or in those who are at risk for developing a prolonged QT interval (eg, heart failure, electrolyte abnormalities, or taking other medications concurrently that may prolong the QT interval).[22] A 12-lead electrocardiogram (ECG) is recommended prior to treatment with droperidol.

Haloperidol is another butyrophenone with some antiemetic effects at low doses (0.5–2 mg).[23] It has been explored as an alternative to droperidol.[24]

Metoclopramide and domperidone (not available in the United States) act as D_2-receptor antagonists centrally in the CTZ and peripherally in the GI tract.[1] They also display cholinergic activity, which increases lower esophageal sphincter tone and promotes gastric motility. Their antiemetic and prokinetic effects are useful in PONV, CINV, gastroparesis, and gastroesophageal reflux disease (GERD).[1,4,14] Metoclopramide is available in injectable, oral solid, and oral liquid dosage forms, allowing for its use in both hospitalized and ambulatory patients.

Metoclopramide crosses the blood–brain barrier and has centrally mediated adverse effects. Young children and the elderly are especially susceptible to these effects, which include somnolence, reduced mental acuity, anxiety, depression, and EPS and occur in 10% to 20% of patients.[1,25]

Domperidone minimally crosses the blood–brain barrier and is less likely to cause centrally mediated adverse effects.[1,25] It should not be used for patients with underlying long QT interval or for those taking medications that prolong the QT interval. Both metoclopramide and domperidone can cause hyperprolactinemia, galactorrhea, and gynecomastia.

▶ *Corticosteroids*

Oral or IV corticosteroids, especially dexamethasone and methylprednisolone, are used alone or in combination with other antiemetics for preventing and treating PONV, CINV, or radiation-induced nausea and vomiting.[3,8,14,23] Efficacy is thought to be due to release of 5-HT, reduced permeability of the blood–brain barrier, and decreased inflammation.[26] Common adverse effects with short-term use include GI upset, anxiety, insomnia, and hyperglycemia.[14] Adverse effects associated with long-term use (eg, decreased bone mineral density, diabetes, cataracts) are not usually seen when corticosteroids are used for acute nausea and vomiting.

▶ *Cannabinoids*

Cannabinoids have antiemetic and appetite stimulant activity when used alone or in combination with other antiemetics.[27]

Table 20–2

Antiemetic Agents: Usual Doses for Adults and Children and Adverse Effects

Drug	Adult Dosing	Pediatric Dosing	Adverse Effects[a]
Anticholinergics			
Scopolamine	TD: 1.5 mg patch applied 1 or more hours before the procedure, 4 hours prior to motion sickness triggers, repeated every 72 hours as needed	N/A	Most common: Dry mouth, drowsiness, blurred vision Rare: Disorientation, dizziness, hallucinations
Antihistamines			
Cyclizine	Oral: 50 mg every 4–6 hours as needed	Oral: 6–11 years: 25 mg every 6–8 hours as needed (max: 3 tablets per day)	Most common: Sedation, dry mouth, constipation Less common: Confusion, blurred vision, urinary retention
Dimenhydrinate	Oral: 50–100 mg every 4–6 hours as needed	Oral: 2–6 years, 12.5–25 mg every 6–8 hours not to exceed 75 mg in 24 hours; 6–12 years, 25–50 mg every 6–8 hours, not to exceed 150 mg in 24 hours	
Diphenhydramine	Oral: 25–50 mg every 4–6 hours IV/IM: 10–50 mg every 2–4 hours as needed	Oral/IV/IM: 2–6 years, 6.25 mg every 4–6 hours	
Doxylamine	Oral: 20–40 mg daily	N/A	
Hydroxyzine	Oral/IV/IM: 25–100 mg every 4–6 hours as needed	Oral: 0.6 mg/kg IM: 0.5–1 mg/kg	
Meclizine	Oral: 12.5–25 mg every 12–24 hours as needed	Oral: ≥ 12 years: use adult dose	
Phenothiazines			
Chlorpromazine	Oral: 10–25 mg every 4–6 hours as needed IV/IM: 25–50 mg every 4–6 hours as needed	Oral: ≥ 6 months, 0.5 mg/kg every 4–6 hours as needed IV/IM: ≥ 6 months, 0.5–1 mg/kg every 6–8 hours	Most common: Sedation, lethargy, skin sensitization Less common: Cardiovascular effects, EPS, cholestatic jaundice, hyperprolactinemia
Prochlorperazine	Oral: 5–10 mg three to four times a day as needed Supp: 25 mg twice daily as needed IV/IM: 2.5–10 mg every 3–4 hours as needed	Oral: > 2 years and > 9 kg: 0.4 mg/kg/day or 10 mg/m^2 daily in two to three divided doses Supp: See oral dosing IM: > 2 years and > 9 kg: 0.13 mg/kg	Avoid using in pediatric patients if possible due to sensitivity to adverse effects. If use is considered necessary, employ the lowest effective dose
Promethazine	Oral/IM/IV/Supp: 12.5–25 mg every 4–6 hours as needed	Oral/IM/IV/Supp: ≥ 2 years, 0.25–0.5 mg/kg or 7.5–15 mg/m^2 four to six times daily	
Butyrophenones			
Droperidol	IM/IV: 0.625–2.5 mg every 4–6 hours as needed	IM/IV: 2–12 years: 0.05–0.1 mg/kg (max 2.5 mg) every 4–6 hours as needed	Most common: Sedation, hypotension, tachycardia Less common: EPS, dizziness, increased blood pressure, chills, hallucinations, QT prolongation
Haloperidol	Oral, IM/IV: 0.5–5 mg every 12 hours as needed	N/A	
Benzamides			
Domperidone	Oral: 10–20 mg every 4–8 hours as needed Supp: 30–60 mg every 4–8 hours as needed	Oral: 0.2–0.4 mg/kg every 4–8 hours as needed for CINV prophylaxis Supp: Max daily dose based on weight	Most common: Sedation, restlessness, diarrhea (metoclopramide), agitation, CNS depression Less common: EPS, hypotension, neuroleptic syndrome, supraventricular tachycardia (with IV), QT prolongation, serotonin syndrome (when used with serotonergic agents)
Metoclopramide	PONV: 10–20 mg oral/IV/IM 10 min prior to anesthesia CINV Prophylaxis: 1–2 mg/kg oral/IV every 2–4 hours	N/A	
Trimethobenzamide	IM: 200 mg two to four times a day as needed	Not recommended	

(*Continued*)

Table 20–2

Antiemetic Agents: Usual Doses for Adults and Children and Adverse Effects (*Continued*)

Drug	Adult Dosing	Pediatric Dosing	Adverse Effects[a]
Corticosteroids			
Dexamethasone	*CINV*: 12–20 mg oral/IV day 1, then 8–12 mg oral/IV daily *PONV*: 4–5 mg oral/IV at induction of anesthesia	*CINV*: 10 mg/m^2 prior to chemotherapy then 5 mg/m^2	Most common: GI upset, anxiety, insomnia Less common: Hyperglycemia, facial flushing, euphoria, perineal itching or burning (with dexamethasone)
Methylprednisolone	125–500 mg oral/IV every 6 hours for total of four doses	N/A	
Cannabinoids			
Dronabinol	Oral: 5–15 mg/m^2 every 2–4 hours as needed	Use adult dose with caution and adjust based on response	Most common: Drowsiness, euphoria, somnolence, vasodilation, vision changes, dysphoria Less common: Diarrhea, flushing, tremor, myalgia
Nabilone	Oral: 1–2 mg two to three times a day as needed	N/A	
Benzodiazepines			
Lorazepam	Oral/IV: 0.5–2 mg prior to chemotherapy	Oral/IV: 2–15 years old: 0.05 mg/kg (up to 2 mg) prior to chemotherapy	Most common: Sedation, amnesia Rare: Respiratory depression, ataxia, blurred vision, hallucinations
Alprazolam	Oral: 0.5–2 mg three times a day prior to chemotherapy	N/A	
Serotonin Antagonists			
Dolasetron	*CINV*: Contraindicated due to dose-dependent QTc prolongation *PONV*: 12.5 mg IV 15 min before end of anesthesia or at onset of N/V or 100 mg PO within 2 hours before surgery	*CINV*: Contraindicated due to dose-dependent QTc prolongation *PONV*: 0.35 mg/kg IV (max 12.5 mg) or 1.2 mg/kg PO (max 100 mg) within 2 hours before surgery	Most common: Headache, QT prolongation Less common: Constipation, asthenia, somnolence, diarrhea, fever, tremor or twitching, ataxia, lightheadedness, dizziness, nervousness, thirst, muscle pain, warm or flushing sensation on IV administration, serotonin syndrome (with ondansetron when used with serotonergic agents) Rare: Transient elevations in hepatic transaminases Granisetron may be degraded by light. Cover patch application site (eg, with clothing) if risk of exposure to sunlight or sunlamps during use and for 10 days after removal
Granisetron	*CINV*: 10 mcg/kg IV prior to chemotherapy; or 1 mg orally 1 hour before chemotherapy and 1 mg 12 hours after first dose, or 2 mg 1 hour before chemotherapy *PONV*: 1 mg IV before induction of anesthesia or immediately before reversal of anesthesia, or at onset of N/V	*CINV*: 2–16 years: Use adult dosing IV or PO regimen *PONV*: Not recommended for pediatric patients	
Granisetron	*CINV*: 1 patch 24–48 hours before chemotherapy; may wear for up to 7 days	N/A	
Ondansetron	*CINV*: Oral: 24 mg single dose prior to chemotherapy, or 8 mg prior to chemotherapy, repeat every 12 hours IV: 0.15 mg/kg, not to exceed 16 mg per dose, for three doses. Give the first dose 30 min prior to chemotherapy. Repeat dose 4 and 8 hours after the first dose *PONV*: 4 mg IV/IM before anesthesia induction or at onset of N/V; 16 mg orally once given 1 hour before anesthesia induction	*CINV*: Oral: 4–11 years, 4 mg 30 min prior to chemotherapy, repeat at 4 and 8 hours and every 8 hours for 1–2 days after chemotherapy completion IV: 6 months to 18 years: 0.15 mg/kg, not to exceed 16 mg per dose, for three doses. Give the first dose 30 min prior to chemotherapy. Repeat dose 4 and 8 hours after the first dose *PONV*: 1 month–12 years: 4 mg IV/IM before anesthesia induction for over 40 kg and 0.1 mg/kg IV for under 40 kg Oral recommendations not available	.
Palonosetron	*CINV*: 0.25 mg IV 30 min before chemotherapy; 0.5 mg orally 1 hour before chemotherapy *PONV*: 0.075 mg IV before anesthesia induction	*CINV*: 20 mcg/kg (maximum 1.5 mg) IV 30 min before chemotherapy	

(*Continued*)

Table 20–2

Antiemetic Agents: Usual Doses for Adults and Children and Adverse Effects (*Continued*)

Drug	Adult Dosing	Pediatric Dosing	Adverse Effects[a]
Neurokinin-1 Antagonist			
Aprepitant	*CINV*: 150 mg IV (fosaprepitant) 30 min before chemotherapy on first day of chemotherapy only; or 125 mg orally on day 1, 1 hour prior to chemotherapy followed by 80 mg on days 2 and 3 *PONV*: 40 mg orally 3 hours prior to anesthesia induction	*CINV*: 12 years and older: 125 mg PO on day 1, 1 hour prior to chemotherapy followed by 80 mg on days 2 and 3 6 months to 12 years: 3 mg/kg (max 125 mg) day 1, then 2 mg/kg (max 80 mg) day 2 and 3	Most common: Fatigue, hiccups Less common: Dizziness, headache, insomnia Rare: Transient elevations in hepatic transaminases
Rolapitant	*CINV*: 180 mg PO on day 1, 1–2 hours prior to chemotherapy	N/A	
Netupitant	*CINV*: Netupitant 300 mg plus palonosetron 0.5 mg combination product on day 1, 1 hour prior to chemotherapy	N/A	
Other			
Doxylamine/ pyridoxine	Oral: 10 mg/10 mg tablets, 2 tablets PO at bedtime, titrate to a maximum of 4 tablets daily for persistent symptoms	N/A	See adverse effects for antihistamines above.
Olanzapine	*CINV*: 10 mg PO daily, days 1–4 of highly emetogenic chemotherapy	N/A	Sedation

[a]Most common, greater than 10%; less common, 1% to 10%; rare, less than 1%. Based on US FDA-approved labeling and generalized to drug class.

CINV, chemotherapy-induced nausea and vomiting; EPS, extrapyramidal symptoms; IM, intramuscularly; Inj, injectable dosage form for IV or IM use; N/A, not available; PO, orally; PONV, postoperative nausea and vomiting; TD, transdermal; Supp, rectal suppository.

Oral dronabinol and nabilone are used for preventing and treating refractory CINV.[14,27] Cannabinoids are thought to exert their antiemetic effect centrally, although the exact mechanism of action is unknown.[27] Sedation, euphoria, hypotension, ataxia, dizziness, and vision difficulties can occur. Medical marijuana is an area of increased interest, but current evidence is insufficient to recommend its use for this indication.[3]

▶ *Benzodiazepines*

Benzodiazepines, especially lorazepam, are used to prevent and treat CINV.[8,14] Lorazepam is used as an adjunct to antiemetic agents.[14] Sedation and amnesia are common side effects. Respiratory depression can occur with high doses or when other central depressants such as alcohol are used concomitantly.

▶ *Serotonin Antagonists*

Serotonin is a neurotransmitter synthesized in neurons in the CNS and in enterochromaffin cells of the GI tract. Chemotherapeutic agents release 5-HT, which is a predominant mediator in nausea and vomiting.[28] This increase in 5-HT concentrations stimulates the visceral vagal nerve fibers and CTZ, thereby triggering nausea and vomiting. Selective 5-HT_3 receptor antagonists (ondansetron, granisetron, dolasetron, and palonosetron) prevent and treat nausea and vomiting due to stimulation of these receptors, especially for CINV and PONV.[4,29] These agents are well tolerated; the most common adverse effects are headache, somnolence, diarrhea, and constipation.[14] Dose-related QT changes (including torsades de pointes) have been reported, and ECG monitoring is recommended for patients with risk factors for QT prolongation who will receive ondansetron or dolasetron.[29] Although the labeling for granisetron and palonosetron does not include a recommendation for ECG monitoring, patients may still be at risk for QT changes.

Palonosetron is the first 5-HT_3 antagonist to be approved for preventing both acute and delayed CINV.[14] Compared to other 5-HT_3 antagonists, palonosetron has a longer serum half-life (40 hours compared to 4–9 hours) and a higher receptor-binding affinity, which may contribute to its efficacy in preventing delayed CINV.[30]

▶ *Neurokinin-1 Receptor Antagonists*

Substance P is a neurokinin neurotransmitter that binds to neurokinin-1 (NK_1) receptors in the GI tract and the brain and is believed to mediate both acute and delayed nausea and vomiting.[31] Aprepitant was the first NK_1 receptor antagonist antiemetic and is effective for preventing acute and delayed CINV when used with a 5-HT_3 antagonist and a corticosteroid.[31,32] It is also effective for preventing PONV.[4,33] Aprepitant has numerous drug interactions because it is an inhibitor and substrate of the CYP 3A4 metabolic pathway.[33]

Netupitant is the second NK_1 receptor antagonist; it is available only as a combination product with palonosetron (Akynzeo) for preventing acute and delayed CINV following moderately or highly emetogenic chemotherapy.[3] Rolapitant is the third NK_1 receptor antagonist.[34] It is available as an oral formulation that may be used in place of aprepitant or netupitant and is given as a single dose due to its long elimination half-life and does

not have the same concerns for drug interactions associated with aprepitant and netupitant. None of the NK_1 antagonists are renally eliminated.

▶ *Olanzapine*

Olanzapine is an antipsychotic agent that has effects at dopamine D_2, 5-HT_{2c}, and 5-HT_3 receptors, among others. Current guidelines recommend the addition of olanzapine to combination therapy for prevention of CINV in patients receiving highly emetogenic chemotherapy.[3] When used for short-term treatment in this way, olanzapine is well tolerated with sedation on day 2 of chemotherapy the only reported significant adverse effect.

Chemotherapy-Induced Nausea and Vomiting

CINV is classified as: (a) acute (within 24 hours after chemotherapy); (b) delayed (more than 24 hours after chemotherapy); or (c) anticipatory (prior to chemotherapy when acute or delayed nausea and vomiting occurred with previous courses).[3,8,14] Risk factors for CINV include poor emetic control with prior chemotherapy, female sex, low chronic alcohol intake, and younger age.[35]

Chemotherapeutic agents are classified according to their emetogenic potential, which aids in predicting CINV.[3,8] Cisplatin, high-dose cyclophosphamide (1.5 gm/m^2 or more), or cyclophosphamide combined with an anthracycline are examples of highly emetogenic chemotherapeutic regimens. Lower doses of cyclophosphamide, ifosfamide, and carboplatin are examples of moderately emetogenic agents. Risk factors for anticipatory nausea and vomiting include poor prior control of CINV and a history of motion sickness or NVP.[3,14]

LO 6

KEY CONCEPT A combination of antiemetics with different mechanisms of action is recommended to prevent acute CINV for patients receiving moderately or highly emetogenic chemotherapy (Table 20–3).[3,8,14] Patients receiving chemotherapeutic agents with low emetogenic potential should receive a single dose of a 5-HT_3 antagonist or an 8-mg dose of dexamethasone as CINV prophylaxis, and those receiving chemotherapy with minimal emetogenic risk do not require prophylaxis.

Delayed nausea and vomiting is more difficult to prevent and treat. It occurs most often with cisplatin- and cyclophosphamide-based regimens, especially if delayed nausea and vomiting occurred with previous chemotherapy courses.[8] Patients who had poorly controlled acute CINV in the past are at greatest risk for delayed CINV.[3,8,35]

Oral and IV antiemetics can be equally effective for CINV, depending on patient characteristics such as ability to take oral medications, dosage form availability, and cost.[3,14] Patients undergoing chemotherapy should have antiemetics available to treat breakthrough nausea and vomiting even if prophylactic antiemetics were given.[3,14] A variety of antiemetics may be used, including lorazepam, dexamethasone, methylprednisolone, prochlorperazine, promethazine, metoclopramide, 5-HT_3 antagonists, dronabinol, and olanzapine. If breakthrough CINV occurs despite prophylaxis, treatment with an antiemetic with a different mechanism of action is recommended.

The best strategy for preventing anticipatory nausea and vomiting is to prevent acute and delayed CINV by using the most effective antiemetic regimens based on the emetogenic potential of the chemotherapy and patient factors. CINV should be aggressively prevented with the first cycle of therapy. If anticipatory nausea and vomiting occurs, benzodiazepines and behavioral therapy such as relaxation techniques may be tried.[8,14]

Table 20–3

Recommended Drug Regimens for Prevention of CINV Based on Emetogenic Risk[3]

Emetogenic Risk	Acute CINV (Day 1)	Delayed CINV (Days 2–4)
Minimal	None	None
Low	Dexamethasone OR 5-HT_3 antagonist	None
Moderate[a,b]	5-HT_3 antagonist + dexamethasone	Dexamethasone (days 2 and 3) for agents with known risk for delayed nausea and vomiting
High (includes AC regimens)	NK_1 receptor antagonist + 5-HT_3 antagonist + dexamethasone[b] + olanzapine	If aprepitant[c] is used, continue days 2 and 3 Continue dexamethasone days 2–4 for non-AC highly emetogenic regimens Olanzapine (days 2–4)

[a]Add NK_1 receptor antagonist if using carboplatin and area under the curve is ≥ 4 mg/mL per minute.

[b]If rolapitant is the NK_1 receptor used, use full dose (20 mg) dexamethasone on day 1. If aprepitant, fosaprepitant, or netupitant are used, dose-adjust dexamethasone (12 mg) on day 1.

[c]If fosaprepitant, netupitant/palonosetron combination or rolapitant are used as the NK_1 receptor antagonist on day 1, no subsequent doses required.

AC, anthracycline (daunorubicin, doxorubicin, epirubicin, or idarubicin) plus cyclophosphamide; CINV, chemotherapy-induced nausea and vomiting.

Postoperative Nausea and Vomiting

PONV is a common complication of surgery that can lead to delayed discharge and unanticipated hospitalization.[4] The overall incidence of PONV is 25% to 30%, but it can occur in 70% to 80% of high-risk patients.[4,5] Risk factors for PONV include patient factors (female sex, nonsmoking status, and history of PONV or motion sickness), anesthetic factors (volatile anesthetics, nitrous oxide, or intraoperative or postoperative opioids), and surgical factors (duration and type of surgery).[4,5]

The first step in preventing PONV is reducing baseline risk factors when appropriate.[4,5] For example, the incidence of PONV may be less with regional anesthesia than general anesthesia, and nonsteroidal anti-inflammatory drugs may cause less PONV than opioid analgesics.

LO 6

KEY CONCEPT Some agents should be administered prior to induction of anesthesia (aprepitant, palonosetron, dexamethasone), whereas others are more effective when administered at the end of surgery (droperidol, 5-HT_3 receptor antagonists). Scopolamine should be administered the evening prior to surgery or 2 hours prior to surgery.[1,4] Aprepitant prevents PONV, but it is not more effective than other agents and is costly.[4,23] Combinations of antiemetics are recommended to prevent PONV for high-risk patients.[23] A 5-HT_3 antagonist plus droperidol or dexamethasone, or dexamethasone plus droperidol are effective combinations.[4,23]

Patient Encounter 1

A 37-year-old woman is having surgery today to remove her gallbladder.

PMH: GERD, hyperemesis gravidarum 5 years ago, and hypotension

SH: Negative for tobacco, occasional alcohol, negative for illicit drugs

FH: Hypertension, dyslipidemia

Current meds: Pantoprazole 40 mg once daily, OTC "motion sickness" medicine when she travels

VS: BP 98/62 mm Hg, HR 95 beats/min, RR 18 breaths/min, T 98.6°F (37.0°C)

Labs: All within normal limits

EKG shows normal sinus rhythm and a QTc of 410 msec

General analgesia is planned for surgery and includes thiopental 4.5 mg/kg, atracurium 0.5 mg/kg, and fentanyl 0.05 mg followed by tracheal intubation, 70% nitrous oxide, and 0.5% to 2% isoflurane in oxygen. Postoperative orders include opioid analgesics for pain control.

What risk factors does this patient have for developing PONV?

What pharmacologic or nonpharmacologic PONV prevention or treatment options are recommended for this patient?

What treatment options would be recommended if she experiences PONV despite receiving prophylactic antiemetic agents?

If PONV occurs despite appropriate prophylaxis, it should be treated with an antiemetic from a pharmacologic class not already administered.[23] If no prophylaxis was used, a low-dose 5-HT_3 antagonist should be used.[23]

Nausea and Vomiting of Pregnancy

LO 6

KEY CONCEPT Nausea and vomiting affect the majority of pregnant women; the teratogenic potential of the therapy is the primary consideration in drug selection, followed by severity of the nausea and vomiting.[6] Risks and benefits of any therapy must be weighed by the health care professional and the patient.

Pyridoxine (vitamin B_6) 10 to 25 mg four times daily alone or in combination with an antihistamine such as doxylamine is first-line pharmacotherapy for NVP.[6,11] A combination product is available (Diclegis) with a recommended dose of two 10 mg/10 mg delayed-release tablets at bedtime. Pyridoxine is well tolerated, but doxylamine and other antihistamines may cause drowsiness.

Ondansetron (pregnancy category B) has been used to treat severe NVP; animal data do not indicate a safety concern in pregnancy, but safety and efficacy data in humans for NVP are sparse. Although the safety of anticholinergics and metoclopramide have been established, data demonstrating efficacy are lacking.[6]

In rare instances (0.3%–3% of pregnancies), NVP progresses to hyperemesis gravidarum.[6] Enteral or parenteral nutrition might be used if oral liquids cannot be tolerated or if dehydration occurs. A corticosteroid such as methylprednisolone may be considered. Because methylprednisolone is associated with oral clefts in the fetus when used during the first trimester, corticosteroids should be reserved as a last resort and should be avoided during the first 10 weeks of gestation.[6,11]

Patient Encounter 2

A 30-year-old woman who is 11 weeks pregnant with NVP seeks your advice. She complains of constant nausea, frequent vomiting, increased thirst, decreased urine output, and weight loss. She has been unable to tolerate oral liquids. Her medications are doxylamine 10 mg-pyridoxine 10 mg delayed release, 2 tablets at bedtime. In addition, she has been taking prenatal vitamins since before her pregnancy and has tried avoiding provoking stimuli, eating frequent small meals, and avoiding spicy and fatty foods.

What type of nausea and vomiting is this patient experiencing?

What nonpharmacologic and pharmacologic treatment options may help prevent and treat this patient's nausea and vomiting?

Should this patient seek additional medical attention for her symptoms?

Motion Sickness and Vestibular Disturbances

Nausea and vomiting can be caused by disturbances of the vestibular system in the inner ear because of infection, trauma, neoplasm, or motion.[16] Patients may experience dizziness and vertigo in addition to nausea and vomiting. If a patient is susceptible to motion sickness, preventive measures include minimizing exposure to movement, restricting visual activity, ensuring adequate ventilation, reducing the magnitude of movement, and taking part in distracting activities.[16]

LO 6

KEY CONCEPT Because the vestibular system is replete with muscarinic type cholinergic and histaminic (H_1) receptors, anticholinergics and antihistamines are the most commonly used agents to prevent and treat motion sickness. Oral medications should be taken prior to motion exposure to allow time for adequate absorption. Once nausea and vomiting due to motion sickness occur, oral medication absorption may be unreliable, making the therapies ineffective. Transdermal scopolamine

Patient Encounter 3

A 70-year-old woman who presents to your practice is planning a 10-day Mediterranean cruise. She has a past medical history significant for overactive bladder and hypertension for which she takes oxybutynin 10 mg XR once daily and lisinopril 10 mg once daily. She has experienced nausea and vomiting during boat rides in the past and states that a friend recommended she purchase "a patch" at her local pharmacy to prevent nausea and vomiting.

What recommendations for nonpharmacologic interventions would you give this patient to help prevent motion sickness?

What are the pharmacologic options for this patient to prevent or treat nausea and vomiting?

What potential adverse effects would you counsel this patient about?

may be considered as a first-line option for patients who cannot tolerate oral medications or who require treatment for a prolonged period.[16] Drowsiness and reduced mental acuity are the most bothersome side effects of antihistamines and anticholinergics. Visual disturbances, dry mouth, and urinary retention can also occur.

Pharmacist's Patient Care Process

Collect Information:

- Obtain a thorough patient history including the prescription, nonprescription, and herbal medications being used. Identify any substances that may be causing or worsening nausea and vomiting.

Assess the Information:

- Assess the patient to determine whether the nausea and vomiting is simple or complex and whether patient-directed therapy is appropriate.
- Determine which treatments for nausea and vomiting have been used in the past and their degree of efficacy.

Develop a Care Plan:

- Eliminate the underlying cause of nausea and vomiting if possible.
- Develop a treatment plan with the patient and other health care professionals if appropriate.
- Choose treatments based on the underlying cause of nausea and vomiting, duration and severity of symptoms, comorbid conditions, medication allergies, presence of contraindications, risk of drug–drug interactions, and adverse-effect profiles.
- Use the oral route for mild nausea with minimal or no vomiting. Seek an alternative route (eg, transdermal, rectal, parenteral) if the patient is unable to retain oral medications due to vomiting.

Implement the Care Plan:

- Counsel the patient to avoid known triggers.
- Provide patient education regarding causes of nausea and vomiting, avoidance of triggers, potential complications, treatment options, medication adverse effects, and when to seek medical attention.
- Educate the patient about nonpharmacologic measures such as stimulus avoidance, dietary changes, acupressure or acupuncture, and psychotherapy.

Follow-up: Monitor and Evaluate:

- To assess efficacy, ask the patient whether nausea or vomiting is resolving with therapy. Assess whether treatment failure is due to inappropriate medication use or the need for additional or different treatments and proceed accordingly.
- Assess adverse effects by asking the patient what he or she has experienced. Patient observation or examination is also useful for diagnosing adverse effects such as EPS.

OUTCOME EVALUATION

LO 7

- The symptoms of simple nausea and vomiting are self-limited or relieved with minimal treatment. Monitor patients for adequate oral intake and alleviation of nausea and vomiting.
- Patients with complex nausea and vomiting may have malnourishment, dehydration, and electrolyte abnormalities.
- If the patient has weight loss, assess whether enteral or parenteral nutrition is needed.
- Assess for dry mucous membranes, skin tenting, tachycardia, and lack of axillary moisture to determine if dehydration is present.
- Obtain blood urea nitrogen (BUN), serum creatinine (SCr), calculated fractional excretion of sodium (FeNa), serum electrolytes, and arterial blood gases.
- Ask patients to rate the severity of nausea.
- Monitor the number and volume of vomiting episodes.
- Ask patients about adverse effects to the antiemetics used. Use this information to assess efficacy and tailor the patient's antiemetic regimen.

Abbreviations Introduced in This Chapter

CINV	Chemotherapy-induced nausea and vomiting
CTZ	Chemoreceptor trigger zone
D_2	Dopamine type 2 receptor
EPS	Extrapyramidal symptoms
FeNa	Fractional excretion of sodium
GERD	Gastroesophageal reflux disease
H_1	Histamine type 1 receptor
$5\text{-}HT_3$	5-Hydroxytryptamine (serotonin) type 3 receptors
NK_1	Neurokinin type 1 receptors
NVP	Nausea and vomiting of pregnancy
PONV	Postoperative nausea and vomiting

REFERENCES

1. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. Ther Adv Gastroenterol. 2016;9:98–112.
2. McQuaid K. Approach to the patient with gastrointestinal disease. In: Goldman L, Schafer AI, eds. Goldman's Cecil Medicine, 24th ed. Philadelphia: Elsevier Saunders; 2012.
3. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Onc. 2017;35(28):3240–3261.
4. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2014;118:85–113.
5. Cao X, White PF, Ma H. An update on the management of postoperative nausea and vomiting. J Anesth. 2017;31:617–626.
6. Nausea and vomiting of pregnancy. Practice Bulletin No. 153. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2015;126:e12–e24.
7. McQuaid KR. Drugs used in the treatment of gastrointestinal diseases. In: Katzung BG, Trevor AJ, eds. Basic and Clinical Pharmacology, 13th ed. New York: McGraw-Hill Education; 2015:1052–1083.
8. Tageja N, Groninger H. Chemotherapy-induced nausea and vomiting: an overview and comparison of three consensus guidelines. Postgrad Med J. 2016;92:34–40.

9. Golding JF, Gersty MA. Pathophysiology and treatment of motion sickness. Curr Opin Neurol. 2015;28:83–88.
10. Gravatt L, Donohoe KL, DiPiro CV. Nausea and vomiting. In: DiPiro JT et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017.
11. Niebyl JR, Briggs GG. The pharmacologic management of nausea and vomiting of pregnancy. J Fam Pract. 2014;63:S31–S37.
12. Miller KE, Muth ER. Efficacy of acupressure and acustimulation bands for the prevention of motion sickness. Aviat Space Environ Med. 2004;75:227–234.
13. Lee A, Fan LT. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2009(2):CD003281. doi: 10.1002/14651858.CD003281.pub3.
14. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011;29:4189–4198.
15. Antor MA, Uribe AA, Erminy-Falcon N, et al. The effect of transdermal scopolamine for the prevention of postoperative nausea and vomiting. Front Pharmacol. 2014;5:55.
16. Brainard A, Gresham C. Prevention and treatment of motion sickness. Am Fam Physician. 2014;90(1):41–46.
17. Cheung BS, Heskin R, Hofer KD. Failure of cetirizine and fexofenadine to prevent motion sickness. Ann Pharmacother. 2003;37:173–177.
18. Ernst AA, Weiss SJ, Park S, Takakuwa KM, Diercks DB. Prochlorperazine versus promethazine for uncomplicated nausea and vomiting in the emergency department: a randomized, double-blind clinical trial. Ann Emerg Med. 2000;36:89–94.
19. Habib AS, Gan TJ. The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: a preliminary report. J Clin Anesth. 2005;17:62–65.
20. Patanwala AE, Amini R, Hays D, Rosen P. Antiemetic therapy for nausea and vomiting in the emergency department. J Emerg Med. 2010;39(3):330–336.
21. Collins RW, Jones JB, Walthall JD, et al. Intravenous administration of prochlorperazine by 15-minute infusion versus 2-minute bolus does not affect the incidence of akathisia: a prospective, randomized, controlled trial. Ann Emerg Med. 2001;38:491–496.
22. DailyMed. US National Library of Medicine. Droperidol drug label information. Updated November 11, 2013 https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=147e033d-d997-4ef6-8bb5-a9ba372590b2. Accessed August 28, 2017.
23. Gan TJ, Meyer TA, Apfel CC, et al. Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2007;105:1615–1628.
24. Rosow CE, Haspel KL, Smith SE, Grecu L, Bittner EA. Haloperidol versus ondansetron for prophylaxis of postoperative nausea and vomiting. Anesth Analg. 2008;106:1407–1409.
25. Stevens JE, Jone KL, Rayner CK, Horowitz M. Pathophysiology and pharmacotherapy of gastroparesis: current and future perspectives. Expert Opin Pharmacother. 2013;14:1171–1186.
26. Minami M, Endo T, Hirafuji M, et al. Pharmacological aspects of anticancer drug-induced emesis with emphasis on serotonin release and vagal nerve activity. Pharmacol Ther. 2003;99:149–165.
27. Davis M, Maida V, Daeninck P, Pergolizzi J. The emerging role of cannabinoid neuromodulators in symptom management. Support Care Cancer. 2007;15:63–71.
28. Trigg ME, Higa GM. Chemotherapy-induced nausea and vomiting: antiemetic trials that impacted clinical practice. J Oncol Pharm Pract. 2010;16:233–244.
29. Smith HS, Cox LR, Smith EJ. 5-HT3 receptor antagonists for the treatment of nausea/vomiting. Ann Palliat Med. 2012;1:115–120.
30. Affronti ML, Bubalo J. Palonosetron in the management of chemotherapy-induced nausea and vomiting in patients receiving multiple-day chemotherapy. Cancer Manag Res. 2014:6;329–337.
31. Navari RM. Management of chemotherapy-induced nausea and vomiting: focus on newer agents and new uses for older agents. Drugs. 2013;73:249–262.
32. dos Santos LV, Souza FH, Brunetto AT, et al. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting: a systematic review. J Natl Cancer Inst. 2012;104:1280–1292.
33. Kovac AL. Update on the management of postoperative nausea and vomiting. Drugs. 2013;73:1525–1547.
34. Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomized, active-controlled, double-blind, phase 3 trials. Lancet Oncol. 2015;16:1079–1089.
35. Rapoport BL. Delayed chemotherapy-induced nausea and vomiting: pathogenesis, incidence, and current management. Front Pharmacol. 2017;8:1–10.

21 Constipation, Diarrhea, and Irritable Bowel Syndrome

Beverly C. Mims

LEARNING OBJECTIVES

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

LO

1. Identify the causes of constipation.
2. Compare the features of constipation with those of irritable bowel syndrome with constipation (IBS-C).
3. Recommend lifestyle modifications and pharmacotherapy for treatment of constipation.
4. Distinguish between acute and chronic diarrhea.
5. Compare diarrhea caused by different infectious agents.
6. Explain how medication use can cause diarrhea.
7. Discuss nonpharmacologic strategies for treating diarrhea.
8. Identify the signs and symptoms of IBS.
9. Contrast IBS with diarrhea (IBS-D) and IBS-C.
10. Establish treatment goals for IBS.
11. Evaluate the effectiveness of pharmacotherapy for IBS.

INTRODUCTION

Constipation and diarrhea are common gastrointestinal (GI) complaints that have various etiologies. Thorough patient assessment is important to accurately identify the underlying cause and implement safe and effective treatment. Functional gastrointestinal disorders (FGIDs) have received increasing attention in recent years.[1] FGIDs are characterized by persistent and recurring GI symptoms due to abnormal GI tract function but without structural or biochemical abnormalities. As a result, many diagnostic tests (eg, x-rays, endoscopic examinations) are often negative. The most common FGID is irritable bowel syndrome (IBS). This chapter will focus on the evaluation and management of constipation, diarrhea, and IBS.

CONSTIPATION

KEY CONCEPT Constipation, when not associated with symptoms of IBS, is a syndrome characterized by infrequent bowel movements (< 3 stools per week) or difficult passage of stools, hard stools, or a feeling of incomplete evacuation. Occasional constipation usually does not require medical evaluation or treatment.

EPIDEMIOLOGY AND ETIOLOGY

Constipation affects people of all ages and occurs in approximately 16% of all adults and in one-third of adults age 60 and older. Although it is rarely life threatening, constipation results in over 8 million physician visits, 1.1 million hospitalizations, and 5.3 million prescriptions annually. In 2016, US sales of nonprescription laxative products totaled more than $1.3 billion.[2]

LO 1

Constipation can be due to primary and secondary causes (Table 21–1). Functional constipation is defined as constantly problematic, infrequent, or seemingly incomplete defecation that does not meet criteria for diagnosis of IBS. Opioid-induced constipation (OIC) is defined as a change from baseline bowel habits and patterns of defecation after initiating opioid therapy that is characterized by reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete bowel evacuation, or the patient's perception of stress related to bowel habits.[3] OIC is an opioid-induced adverse effect that can overlap with and worsen functional constipation.[4] OIC constipation is associated with significant economic burden. In cancer patients taking opioids for pain the incidence of OIC constipation approached 94%.[5] Constipation is associated with significant socioeconomic costs and considerable quality-of-life ramifications.[5,6] Physiological, environmental, and demographic factors may play roles in the development of constipation. Some diseases and many medications are associated with constipation.[7,8]

PATHOPHYSIOLOGY

Primary or idiopathic constipation is categorized as normal-transit constipation (NTC), slow-transit constipation (STC), or defecatory or rectal evacuation disorders. In NTC, colonic motility is unchanged, and patients experience hard stools despite normal movements. In STC, motility is decreased or caloric intake is inadequate, resulting in infrequent, harder, drier stools. Dyssynergic defecatory or rectal evacuation disorders involve prolonged rectal storage of fecal residue or disorders of evacuation with normal or delayed colonic transit resulting in incomplete expulsion of feces from the rectum. Underlying causes may include inadequate relaxation of muscles or paradoxical

Table 21–1

Some Causes of Constipation

Primary Causes
Normal-transit constipation
Slow-transit constipation (disturbances of neurogastroentero- and brain-gut interactions, inadequate caloric intake)
Defecatory or colonic/rectal evacuation disorders

Secondary Causes (Selected)
Endocrine/metabolic conditions (diabetes mellitus, hypercalcemia, hypokalemia, hypomagnesemia, hypothyroidism, uremia)
Myopathies (amyloidosis, scleroderma)
Neurogenic conditions (brain trauma, stroke, Parkinson disease, multiple sclerosis, spinal cord injury or tumor)
Mechanical obstruction (colon cancer, lesion compression, stricture, rectocele)
Medications (analgesics, anticholinergics, antidiarrheals, antihistamines, some antipsychotics and antidepressants, aluminum-containing products, calcium channel blockers, calcium-containing products, clonidine, diuretics, iron-containing supplements, ondansetron, phenothiazines)
Other (autonomic neuropathy, cardiac disease, cognitive impairment, diet, volume depletion, immobility, laxative abuse, postponing urge to defecate, deliberate suppression of defecation, psychological distress, perceptions about bowel frequency)

contractions of the pelvic diaphragm, perineal membrane and deep perineal pouch (the pelvic floor), and the external anal sphincter during defecation.[7-9] Chronic constipation without an identifiable cause is often referred to as chronic idiopathic constipation (CIC).

Physiologic changes associated with OIC occur when opioids activate GI tract G-protein–coupled opioid μ, κ, and δ receptors. Activation of these receptors reduces acetylcholine release, which contributes to physiologic changes such as decreased propulsive activity; increased nonpropulsive contractions; decreased pancreatic, biliary and gastric secretions; and increased anal tone. All of these changes may contribute to constipation.[10]

CLINICAL PRESENTATION AND DIAGNOSIS

A medical history is important to ascertain the frequency and character of bowel movements and the duration of symptoms (see accompanying box for the clinical presentation of constipation). It is important to understand the symptoms that the patient considers to constitute constipation. Dietary, hydration, and physical activity habits should also be determined to identify potential contributing factors. Family history should be assessed for the presence of inflammatory bowel disease and colon cancer. A complete record of prescription medications, over-the-counter products, and dietary supplements is mandatory to identify drug-related causes.

KEY CONCEPT The diagnosis of constipation is based on clinical history, physical examination, minimal laboratory tests, colonoscopy or other procedures, and specific tests to evaluate underlying pathophysiology.

Endoscopy is required in patients with weight loss greater than 10 pounds in 3 months, rectal bleeding, or anemia to exclude cancer or strictures, especially in patients older than 50 years. Anorectal examination, manometry, radiography, colonoscopy, and other procedures may be useful in certain circumstances.

Clinical Presentation and Diagnosis of Constipation

Symptoms of Constipation

- Infrequent bowel movements (fewer than three per week); straining; lumpy or hard stools; painful or difficult defecation; abdominal pain or distention; bloating; sensation of incomplete evacuation, anorectal obstruction, or blockage; and need for manual maneuvers to facilitate defecations.
- Alarm (or "red flag") findings include worsening of constipation, sudden change in bowel habits after age 50, rectal bleeding in the absence of documented hemorrhoids or anal fissures, unintentional weight loss (> 10% within 3 months), family history of colon cancer or family polyposis syndromes, anemia, or recent constipation onset without explanation. These findings require prompt medical evaluation and appropriate intervention.

Physical Examination

- Presence of central nervous system (CNS) or spinal cord lesions may suggest an underlying cause.
- Abdominal examination findings may include distention, hard stool in a palpable colon, or abdominal mass.
- Rectal examination may indicate fecal impaction, anal stricture, or rectal mass.

Laboratory Tests (to Identify Secondary Causes)

- Thyroid-stimulating hormone (hypothyroidism)
- Serum calcium (may be increased or decreased)
- Glucose (diabetes mellitus)
- Serum electrolytes (dehydration, volume depletion)
- Urinalysis (dehydration)
- Complete blood count (anemia)

Other Tests

- Screening colonoscopy and other specialized tests may be conducted based on presenting signs and symptoms.

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In most cases, the physical examination is normal, and no underlying cause of constipation is identified. However, evaluation may reveal one or more of the following conditions: (a) IBS with constipation (IBS-C); (b) STC with normal pelvic floor function and evidence of slow transit; (c) a defecatory disorder; (d) a combination of IBS-C and STC; (e) organic constipation (mechanical obstruction or adverse drug effect); and (f) secondary constipation (metabolic disorder).[7,8]

TREATMENT

Desired Outcomes

The primary goals of treatment are to: (a) educate the patient, (b) identify underlying causes, (c) treat or remove secondary causes, (d) relieve symptoms, and (e) restore normal bowel function.[1,7,8] The treatment of constipation depends on the characteristics, severity, and cause of symptoms.

Nonpharmacologic Therapy

KEY CONCEPT In many cases nonpharmacologic treatment including lifestyle and dietary modifications should be employed prior to recommending pharmacotherapy. The patient should be

educated about possible causes of constipation and appropriate use of nonpharmacologic measures described below. Medication use should be evaluated to identify possible contributing factors. Patients should be encouraged to schedule routine bathroom time after the morning or evening meal. It may be helpful to elevate the feet with a stool during defecation.

LO 3 Increased dietary fiber intake or fiber supplementation (total 20–30 g/day) can improve NTC, whereas patients with STC or drug-induced constipation are unlikely to respond to increased fiber. High-fiber foods include beans, whole grains, bran cereals, fresh fruits, and vegetables such as asparagus, brussels sprouts, cabbage, and carrots.

There are two types of fiber: soluble and insoluble. Soluble fiber is dissolved by water and forms a gel that slows digestion. Some sources of soluble fiber include lentils, apples, nuts, flaxseed, and psyllium. Insoluble fiber does not dissolve in water and remains mostly intact as it decreases the time at which food and feces traverse the intestines. Insoluble fiber adds bulk to the diet and helps prevent constipation. Some sources of insoluble fiber include whole wheat, corn bran, couscous, dark leafy green vegetables, and root vegetable skins.

LO 3 Adequate fluid intake is important, especially in patients with evidence of volume depletion. Adult men aged 19 years and over should ingest 3.7 L and women aged 19 and over should ingest 2.7 L of water daily. The thirst mechanism changes with age; keeping a daily intake diary may assist patients who need to be reminded to drink fluids. Increased exercise may improve symptoms of constipation.[1,3] Some trials have indicated that ingestion of **probiotics** may improve stool consistency and stool frequency in patients with constipation.[3]

LO 3 Biofeedback-aided pelvic floor training may be useful for treatment of defecatory disorders. Patients are guided to demonstrate the ability to coordinate abdominal and pelvic floor motion during evacuation.[3]

LO 3 Surgery may be considered after all other approaches have failed and activities of daily living are compromised. Colectomy and ileorectal anastomosis may be considered in select patients with slow-transit constipation.[3]

Pharmacologic Therapy

LO 3 KEY CONCEPT Oral laxatives are the primary pharmacologic intervention for relief of most forms of constipation, including OIC; several different drug classes are available (Table 21–2). Additional treatment options for OIC include a calcium-channel activator and peripherally acting μ-opioid receptor antagonists.[11]

▶ *Bulk Producers*

These agents are either naturally derived (psyllium), semisynthetic (polycarbophil), or synthetic (methylcellulose) fiber supplements. They act by swelling in intestinal fluid, forming a gel that aids in fecal elimination and promoting peristalsis. They may cause flatulence (less commonly with methylcellulose), bloating, distention, and abdominal cramping. Fiber supplements may result in less improvement in patients with delayed colon transit constipation and/or obstruction. Bulk-forming or fiber laxatives must be taken with sufficient water (240 mL/dose) to avoid becoming lodged in the esophagus and producing obstruction or worsening constipation. Hypersensitivity reactions may occur and rarely may be manifested as an anaphylactic reaction.

▶ *Osmotics*

Lactulose, sorbitol, and glycerin are osmolar sugars. These products cause water to enter the lumen of the colon and may

Table 21–2

Dosage Recommendations for Treatment of Constipation

Agent	Adults and Children Ages 12 and Over	Children Ages 6–11 Years
OTC Agents That Cause Softening of Feces in 1–3 Days		
Bulk-forming agents/osmotic laxatives		
Methylcellulose	4–6 g/day PO	0.45–1.5 g PO per dose up to 3 g/day
Polycarbophil	4–6 g PO daily	On advice of practitioner
Psyllium	Varies with product	On advice of practitioner
Emollients		
Docusate sodium	50–360 mg PO daily	50–100 mg PO daily
Docusate calcium	50–360 mg PO daily	On advice of practitioner
Docusate potassium	100–300 mg PO daily	100 mg PO daily
Lactulose	15–30 mL PO daily	7.5 mL (5 g) PO daily
Sorbitol	30–50 g/day PO daily	2 mL/kg (as 70% solution) PO daily
Mineral oil	15–30 mL PO daily	5–15 mL PO daily
OTC Agents That Result in Soft or Semifluid Stool in 6–12 Hours		
Bisacodyl (oral)	5–15 mg PO	5–10 mg (0.3 mg/kg) PO
Senna	Dose varies with formulation	6–25 mg PO once or twice daily
OTC Agents That Cause Watery Evacuation in 1–6 Hours or Less		
Magnesium citrate	120–300 mL PO	100–150 mL PO
Magnesium hydroxide[a]	30–60 mL PO (15–30 mL of concentrate PO)	2.5–5 mL PO up to four times
Magnesium sulfate[a]	10–30 g PO	5–10 g PO
Bisacodyl (suppository)	10 mg rectally	5 mg rectally (1/2 suppository)
Polyethylene glycol–electrolyte preparations	Up to 4 L PO	Safety and efficacy not established
Miscellaneous Agents		
Linaclotide	145 mcg PO once daily	Safety and efficacy not established in patients under age 18; contraindicated in children < 6 years old
Plecanatide	3 mg PO once daily with or without food	Safety and efficacy not established in age <18 years; contraindicated in < 6 years of age; avoid use in ages 6–18 years. Watch for diarrhea and dehydration in all ages

[a]Magnesium can accumulate in renal dysfunction.

stimulate peristalsis. Lactulose acidifies colonic contents, increases water content of the gut, and softens the stool. Glycerin causes local irritation and possesses hyperosmotic action. Glycerin may be administered rectally and can cause rectal discomfort. Sorbitol can cause intestinal irritation and may affect blood glucose levels in diabetic patients. Osmotic agents may cause flatulence, abdominal cramping, and bloating. Polyethylene glycol (PEG) 3350 (MiraLAX) is used to treat occasional constipation and is expected to produce a bowel movement within 1 to 3 days. In patients with kidney disease this over-the-counter product should be used only on the advice and supervision of a physician.

Ingestion of PEG 3350 with electrolytes, a prescription product (eg, GoLYTELY, Colyte), is used for acute complete bowel evacuation prior to GI examination. PEG can cause distention and diarrhea.

▶ *Lubricants*

Lubricant laxatives coat the stool, allowing it to be expelled more easily. The oily film covering the stool also keeps the stool from losing its water to intestinal reabsorption processes. Oral mineral oil (liquid petrolatum) is a nonprescription heavy oil that should be used with caution, if at all, because it can be aspirated into the lungs and cause lipoid pneumonia. This is of particular concern in the young and elderly. It may also inhibit absorption of fat-soluble vitamins.

▶ *Stimulant Laxatives*

Diphenylmethane derivatives (eg, bisacodyl) and anthraquinones (eg, senna) have a selective action on the nerve plexus of intestinal smooth muscle leading to enhanced motility. Enteric-coated bisacodyl tablets should be swallowed whole to avoid gastric irritation and vomiting. Ingestion should be avoided within 1 to 2 hours of antacids, H_2-receptor antagonists, proton pump inhibitors, and milk. Bisacodyl oral tablets, rectal suppository, and enema products are available. The onset of effect is more rapid with rectal administration. The effects can be harsh (cramping), depending on the dose taken. Castor oil is used less frequently; it is pregnancy category X and is associated with uterine contractions and rupture. Use of castor oil in breastfeeding is considered "possibly unsafe."

▶ *Emollients*

Also known as surfactants and stool softeners, emollients (eg, salts of docusate) act by increasing the surface-wetting action on the stool leading to a softening effect. They reduce friction and make the stool easier to pass. The onset of action of stool softeners is longer than with most stimulants and may take up to 72 hours. These agents tend to be less effective in treating constipation of long duration.

▶ *Saline Agents*

Salts of sodium, magnesium, and phosphate pull water into the lumen of the intestines resulting in increased enteral pressure. Magnesium and phosphate may accumulate in patients with renal dysfunction. Principal concerns with sodium phosphate derivatives include dehydration, hypernatremia, hyperphosphatemia, acidosis, hypocalcemia, and worsening renal function. Elderly individuals and patients with heart failure and renal dysfunction should be advised to avoid saline agents. Nonprescription oral sodium phosphate solutions are no longer available because of the risk of acute phosphate nephropathy, a form of acute kidney injury. Prescription oral sodium phosphate products (eg, Visicol, OsmoPrep) used to cleanse the bowel prior to colonoscopy or other medical procedures contain a black box warning about this complication in high-risk patients.

Table 21–3

Medications for Treatment of Opioid-Induced Constipation[a]

Agent	Adults and Children Ages 12 and Over
Lubiprostone	24 mcg PO twice daily with food and water
Methylnaltrexone bromide	Given subcutaneously every other day based on body weight: 12 mg if 62–114 kg; 8 mg if 38–61 kg; other doses based on weight if outside these parameters
Naloxegol	25 mg PO once daily in the morning on an empty stomach or if not tolerated 12.5 mg PO daily
Naldemedine	0.2 mg PO once daily with or without food

[a]Safety and efficacy have not been established in children younger than age 12.

▶ *Intestinal Secretagogues*

Lubiprostone (Amitiza) This oral agent is derived from prostaglandin E_1 and acts locally on intestinal chloride channels to increase intestinal fluid secretion, resulting in increased intestinal motility and passage of stool.[11] It is approved for treatment of CIC and OIC in adults with chronic noncancer pain (Table 21–3). Efficacy and safety have not been established for constipation due to methadone (a diphenylheptane opioid derivative) or in children. Adverse effects of lubiprostone include dyspnea, nausea, diarrhea, abdominal distention and pain, flatulence, vomiting, and loose stools. Nausea may be minimized by taking lubiprostone with food. The capsule should be swallowed whole; it should not be chewed or broken apart. Lubiprostone is classified as pregnancy category C.[11-14]

Linaclotide (Linzess) The parent compound and its active metabolite activate guanylate cyclase-C (GC-C) act locally by increasing intracellular and extracellular concentrations of cyclic guanosine monophosphate (GMP). Cyclic GMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased interstitial fluid and intestinal transit. Linaclotide is indicated for treatment of IBS-C and CIC in adults only.[15]

The linaclotide dose for CIC is 145 mcg is administered once daily on an empty stomach at least 30 minutes before the first meal of the day; 72 mcg once daily can be used based on patient presentation and tolerability (Table 21–3). The capsule should be swallowed whole and not be broken or chewed.

Adverse effects of linaclotide include diarrhea, headache, fatigue, dehydration, abdominal pain, flatulence, and abdominal distention. Loose stools and greater stool frequency may occur after administration with a high-fat breakfast. Patients should be monitored for fluid and electrolyte loss. Linaclotide is classified as pregnancy category C.

Plecanatide (Trulance) This medication functions as a guanylate cyclase-C (GC-C) agonist. It is indicated for treatment of CIC in adults. The efficacy and safety of plecanatide have not been established in children less than 18 years of age, and it should be avoided in persons ages 6 to 18 years. It is contraindicated in children under the age of 6 years because increased fluid secretion may lead to serious dehydration.[16]

It is also contraindicated in patients with known or suspected mechanical GI obstruction.

The recommended adult dose of plecanatide is 3 mg orally once daily. The tablet can be given with or without food and should be swallowed whole. For adults with swallowing difficulties, the tablets can be crushed and administered orally either in applesauce or with water or given with water via a nasogastric or gastric feeding tube.

The major adverse effect associated with plecanatide is diarrhea, which may lead to discontinuation in some patients. Less common adverse effects include sinusitis, upper respiratory tract infection, abdominal distention, flatulence, abdominal tenderness, and increased hepatic enzymes. Although there is insufficient data on potential harm in pregnancy, plecanatide and its active metabolite are absorbed negligibly, and maternal use is not expected to result in fetal drug exposure.[16] No human lactation studies have yet been conducted.

▶ *Peripherally Acting μ-Opioid Receptor Antagonists (PAMORAs)*

There are currently three antagonists of opioid binding at the mu-opioid receptor that have negligible ability to cross the blood–brain barrier: methylnaltrexone bromide, naloxegol, and naldemedine (Table 21–3). They function as peripherally acting μ-opioid receptor antagonists (PAMORAs) in tissues such as the GI tract, thereby decreasing the constipating effects of opioids without diminishing the opioid analgesic effects in the CNS. They are indicated for treatment of OIC in adults with chronic pain that is not caused by active cancer (including chronic pain related to prior cancer or its treatment) who do not require frequent (eg, weekly) opioid dosage escalation.[17-19] The opioid analgesic regimen does not need to be altered before starting a PAMORA. Patients should be near toilet facilities after a PAMORA is administered. Patients receiving opioids for less than 4 weeks may be less responsive to these agents. All maintenance laxative therapy should be discontinued before starting a PAMORA; laxatives may be resumed if there is suboptimal response to the PAMORA after 3 days. Concomitant PAMORA use with other opioid antagonists can result in additive adverse effects and should be avoided. PAMORA treatment should be stopped if opioid therapy is discontinued.

The most common PAMORA adverse effects are abdominal pain, nausea, diarrhea, flatulence, and vomiting. GI perforation has been reported in patients with other conditions that reduce the structural integrity of the GI tract wall (eg, peptic ulcer disease, Crohn disease); the PAMORA should be discontinued if severe, persistent, or worsening abdominal pain occurs. Symptoms of opioid withdrawal may occur (sweating, chills, diarrhea, abdominal pain, anxiety, yawning) in patients physically dependent on opioids.

Methylnaltrexone Bromide (Relistor) is a quaternary amine derivative of naltrexone. The recommended oral dose is 450 mg (3 × 150-mg tablets) once daily with water on an empty stomach at least 30 minutes before the first meal of the day; there is a subcutaneous (SC) product that can also be used for treating OIC in adults with chronic noncancer pain; the dose is 12 mg SC once daily. The SC injection is also indicated for treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.[20] The SC injection is usually given every-other-day as needed; the dose is weight-based for this indication (refer to product labeling). The oral or SC methylnaltrexone dose must be reduced in patients with moderate to severe renal or hepatic dysfunction.

Naloxegol (Movantik) is a pegylated derivative of naloxone. The recommended dose is 25 mg orally once daily on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal. The dose may be reduced to 12.5 mg daily if the larger dose is not tolerated. The starting dose should also be reduced to 12.5 mg daily in patients with moderate to severe renal impairment. If a patient cannot swallow the tablet whole, it may be crushed to a powder, mixed with 4 oz (120 mL) of water, and administered immediately; the glass should then be refilled with 4 oz water, stirred, and the contents drunk.[21] Patients should avoid consumption of grapefruit and grapefruit juice because these foods may increase plasma naloxegol concentrations.

Naloxegol is contraindicated in patients receiving strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole) and should be avoided if possible in patients taking moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, verapamil) due to increased naloxegol concentration that may increase the risk of adverse reactions.

Naldemedine (Symproic) is a derivative of naltrexone that contains an added side chain that increases molecular weight and reduces its ability to cross the blood–brain barrier. It has binding affinities for μ-, δ-, κ-opioid receptors. The recommended dose is 0.2 mg orally once daily with or without food.[22]

Concomitant use of strong CYP3A inducers such as rifampin should be avoided because decreased naldemedine concentrations can occur. On the other hand, increased naldemedine concentrations can occur when moderate (eg, fluconazole) or strong (eg, itraconazole) CYP3A4 inhibitors are used concomitantly; patients should be monitored for adverse reactions. Naldemedine is also a substrate of the P-glycoprotein (P-gp) efflux transporter; patients taking P-gp inhibitors (eg, amiodarone, captopril, cyclosporine, verapamil) should be monitored for adverse effects due to increased naldemedine concentrations.

Treatment Recommendations

LO 3

The conventional effective, safe, and inexpensive modalities (fluid intake; dietary and supplemental fiber; stool softeners; and saline, stimulant, or osmotic laxatives) should be attempted before agents such as secretagogues are prescribed. The μ-receptor antagonists are indicated only for treatment of OIC.

Patients who are not constipated but need to avoid straining (eg, patients with hemorrhoids, hernia, or myocardial infarction) may benefit from stool softeners or mild laxatives such as PEG 3350.

Pregnant women should be advised to eat regular meals that are balanced among fruits, vegetables, and whole grains and maintain adequate water intake to avoid constipation. Bulk producers and stool softeners are probably safe during pregnancy because they are poorly absorbed. Lactulose and magnesium products are pregnancy category B. Magnesium-based antacids have minimal absorption and are considered low risk in pregnant women. Long-term use of magnesium citrate should be avoided (pregnancy category B). Laxatives may provide relief for constipation occurring during the postpartum period when the mother is not breastfeeding.

Children younger than 6 years old should be evaluated by a healthcare provider before being given a laxative because they may not be able to describe their symptoms well. Evaluation of patients' ability to recognize and self-report constipation symptoms should be considered. Treating secondary causes may resolve constipation without use of laxatives. As in adults, children benefit from a balanced diet and adequate water intake.

Patient Encounter 1

An 89-year-old man with chronic constipation was admitted to the hospital after a fall. He lives with his daughter and her family. Review of his medication profile revealed the following: amlodipine 10 mg orally daily, calcium carbonate 650 mg plus vitamin D 4000 IU twice daily. The patient stated that he fell at about 10:30 AM as he was leaving the bathroom. The medical team determined that he suffered no serious injury and had no cognitive impairment. All laboratory tests were within the reference ranges, and the patient was discharged to home.

What general approach to this patient should be employed?

What are the possible contributing causes of his constipation?

What nonpharmacologic and pharmacologic therapies would be appropriate for his condition?

Because many older persons experience constipation, laxative use is sometimes viewed as a normal part of daily life. However, oral ingestion of mineral oil can present a particular hazard to bedridden individuals because inhalation of oil droplets can lead to pneumonia. Lactulose may be a better choice in this situation. Regular use of any laxative that affects fluid and electrolytes may result in significant adverse effects.

Patients with the following conditions should use laxatives only under the supervision of a health care provider: (a) colostomy; (b) diabetes mellitus (some laxatives contain sugars such as dextrose, galactose, and/or sucrose); (c) heart disease (some products contain sodium); (d) kidney disease; and (e) swallowing difficulty (bulk-formers may produce esophageal obstruction). Saline laxatives containing magnesium, potassium, or phosphates should be used cautiously in persons with reduced kidney function. Monitor appropriate serum electrolyte concentrations in patients with unstable renal function evidenced by changing serum creatinine or creatinine clearance.

OUTCOME EVALUATION

- Ask the patient about symptom improvement to determine effectiveness of laxative therapy. Patients should have an increase in stool frequency to three or more well-formed stools per week. Patients should report reduced defecation time or absence of excessive straining.
- When acute overuse or chronic misuse of saline or stimulant laxatives is suspected, electrolyte disturbances should be evaluated (eg, hypokalemia, hypernatremia, hyperphosphatemia, hypocalcemia).
- Some laxatives (eg, bulk producers) contain significant amounts of sodium or sugar and may be unsuitable for salt-restricted or diabetic patients. Monitoring of fluid retention (edema) and blood pressure changes is indicated in patients on sodium-restricted diets. Glucose monitoring may be required in diabetic patients with chronic use. Use of low-sodium or sugar-free products may be indicated.
- All laxatives are contraindicated in patients with undiagnosed abdominal pain, nausea, or vomiting. Patients should consult their health care providers if changes in bowel habits persist for more than 14 days or if laxative use for 7 or more days results in no effect.

Patient Care Process for Constipation

Collect Information:

- Ask about symptoms to determine if patient-directed therapy is appropriate or if the patient should be evaluated by a physician. Determine type, frequency, and duration of symptoms; presence or absence of abdominal pain; and exclude the presence of alarm symptoms.
- Review available information to determine potential causes and type of constipation. List factors that seem to make it better or worse. Assess dietary habits, fluid intake, and level of physical activity. Use of bowel and medication diary may help identify patterns. Use of the Bristol Stool Form Scale may be considered (see https://en.wikipedia.org/wiki/Bristol_stool_scale).

Assess the Information:

- Obtain a thorough history of prescription medication, nonprescription product, and dietary supplement use. Determine what treatments have been helpful in the past, whether the patient is taking any medications that may contribute to constipation, usual diet, and fluid intake. Assess for the presence of adverse drug reactions, drug allergies, and drug interactions.
- Assess the presence of pain to help differentiate functional constipation condition from possible IBS-C.

Develop a Care Plan:

- Recommend administration of soluble dietary fiber such as psyllium, then an osmotic agent such as PEG, then a magnesium-based or stimulant/stool softener-based product.
- Provide patient education about constipation, dietary modifications, and drug therapy. Consider asking, "Do you take the time to have a bowel movement?"

Implement the Care Plan:

- Educate the patient about causes of constipation and recommend ways to avoid it.
- Counsel the patient about appropriate laxative use, when to expect onset of relief, need for adequate fluid intake, and to seek medical attention if there is no improvement with laxative use in 3 or more days or if symptoms worsen.
- Advise the patient to seek medical attention if alarm symptoms occur.

Follow-up: Monitor and Evaluate:

- Develop a plan to assess the effectiveness of laxative use.

DIARRHEA

The definition of diarrhea is based on two characteristics of stool: frequency and consistency.[23] Diarrhea can be defined as increased frequency of passing abnormally liquid or unformed stools. Functional diarrhea is defined as the presence of loose or watery stools, without predominant abdominal pain or bothersome bloating, occurring in more than 25% of stools. The symptoms must be present for the last 3 months with symptom onset at least 6 months before the diagnosis is made. Patients

LO 4 meeting the criteria for IBS-D should be excluded. Diarrhea is defined as acute if it lasts less than 2 weeks, persistent if it lasts from 2 to 4 weeks, and chronic if it lasts longer than 4 weeks.[23] The World Health Organization (WHO) describes three levels of severity: (1) mild (diarrhea three or more times a day with occasional abdominal discomfort); (2) moderate (diarrhea three or more times a day with painful abdominal cramps and thirst); and (3) severe (diarrhea three or more times a day with severe abdominal cramps, thirst, nausea, and tiredness).[24] Diarrhea can also be classified based on the appearance of the stool: fatty, inflammatory (associated with blood in the stool), or watery.[24]

EPIDEMIOLOGY AND ETIOLOGY

The WHO reported that in 2015 diarrhea was the eighth-leading cause of death globally (more than 1.3 million deaths), the second most common cause of death in low-income economies (> 57.2 million deaths) and the sixth most common cause of death in lower-middle income economies (over 30.9 million deaths).[25]

Acute Diarrhea

Acute diarrhea generally involves the sudden onset of three or more loose or liquid stools above baseline in a 24-hour period. More than 90% of cases of acute diarrhea are caused by infectious agents. Acute diarrheal infection is also referred to as gastroenteritis. Most infectious diarrheas are acquired by fecal–oral transmission or via ingestion of food or water contaminated with human or animal fecal pathogens. Many of these cases are accompanied by abdominal pain and cramps, bloating, flatulence, passage of bloody stools, tenesmus, fecal urgency, fever, and vomiting. Some acute GI infections may cause vomiting as a predominant symptom with little to no diarrhea.[25] The remaining 10% of acute diarrhea cases are caused by medications, toxic ingestions, ischemia, food intake, and other conditions. Acute diarrhea is a leading cause of outpatient visits and hospitalizations and has a direct negative impact on quality of life.[24]

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Viruses cause a large proportion of acute diarrhea cases. Common culprits include Rotavirus, Norwalk, and adenovirus. Bacterial causes include *Escherichia coli*, *Salmonella* species, *Shigella* species, *Vibrio cholerae*, and *Clostridium difficile* (especially if antibiotics had been administered). The term *dysentery* describes some of these bacterial infections when associated with serious occurrences of bloody diarrhea.[26]

Acute or persistent diarrheal conditions can also result from parasites and protozoa such as *Entamoeba histolytica*, *Microsporidium*, *Giardia lamblia*, and *Cryptosporidium parvum*. Most of these infectious agents can cause **traveler's diarrhea**, a common condition that can afflict travelers worldwide. It usually occurs during or just after travel following ingestion of food or water that is contaminated with feces. It has an abrupt onset but usually subsides within 2 to 3 days (see Chapter 76, Gastrointestinal Infections, for more detailed information on traveler's diarrhea).

Brainerd diarrhea may be associated with subtle distal small intestine or proximal colonic inflammatory changes and is believed to be caused by an infectious origin. It is described as an abrupt-onset diarrhea that persists for 4 weeks and may last 1 to 3 years. It is named after Brainerd, Minnesota, the community where the first outbreak occurred in 1983.

Noninfectious causes of acute diarrhea include drugs and toxins, laxative abuse, food intolerance, IBS, inflammatory bowel disease, ischemic bowel disease, lactase deficiency, vitamin B_{12} deficiency anemia, diabetes mellitus, malabsorption, fecal impaction, diverticulosis, and celiac sprue.

Lactose intolerance is responsible for many cases of acute diarrhea, especially in persons of African descent, Asians, and Native Americans. Possible food-related causes include fat substitutes, dairy products, and products containing nonabsorbable carbohydrates.

The diarrhea of IBS is sudden, perhaps watery but likely loose, usually accompanied by urgency, bloating, and abdominal pain often in the morning or immediately following a meal. Inflammatory bowel disease is typically associated with the sudden onset of bloody diarrhea accompanied by urgency, crampy abdominal pain, and fever. Patients who experience bowel ischemia may develop bloody diarrhea, particularly if they progress to shock.

In the United States, high-risk groups for acquiring acute diarrhea include travelers, consumers of certain foods, immunodeficient persons, daycare attendees and their family members, and institutionalized persons.

Chronic Diarrhea

Chronic diarrhea is much less likely to be infectious and usually results from functional or inflammatory bowel disorders, endocrine disorders, malabsorption syndromes, and drugs (including laxative abuse). Daily watery stools may not occur with chronic diarrhea. Diarrhea may be either intermittent or continual.[27]

PATHOPHYSIOLOGY

Approximately 9 L (2.4 gallons) of fluid normally traverse the GI tract daily. Of this amount, 2 L represent gastric juice, 1 L is saliva, 1 L is bile, 2 L are pancreatic juice, 1 L is intestinal secretions, and 2 L are ingested. Of the 9 L of fluid presented to the intestine, only about 150 to 200 mL remain in the stool after reabsorptive processes occur.

Any event that increases the amount of fluid retained in the stool may result in diarrhea. Large-stool diarrhea often signifies small intestinal involvement, whereas small-stool diarrhea usually originates in the colon. Diarrhea may be classified according to pathophysiologic mechanisms, including osmotic, secretory, inflammatory, and altered motility.

Osmotic diarrhea results from the intake of nonabsorbable, water-soluble solutes in the intestinal lumen leading to water retention. Common causes include lactose intolerance and ingestion of magnesium-containing antacids.

Secretory diarrhea results from increased movement (secretion) of ions into the intestinal lumen, leading to increased intraluminal fluid. Medications, hormones, and toxins may be responsible for secretory activity.

Inflammatory (or exudative) diarrhea results from changes to the intestinal mucosa that damage absorption processes leading to increased proteins and other products in the intestinal lumen with fluid retention. The presence of blood or fecal leukocytes in the stool indicates an inflammatory process. The diarrhea of inflammatory bowel disease fits this classification.

Increased motility results in decreased contact time of ingested food and drink with the intestinal mucosa, leading to reduced reabsorption and increased fluid in the stool. Diarrhea resulting from altered motility is often established after other mechanisms have been excluded. IBS-related diarrhea is due to altered motility.

Diarrhea may be attributed to a single or to multiple overlapping mechanisms. For example, malabsorption syndromes and traveler's diarrhea are associated with both secretory and osmotic mechanisms.

Table 21–4

Selected Drugs and Substances That May Cause Acute Diarrhea

Drugs			
Antibiotics	Hydralazine	Metformin	Sorbitol
Colchicine	Laxatives	Misoprostol	Theophylline
Digitalis	Mannitol	Quinidine	Thyroid products
Dietary Supplements			
St. John's wort	Echinacea	Ginseng	Aloe vera
Poisons			
Arsenic	Cadmium	Mercury	Monosodium glutamate

LO 6

Drugs are a common cause of diarrhea (Table 21–4). Drug-induced diarrhea can occur by several mechanisms. First, water can be drawn into the intestinal lumen osmotically (eg, saline laxatives). Second, the intestinal bacterial ecosystem can be upset leading to emergence of invasive pathologic organisms triggering secretory and inflammatory processes (eg, antibiotic use). Third, some drugs increase intestinal motility. Other drugs produce diarrhea through undetermined mechanisms (eg, procainamide, colchicine). Discontinuation of the offending drug may be the only measure needed to ameliorate diarrhea.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients with diarrhea should be questioned about the onset of symptoms, recent travel, diet, source of water, and medication use; see accompanying box for the clinical presentation of diarrhea. Other important considerations include duration and severity of the diarrhea and the presence of abdominal pain or vomiting; blood in the stool; stool consistency, appearance, and frequency; and weight loss. Although most cases of diarrhea are self-limited, infants, children, elderly persons, and immunocompromised patients are at risk for increased morbidity.

Findings on physical examination can assist in determining hydration status and disease severity. The presence of blood in the stool suggests an invasive organism, an inflammatory process, or perhaps a neoplasm. Large-volume stools suggest a small-intestinal disorder, whereas small-volume stools suggest a colon or rectal disorder. Further investigation should be performed in patients who present with diarrhea in the presence of alarm symptoms such as unintentional weight loss, diarrhea awakening the patient, recent antibiotic use, hematochezia (in the absence of documented bleeding hemorrhoids or anal fissures), very frequent bowel movement (> 6–10 daily), high volume diarrhea (> 250 mL of feces daily), evidence of malnutrition, family history of new or abnormal growth of colorectal tissue, celiac disease, or inflammatory bowel disease (IBS). Patients with prolonged or severe symptoms may require colonoscopic evaluation to identify the underlying cause.

TREATMENT

Acute diarrhea is generally self-limited, lasting 3 to 4 days even without treatment. Most healthy adults with diarrhea do not develop significant dehydration or other complications and can self-medicate symptomatically if necessary. KEY CONCEPT Dehydration can occur when diarrhea is severe and oral intake is limited, particularly in older persons and infants. Other complications of diarrhea resulting from fluid loss include electrolyte disturbances, metabolic acidosis, and cardiovascular collapse.

Children are more susceptible to dehydration (particularly when vomiting occurs) and may require medical attention early in the course, especially if younger than 3 years. Physician intervention is also necessary for elderly patients who are sensitive to fluid loss and electrolyte changes due to concurrent chronic illness.

Patients should undergo medical evaluation in the following circumstances: (a) moderate to severe abdominal tenderness, distention, or cramping; (b) bloody stools; (c) evidence of dehydration (eg, thirst, dry mouth, fatigue, dark-colored urine, infrequent urination, reduced urine, dry skin, reduced skin elasticity, rapid pulse, rapid breathing, muscle cramps, muscle

Clinical Presentation of Diarrhea

Signs and Symptoms of Acute Diarrhea

- Acute diarrhea presents abruptly as loose, watery, or semi-formed stools.
- Abdominal cramps and tenderness, rectal urgency, nausea, bloating, and fever may be present.
- Patients infected with invasive organisms may have bloody stools and severe abdominal pain.

Laboratory Tests in Acute Diarrhea

- Stool cultures can help identify infectious causes. Methods using real-time polymerase chain reaction shorten the reporting time.
- Stool may be analyzed for mucus, fat, osmolality, fecal leukocytes, and pH. Mucus fragments suggest colonic involvement; fat in the stool suggests malabsorption. Fecal leukocytes are present in inflammatory diarrheas including bacterial infections. Stool pH (normally > 6) is decreased by bacterial fermentation processes.
- Assessment of stool volume and electrolytes in large-volume watery stools may identify osmotic or secretory diarrhea.
- CBC and blood chemistries to determine extent of vitamin and electrolyte deficiencies may be helpful when symptoms persist. Findings of anemia, leukocytosis, or neutropenia offer further clues to the underlying cause.

Signs and Symptoms of Chronic Diarrhea

- Presenting symptoms may be severe or mild. Weight loss can be demonstrated, and weakness may be present.
- Dehydration may manifest as decreased urination, dark-colored urine, dry mucous membranes, increased thirst, and tachycardia.

Laboratory Tests in Chronic Diarrhea

- Tests described for acute diarrhea are also useful to diagnose chronic diarrhea; the differential diagnosis is more complicated. Results can help categorize the diarrhea as watery, inflammatory, or fatty, narrowing the focus on a primary disorder.
- Colonoscopy allows visualization, and biopsy of the colon and is preferred when there is blood in the stool or if the patient has acquired immune-deficiency syndrome.

weakness, sunken eyes, or lightheadedness); (d) high fever (38.3°C or 101°F or higher); (e) evidence of weight loss greater than 5% of total body weight; and (f) diarrhea that lasts longer than 48 hours.

Desired Outcomes

The goals of treatment for diarrhea are to relieve symptoms, maintain hydration, treat the underlying cause(s), and maintain nutrition. KEY CONCEPT The primary treatment of acute diarrhea includes fluid and electrolyte replacement, dietary modifications, and drug therapy.

Nonpharmacologic Therapy

▶ *Fluid and Electrolytes*

LO 7

Fluid replacement is not a treatment to relieve diarrhea but rather an attempt to restore fluid balance. In many parts of the world where diarrheal states are frequent and severe, fluid replacement is accomplished using oral rehydration solution (ORS), a measured mixture of water, salts, and glucose. The solution recognized by the WHO consists of 75 mEq/L (mmol/L) sodium, 75 mmol/L glucose, 65 mEq/L (mmol/L) chloride, 20 mEq/L (mmol/L) potassium, and 10 mEq/L (3.3 mmol/L) citrate, having a total osmolarity of 245 mOsm/L (mmol/L). A simple solution can be prepared from 1 L water mixed with eight teaspoonfuls of sugar and one teaspoonful of table salt. Some commercial products include Pedialyte, Rehydralyte, and CeraLyte.

Consistent intake of water (perhaps by slowly sipping), along with eating as tolerated, should restore lost fluids and salt for typical diarrhea sufferers. Patients may also replace lost fluid by drinking flat soft drinks such as ginger ale, tea, fruit juice, broth, or soup. Although sports drinks may be used to treat dehydration, caution should be exercised so they are not viewed as a casual panacea. Severe diarrhea may require use of parenteral solutions, and parenteral products should be used if patients are vomiting or unconscious.[23,24]

▶ *Dietary Modifications*

During an acute diarrheal episode, patients typically eat less as they focus on the diarrhea. Both children and adults should attempt to maintain nutrition because food helps replete lost nutrients and fluid volume. However, food-related fluid may not be sufficient to compensate for diarrheal losses. Some foods may be inappropriate if they irritate the GI tract or if they are implicated as the cause of the diarrhea. Patients with chronic diarrhea may find that increasing bulk in the diet may help (eg, rice, bananas, whole wheat, and bran).

Pharmacologic Therapy

The goal of drug therapy is to control symptoms, enabling the patient to continue with as normal a routine as possible while avoiding complications (Table 21–5). Most infectious diarrheas are self-limited or curable with anti-infective agents.

▶ *Adsorbents and Bulk Agents*

Attapulgite adsorbs excess fluid in the stool with few adverse effects. Formulations of attapulgite are available in Canada but not within the United States. Calcium polycarbophil is a hydrophilic polyacrylic resin (widely available in the United States) that also works as an adsorbent, binding about 60 times its weight in water and leading to formation of a gel that enhances stool formation. Neither attapulgite nor polycarbophil is systemically absorbed. Calcium polycarbophil is effective in reducing fluid in the stool. However, caution must be exercised because it can also adsorb nutrients and other medications, thereby reducing their benefits. Its administration should be separated from other oral medications by 2 to 3 hours. Psyllium and methylcellulose products may also be used to reduce fluid in the stool and relieve chronic diarrhea.

Table 21–5

Pharmacotherapy for Diarrhea

Drug	Usual Oral Dose	Type of Diarrhea
Calcium polycarbophil (OTC)	Adults: 1000 mg four times daily PO or after each loose stool, not to exceed 12 tablets per day Children 6–12 years: 500 mg PO three times daily Children 3–6 years: 500 mg twice daily	Chronic
Loperamide (OTC, RX)	Adults: 4 mg initially, then 2 mg PO after each subsequent loose stool. Maximum: 8 mg in 24 hours (OTC), 16 mg in 24 hours (RX) Children maximum daily doses: Age 2–5: 3 mg Age 6–8: 4 mg Age 8–12: 6 mg	Acute and chronic
Diphenoxylate/atropine (RX)	Adults: Two tablets (5 mg) initially, then one tablet PO every 3–4 hours, not to exceed 20 mg in 24 hours Children 2–12 years: Oral solution (avoid tablets) 0.3–0.4 mg/kg/day in divided doses. Do not administer to children younger than 2 years	Acute and chronic
Bismuth subsalicylate (OTC) (Kaopectate, PeptoBismol)	Adults and children 12 years and over: 524 mg/30 mL PO every 30–60 minutes as needed; Do not exceed 8 doses (240 mL or 16 tablets) per day Children: Consumers should speak with a physician before giving to children under 12 years of age	Traveler's and nonspecific acute diarrhea

OTC, over the counter; PO, by mouth; RX, prescription only.

▶ *Antiperistaltic (Antimotility) Agents*

Antiperistaltic drugs prolong intestinal transit time, thereby reducing the number of stools and the amount of fluid lost in the stool. The two drugs in this category are loperamide HCl (available over-the-counter as Imodium A–D and generically) and diphenoxylate HCl with atropine sulfate (available by prescription as Lomotil and generically). The atropine is included only as an abuse deterrent; when taken in large doses, the unpleasant anticholinergic effects of atropine negate the euphoric effect of diphenoxylate. Both loperamide and diphenoxylate are effective in relieving symptoms of acute noninfectious diarrhea and are

safe for most patients experiencing chronic diarrhea. These products should be discontinued in patients whose diarrhea worsens despite therapy.

Loperamide is considered safe when used in recommended doses. When excessive doses are ingested, severe problems such as cardiac arrhythmias and death can occur. Loperamide misuse and abuse has been reported. Coadministration of potent CYP450 3A4 inhibitors (eg, azole antifungals, clarithromycin, conivaptan, delavirdine, erythromycin, nefazodone, protease inhibitors, telithromycin) and 2C8 inhibitors (eg, gemfibrozil, clopidogrel) with loperamide may increase plasma loperamide concentrations and adverse effects. Patients who have ingested large doses of loperamide alone or with medications that can enhance loperamide effect may experience dizziness, lightheadedness, fainting, palpitations, irregular heart rhythm, shortness of breath, or syncope and should be advised to discontinue loperamide and seek medical attention.[28-31]

▶ *Antisecretory Agents*

Bismuth subsalicylate (BSS) is thought to have antisecretory and antimicrobial effects and is used to treat acute diarrhea. Although it passes largely unchanged through the GI tract, the salicylate portion is absorbed in the stomach and small intestine. For this reason, BSS should not be given to people who are allergic to salicylates, including aspirin. Caution should be exercised with regard to the total dose given to patients taking salicylates for other reasons to avoid **salicylism**. Patients taking BSS should be informed that their stool will turn black.

Octreotide is an antisecretory agent used for severe secretory diarrhea associated with cancer chemotherapy, human immunodeficiency virus, diabetes, gastric resection, and GI tumors. It is administered as a subcutaneous or IV bolus injection in an initial dose of 50 mcg three times daily to assess the patient's tolerance to GI adverse effects. Possible adverse effects include nausea, bloating, pain at the injection site, and gallstones (with prolonged therapy).

▶ *Probiotics, Prebiotics, and Synbiotics*

Probiotics are dietary supplements containing bacteria (*Lactobacillus* species, *Bifidobacterium* species, and others) that may promote health by enhancing the normal microflora of the GI tract while resisting colonization by potential pathogens. Probiotics can stimulate the immune response and suppress the inflammatory response. Probiotics can be taken in tablets, gummies, capsules, powders, and liquids. The type of product is not as important as the viability and number of organisms present.

Yogurt may provide relief from diarrhea due to lactose intolerance. The *Lactobacillus acidophilus* in yogurt, cottage cheese, and acidophilus milk improve digestion of lactose and may prevent or relieve diarrhea related to lactose deficiency and milk intake. Although lactase is not a probiotic, lactase tablets may also be used to prevent diarrhea in susceptible patients.

Patient Encounter 2

A 22-year-old female first-grade school teacher visited the urgent care clinic 3 weeks after the fall school year began complaining of fatigue, nausea, vomiting, episodes of mild abdominal pain, and frequent watery stools. She stated that she has increased thirst and her saliva has been thick and sticky. She also stated that her heart was racing after her evening walks the past few nights. She was excited to begin her teaching career but hasn't felt well for the past 3 days. Her temperature at home last night was 100°F (37.8°C). She is healthy and reports no known allergies; she recently began taking vitamin C to "improve resistance to infections."

Assess the likelihood that her diarrhea is due to an invasive microorganism.

Identify which of her symptoms suggest the presence of dehydration.

Discuss potential treatment measures for this woman.

Patient Care Process for Diarrhea

Collect Information:

- Determine symptoms, severity, frequency, and exacerbating factors.
- Review hydration status.
- Determine if patient-directed therapy is appropriate or a referral is needed.
- Inquire about recent foreign travel.
- Obtain history of prescription, nonprescription, and dietary supplement use.

Assess the Information:

- Review current therapy as potential cause(s) of diarrhea.
- Determine if any diarrhea treatments have been attempted, including home remedies.
- Assess need for medical evaluation if patient is pregnant, breastfeeding, younger than 3 years or older than 70 years, or has multiple medical conditions.

Develop a Care Plan:

- If home care is recommended, provide clear instructions about how to proceed if symptoms do not improve or new symptoms emerge.
- Discuss the importance of maintaining nutrition by diet modification.
- Educate the patient about: (a) acute and chronic diarrhea causes, (b) possible complications, (c) treatment goals, (d) the medication used to manage diarrhea, and (e) if appropriate, the circumstances when antibiotics are necessary.

Implement the Care Plan:

- Educate the patient about diarrhea and its likely causes.
- Advise the patient to seek medical attention if diarrhea does not resolve.

Follow-up: Monitor and Evaluate:

- Although most diarrheal episodes resolve with minimal intervention, individuals with a protracted course should be followed until symptoms have abated or are under control. Pay special attention to the very young, the aged, and those who are medically compromised.
- Refer the patient for medical attention if needed.

Prebiotics are nondigestible food ingredients that are fermentable in the colon and stimulate potentially health-promoting bacteria such as bifidobacteria and lactobacilli. Synbiotics are formed when prebiotics and postbiotics are joined. The use of fecal microbiota as biological agents in the treatment of diarrhea is being studied.

OUTCOME EVALUATION

- Monitor the patient with diarrhea from the point of first contact until symptoms resolve, keeping in mind that most episodes are self-limiting.
- Question the patient to determine whether symptom resolution occurs within 48 to 72 hours in acute diarrhea.
- Monitor for the maintenance of hydration, particularly when symptoms continue for more than 48 hours. Ask about increased thirst, decreased urination, dark-colored urine, dry mucous membranes, and rapid heartbeat, which suggest dehydration especially when nausea and vomiting are present.
- Monitor for symptom control in patients with chronic diarrhea.
- When antibiotics are used, monitor for completion of the course of therapy.

IRRITABLE BOWEL SYNDROME

KEY CONCEPT IBS is a functional bowel disorder (FBD) in which recurrent abdominal pain is associated with defecation or a change in bowel habits. In the absence of alarm symptoms such as rectal bleeding, family history of colon cancer, or unintentional weight loss, disordered bowel habits such as constipation, diarrhea, or a mix of constipation and diarrhea and symptoms of abdominal bloating/distention are usually present. IBS is classified into one of four types: (1) constipation predominant (IBS-C), (2) diarrhea predominant (IBS-D), (3) mixed with both constipation and diarrhea (IBS-M), or (4) unsubtyped (IBS-U; hard or lumpy stools < 25% of the time and loose or watery stools < 25% of the time). IBS is associated with frequent fluctuation in symptoms, loss of productivity, and decreased quality of life.[32]

LO 9

EPIDEMIOLOGY AND ETIOLOGY

The incidence and prevalence of IBS are unknown in many countries; therefore, global epidemiological features are difficult to determine. Furthermore, the current definition of IBS according to Rome IV criteria and consideration for cultural perspectives may affect the epidemiology of IBS.[1,32] IBS is one of the most common disorders seen in primary care and the most common reason for referral to gastroenterologists. Although between 15% and 20% of Americans suffer from IBS, only about one-quarter of those affected seek medical attention. The associated costs to society are estimated to be billions of dollars, and the recurrent nature of IBS contributes to these costs through missed workdays, inattention on the job, and high consumption of health care services.

In the United States, IBS affects women about twice as often as men. However, this may simply reflect a greater tendency to seek medical care. IBS can occur at any age but is most common between 20 and 50 years; onset beyond age 60 is rare.

IBS is associated with psychiatric distress, sleep disturbance, affective vulnerability, and difficulty adjusting behavior to environmental demands. Alcohol consumption and smoking have not been shown to be risk factors for developing IBS. However, alcohol may worsen symptoms in affected persons.

Some people show first evidence of IBS after contracting gastroenteritis (sometimes referred to as postinfectious IBS). This has led to speculation about whether infection heightens GI tract susceptibility. Menstrual periods may trigger symptoms in some women.[32]

PATHOPHYSIOLOGY

Enteric nerves control intestinal smooth muscle action and are connected to the brain by the autonomic nervous system. IBS is thought to result from dysregulation of this "brain–gut axis." The enteric nervous system is composed of two ganglionated plexuses that control gut innervation: the submucous plexus (Meissner plexus) and the myenteric plexus (Auerbach plexus). The enteric nervous system and the CNS are interconnected and interdependent. A number of neurochemicals mediate their function, including serotonin (5-hydroxytryptamine or 5-HT), acetylcholine, substance P, and nitric oxide, among others.[33]

Serotonin is particularly important because the GI tract contains the largest amounts in the body. Two 5-HT receptor subtypes, 5-HT_3 and 5-HT_4, are involved in gut motility, visceral sensitivity, and gut secretion. The 5-HT_3 receptors slow colonic transit and increase fluid absorption, whereas 5-HT_4 receptor stimulation accelerates colonic transit.

Although no single pathologic defect accounts for the pattern of exacerbation and remission in IBS, CNS abnormalities, dysmotility, visceral hypersensitivity, and other factors have been implicated.[33]

The passage of fluids into and out of the colon is regulated by epithelial cells. In IBS, the colonic lining (epithelium) appears to function properly. However, increased movement of the contents in the colon can overwhelm its absorptive capacity. Disturbed intestinal motility appears to be a central feature of IBS, which leads to altered stool consistency. Studies suggest that the colon of IBS sufferers is abnormally sensitive to normal stimuli. Enhanced visceral sensitivity manifests as pain, especially related to gut distention.

Some IBS patients demonstrate sensitivity to common foods such as wheat, beef, pork, soy, and eggs. Evidence suggests that an immune component may be involved in IBS patients who experience bloating and dysmotility-like dyspepsia and that gender specificity exists.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to the accompanying box for the clinical presentation of IBS. KEY CONCEPT The diagnosis of IBS is made by symptom-based criteria, the absence of alarm symptoms, and the exclusion of organic disease. Patient diagnosis is categorized by the predominant disorder (IBS-C, -D, -M, or -U).

IBS is diagnosed by obtaining a thorough history to distinguish the characteristic symptoms of IBS from other conditions having similar symptoms, physical examination including anorectal examination, limited diagnostic tests, and careful follow-up. Patients should be questioned about the frequency, consistency, color, and size of stools. Because of the functional nature of IBS, a patient may present with symptoms of upper GI problems such as gastroesophageal reflux disease or with excessive flatulence. Patients should also be questioned about diet to establish any symptom relationship to meals or specifically after consumption of certain foods.

Barium enema, **sigmoidoscopy**, or **colonoscopy** may be indicated in the presence of red flag symptoms (fever, weight loss, bleeding, anemia, and persistent severe pain), which often point to a potentially serious non-IBS problem. A barium enema may identify polyps, diverticulosis, tumors, or other abnormalities that might be responsible for the symptoms. Furthermore, barium enema may detect exaggerated haustral contractions, which can impede stool movement and contribute to constipation. Flexible sigmoidoscopy can identify obstructions in the rectum and lower colon, whereas colonoscopy can evaluate the entire colon for organic disease.

The Rome IV diagnostic criteria for IBS include symptoms of recurrent abdominal pain occurring on average at least 1 day per week in the last 3 months, associated with two or more of the following: (1) related to defecation, (2) associated with a change in frequency of stool, or (3) associated with a change in form (appearance of stool). These findings should exist for the last 3 months with symptom onset at least 6 months prior to diagnosis.[1]

TREATMENT

Desired Outcomes

LO 10

KEY CONCEPT The principal goal of IBS treatment is to reduce or control symptoms. The treatment strategy is based on: (a) the prevailing symptoms and their severity, (b) the degree of functional impairment, and (c) the presence of psychological components. A standard treatment regimen is not possible because of the heterogeneous nature of the IBS patient population. Patients suffering from IBS can benefit from clinician support and reassurance.

Nonpharmacologic Therapy

▶ *Diet and Other General Modifications*

Dietary modification is a standard therapeutic modality. Food hypersensitivities and adverse effects have been associated with IBS, especially IBS-D. Elimination diets are the most commonly used strategy, usually focusing on milk and dairy products,

Clinical Presentation of IBS

LO 8

Symptoms

- Patients report a history of abdominal pain or discomfort that is relieved with defecation. Symptom onset is associated with change in frequency or appearance of stool. Some persons experience hard, dry stools; others have loose or watery stools. Stools may be small and pellet-like or narrow and pencil-like in appearance.
- KEY CONCEPT Symptoms can typically be categorized as either IBS-D or IBS-C. Patients with IBS-D usually report more than three loose or watery stools daily. Those with IBS-C usually have fewer than three bowel movements per week; stools are typically hard and lumpy and accompanied by straining. However, stool frequency may be normal in many cases.
- IBS-C can often be distinguished from functional constipation by the presence of abdominal pain and discomfort. Although pain and discomfort may be present in some patients with functional constipation, it is an expected feature of IBS.
- Some patients report alternating episodes of diarrhea and constipation (IBS-M).
- Patients with IBS-U report hard or lumpy stools less than 25% of the time and loose or watery stools less than 25% of the time.
- Other common symptoms include: (a) feelings of incomplete evacuation, (b) abdominal fullness, (c) bloating, (d) flatulence, (e) passage of clear or white mucus with stool, and (f) occasional fecal incontinence.
- Periods of normal stools and bowel function are punctuated by episodes of sudden symptoms.
- Symptoms are often exacerbated by stress.
- Left lower quadrant abdominal pain is often brought on or made worse by eating. Passage of stool or flatus may provide some relief.
- Patients with IBS may experience comorbidities outside the GI tract such as fibromyalgia, sleep disturbances, headaches, dyspareunia, and temporomandibular joint syndrome.

Signs

- The physical examination is often normal in IBS.
- The patient may appear to be anxious.
- Palpation of the abdomen may reveal left lower quadrant tenderness, which may indicate a tender sigmoid colon.
- Abdominal distention may be present in some cases.
- The following "red flag" or alarm features are *not* associated with IBS and may indicate inflammatory bowel disease, cancer, or other disorders: fever, weight loss, bleeding, anemia, and persistent severe pain.

Laboratory Tests

- In most cases, laboratory testing reveals no abnormalities, but certain tests can help identify other causes for the patient's symptoms:
  - CBC may identify anemia, which may suggest blood loss and an organic source for GI symptoms.
  - Serum electrolytes and chemistries may indicate metabolic causes of symptoms.
  - Thyroid-stimulating hormone (TSH) should be ordered when thyroid dysfunction is suspected. Hypothyroidism may be responsible for constipation and related symptoms.
  - Stool testing for ova and parasites may identify *C. difficile* and amoebae as possible causes of diarrhea rather than IBS.
  - Fecal leukocytes can be found in inflammatory diarrhea, especially when due to invasive microorganisms.
  - A positive stool guaiac test indicating blood in the GI tract does not support a diagnosis of IBS.
  - An elevated erythrocyte sedimentation rate is consistent with a systemic inflammatory process such as inflammatory bowel disease rather than IBS.
  - Testing for lactase deficiency can confirm the presence of lactose intolerance, which may explain the symptoms.

Patient Encounter 3, Part 1

A recently widowed 38-year-old woman presents to the clinic complaining of headaches, sleep disturbances, cramping abdominal pain, bloating, excessive flatulence, and small amounts of hard, dry stools. When asked to show where her abdomen hurts, she points to both her lower left and lower right abdomen. She indicates that the pain seems to lessen after a bowel movement. Further, she states that the symptoms have become worse over the last month with dry stools that make it difficult to defecate. During some weeks, she can go a few days without a single bowel movement. She was diagnosed with fibromyalgia 7 months ago and was started on pregabalin. She states that the pregabalin has helped somewhat.

Identify symptoms characteristic of IBS in this patient.

Discuss how this patient fits within the typical epidemiologic profile of patients with IBS.

fructose and sorbitol, wheat, and beef. Flatulence may be controlled by reducing gas-causing foods (beans, celery, onions, prunes, bananas, carrots, and raisins). Response to elimination diets varies widely, but they may be useful in individual patients. Care should be taken to avoid nutritional deficits while attempting to eliminate offending foods.

The low FODMAP diet is said to control IBS symptoms in some patients. FODMAPs are carbohydrates (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) that are poorly absorbed and quickly fermented by bacterial action in the gut. The gas byproduct of the bacterial action is thought to contribute to IBS symptoms.[34]

Probiotics may also be an option for some patients with IBS. *Bifidobacterium infantis* is one product used for its effect in constipation, diarrhea, gaseousness, bloating, and abdominal discomfort. It has not been associated with significant untoward effects. The usual dose is one 4-mg capsule daily.

▶ *Psychological Treatments*

Psychotherapy focused on reducing the influence of the CNS on the gut has been studied. Cognitive behavioral therapy (CBT), dynamic psychotherapy, relaxation therapy, and hypnotherapy have been effective in some patients. However, psychological approaches are not considered replacements for usual care.

Pharmacologic Therapy

▶ *Agents for Pain and Bloating*

Botanicals Peppermint oil is widely advocated; it acts as an antispasmodic agent due to its ability to relax GI smooth muscle. However, it also relaxes the lower esophageal sphincter, which could allow reflux of gastric contents into the esophagus. The usual dose is one to two enteric-coated capsules containing 0.2 mL of peppermint oil two to three times daily. *Matricaria recutita*, known as German chamomile, is also purported to have antispasmodic properties. It is taken most often as a tea up to four times a day. Benzodiazepine, alcohol, and warfarin users should be cautioned against taking this product because it can cause drowsiness, and it contains coumarin derivatives. Primrose oil is used by some patients, but evidence of effectiveness is lacking.

Patient Encounter 3, Part 2

Upon further questioning, the patient recalls experiencing similar symptoms about 15 years ago when she thought she would have to leave school because of dwindling finances. She did not seek medical attention then because she couldn't afford it. She is a full-time pharmacy technician and recently started studying for the PCAT. Her diet consists mostly of fast food.

PMH: Insomnia, headaches, fibromyalgia

FH: None

SH: Has a glass of wine occasionally with dinner

Meds: Pregabalin 150 mg two times daily for fibromyalgia; melatonin 3 mg one tablet 1 to 2 hours before bedtime as needed for insomnia; ibuprofen 600 mg every 6 hours as needed for headache; loperamide 2 mg as needed for diarrhea; docusate sodium 100 mg as needed for constipation

Allergies: Penicillin (rash, hives, and difficulty breathing after taking amoxicillin at the age of 9)

PE:

General: Well nourished; somewhat anxious and nervous when speaking

VS: BP 135/87 mm Hg; Pulse 86 beats/min; RR 18 breaths/min; T 97.4°F (36.3°C); Ht. 5'5" (165 cm); Wt. 148 lbs. (67.1 kg)

Integ: Nails are chewed up; skin appears dry and scaly

HEENT: PERRLA, EOMI

Ext: Normal, no swelling

Chest: Clear to A and P bilaterally

CV: RRR

Abd: (+) BS, tender LLQ and LRQ

Rectal: No abnormalities, negative stool guaiac test

Which of this patient's findings are indicative of IBS?

Propose a comprehensive treatment approach to IBS in this patient. Where appropriate, consider the presence and influence of comorbidities.

▶ *Agents for Constipation Predominance (IBS-C)*

LO 11 **Bulk Producers** These agents may improve stool passage in IBS-C but are unlikely to have a favorable effect on pain or global IBS symptoms. Psyllium may increase flatulence, which can worsen discomfort in some patients. Methylcellulose products are less likely than psyllium to increase gas production. Although fiber-based supplement use is common in IBS-C, methylcellulose may be dose-adjusted in diarrhea to increase stool consistency.

LO 11 **Osmotic Laxatives** More studies are needed to determine the evidence of benefit on quality of life, number of stools, symptom improvement, and ability to continue therapy in patients with IBS-C with use of polyethylene glycol 3350 (PEG) or PEG 3350 with electrolytes.

Linaclotide (Linzess) This drug is a guanylate cyclase-C (GC-C) agonist indicated for treatment of IBS-C in adults. In IBS-C the recommended linaclotide dose is 290 mcg orally once daily. Linaclotide relieves the abdominal pain, bloating and constipation associated with IBS-C while exhibiting a low

tendency for systemic side effects. However, diarrhea may lead to discontinuation in some patients. Clinical trials have demonstrated symptom relief and improved quality of life in treated patients. Studies of linaclotide had high overall quality of evidence across all critical outcomes such as abdominal pain response, spontaneous complete bowel movement response, improvement in quality of life, and improvement in stool consistency and urgency.[35]

LO 11

Lubiprostone (Amitiza) This agent is also FDA approved for treatment of IBS-C, but only in women age 18 years and older. Lubiprostone is generally well tolerated in such patients. It is typically given in smaller doses than those used in CIC. However, as with treatment for constipation, nausea may limit its use. Diarrhea leading to treatment discontinuation may occur. Recent evidence indicated a moderate degree of symptom relief and improvement in quality of life with lubiprostone use.[35] No clinical studies currently exist that compare the beneficial effects or harm associated with the use of linaclotide versus lubiprostone.

LO 11

Plecanatide (Trulance) This guanylate cyclase-C agonist is indicated for treatment IBS-C.[36] Plecanatide and its active metabolite act locally on the luminal surface of the intestinal epithelium to increase availability of intra- and extracellular cyclic GMP. In animal models increased availability of cyclic GMP has been associated with decreased activity of pain-sensing nerves of visceral pain, and stimulation of secretion of chloride and bicarbonate via activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit. Due to risk of serious dehydration, plecanatide is contraindicated in patients less than 6 years of age, and its use should be avoided in patients aged 6 to 18 years of age. The safety and efficacy of plecanatide in patients less than 18 years of age has not been established. The recommended adult dosage for treating IBS-C is one 3-mg tablet orally once daily.[37] The tablet should be swallowed whole and can be taken with or without food. Upon receipt of the medication the patient should be instructed to read the accompanying medication guide. Diarrhea leading to discontinuation is the most common adverse reaction associated with plecanatide. Most cases of diarrhea occurred within the first 4 weeks of therapy, but severe diarrhea has been reported within the first day of treatment. Less commonly reported adverse effects included nausea, nasopharyngitis, upper respiratory tract infection, urinary tract infection, and dizziness. Increased liver alanine aminotransferase (AST) levels have been reported.

Tegaserod maleate (Zelnorm) is indicated for men and women with IBS-C and women under the age of 55 with CIC. It enhances intestinal secretion and motility through its partial 5-hydroxytryptamine (5-HT_4) receptor partial agonist activity. The availability and use of tegaserod maleate is restricted because of an increased risk of heart attack, stroke, and unstable angina. When no other satisfactory alternative therapy is available, physicians may obtain tegaserod maleate under the FDA Expanded Access Program for a single patient emergency use by submitting a Single Patient IND application to the FDA. Medical conditions that are cause for denial of use include prior history of heart attack or stroke, unstable angina, hypertension, hyperlipidemia, diabetes, age greater than 55 years, smoking obesity, depression anxiety, and suicidal ideation.[38]

▶ *Agents for Diarrhea Predominance (IBS-D)*

Loperamide This antidiarrheal inhibits peristalsis and fluid secretion, thereby improving stool consistency and reducing the number of stools. Consequently, it is most useful in patients who have diarrhea as a prominent symptom. However, it does not lessen abdominal pain and can occasionally aggravate pain. Recent evidence indicates that the level of symptom relief and improvement in quality of life with loperamide is very low.[35] As described in the Diarrhea section, excessive dosing can result in serious cardiovascular adverse effects; patients should be instructed not to exceed the maximum recommended dose of 8 mg (OTC) or 16 mg (prescription) daily.

LO 11

Antispasmodics Dicyclomine and hyoscyamine have been among the most frequently used medications for treating abdominal pain in patients with IBS (Table 21–6). They have shown improvement in global symptoms and abdominal pain associated with IBS. Nevertheless, the overall quality of evidence across all critical outcomes for antispasmodics is low.

LO 11

Side effects include dry mouth, dizziness, blurred vision, constipation, urinary retention, and (rarely) psychosis. Although their effectiveness remains unconfirmed, these drugs may deserve a trial in patients with intermittent postprandial pain.[35]

Antidepressants Tricyclic antidepressants (TCAs) (eg, amitriptyline, desipramine, trimipramine, doxepin) may help patients with IBS who predominantly experience abdominal pain. They modulate pain principally through effects on neurotransmitter reuptake, especially norepinephrine and serotonin. Their effectiveness in functional GI disorders seems independent of mood-altering effects normally associated with these agents. Continued TCA therapy may be limited by adverse effects. The overall effect of TCAs on quality of life, symptom relief, and presence of adverse events leading to treatment discontinuation is reported as low.[35]

LO 11

The selective serotonin-reuptake inhibitors (SSRIs) paroxetine, fluoxetine, and citalopram are potentially useful due to the significant effect of serotonin in the gut. SSRIs principally act on 5-HT_1 or 5-HT_2 receptors, but they can also have some effect on gut-predominant 5-HT_3 and 5-HT_4 receptors, perhaps reducing visceral hypersensitivity. They may be beneficial for patients with IBS-C or when the patient presents with IBS complicated by a mood disorder. IBS patients receiving SSRIs may report improved well-being, mood, and GI symptoms. Serotonin–norepinephrine reuptake inhibitors (SNRIs) do not offer significant improvement of global symptoms or abdominal pain. Recent evidence indicates that use of SSRIs in IBS patients in relationship to the overall quality of evidence across all critical outcomes was rated as low.[35]

LO 11

Rifaximin (Xifaxan) This semisynthetic antibacterial agent is structurally similar to rifampin. It has very low systemic absorption and is FDA approved for treatment of IBS-D in adults. Research suggests bacterial overgrowth plays a role in producing bloating experienced by some IBS patients. Rifaximin is not to be used in patients with diarrhea accompanied by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*. It should be used with caution in patients with severe (Child-Pugh Class C) hepatic impairment. Rifaximin has proven to be better than placebo in relieving bloating, and its lack of absorption reduces the likelihood of adverse effects. The overall quality of evidence across outcomes such as pain relief, stool consistency, and return of complete spontaneous bowel movements is considered to be moderate.[35]

LO 11

For treatment of IBS-D, rifaximin 550 mg tablets are administered orally 3 times daily for 14 days. The same regimen can be repeated up to 2 times in patients who experience recurrence. Potential adverse reactions include nausea, increased alanine aminotransferase (ALT) and creatine kinase (CK) enzymes, *C. difficile*-associated colitis, myalgia, and hypersensitivity reactions including exfoliative dermatitis, rash, swelling of the

Table 21–6

Pharmacologic Treatments for IBS

Generic Name	Dose
Antispasmodics	
Dicyclomine	10–20 mg PO every 4–6 hours as needed
Hyoscyamine	0.125–0.25 PO mg or sublingually every 4 hours as needed
Propantheline bromide	15 mg PO three times a day (before meals) and 30 mg at bedtime
Clidinium bromide plus chlordiazepoxide HCl	5–10 mg PO three to four times a day
Hyoscyamine, scopolamine, atropine, phenobarbital	One to two tablets PO three to four times daily
Tricyclic Antidepressants	**In IBS with Diarrhea:**
Amitriptyline	50–150 mg PO daily
Doxepin	10–150 mg PO daily
Selective Serotonin-Reuptake Inhibitors	**In IBS with Constipation:**
Paroxetine (others can be used)	10–40 mg PO daily
Bulk-Forming Laxatives	
Psyllium	2.5–4 g PO daily
Methylcellulose	4–6 g PO daily
Antimotility Agents	
Loperamide	4 mg PO; then 2 mg PO after each loose stool; daily maximum: 8 mg (OTC) or 16 mg (RX)
5-HT$_3$ Receptor Antagonist	
Alosetron[a]	0.5 mg PO two times a day for 4 weeks; then assess appropriate dose
5-HT$_4$ Receptor Agonist	
Tegaserod maleate[a]	6 mg PO twice daily
Guanylate Cyclase-C (GC-C) Agonist	
Linaclotide	290 mcg PO once daily
Plecanatide	3 mg PO once daily
Nonabsorbable antibiotic	
Rifaximin	550 mg PO three times daily for 14 days; patients who experience symptom recurrence can be retreated up to two times with the same dosage regimen
Mu-Opioid Receptor Agonist	
Eluxadoline	100 mg PO twice daily with food; 75 mg PO twice daily is recommended for select patients (eg, hepatic impairment)
Chloride Channel Activator	
Lubiprostone	8 mcg PO twice daily with food and water

[a]Withdrawn from general use; available only as emergency treatment.

face and tongue and difficulty swallowing. Hypersensitivity reactions can occur within 15 minutes of rifaximin ingestion. Rifaximin use for treatment of IBS-D has not been studied in pregnant women or children under the age of 18. Caution should be used in patients with liver dysfunction.[39]

Alosetron (Lotronex) Stimulation of 5-HT$_3$ receptors triggers hypersensitivity and hyperactivity of the large intestine. Alosetron, a selective 5-HT$_3$ antagonist, blocks these receptors and is indicated only for women with severe IBS-D who have: (1) chronic IBS symptoms (6 months or longer); (2) no anatomic or biochemical abnormalities of the GI tract; and (3) not responded adequately to conventional therapy. Recent evidence found moderate improvement in symptoms and quality of life with alosetron.[35] The recommended starting dose is 0.5 mg twice daily, increasing to 1 mg twice a day after 4 weeks if the starting dosage is well tolerated but does not adequately control IBS symptoms. The most common adverse effects are constipation, abdominal discomfort and pain, nausea, and GI discomfort and pain. Alosetron labeling contains a black box warning related to serious GI adverse reactions, including ischemic colitis and serious complications of constipation that have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.

LO 11

Eluxadoline (Viberzi) This μ-opioid receptor agonist reduces bowel contractions and is FDA approved for treatment of adults with IBS-D.[40,41] The recommended dose is 100 mg orally twice daily taken with food. The dose can be reduced to 75 mg twice daily with food in patients who cannot tolerate the 100-mg dose and in patients with mild or moderate hepatic impairment. The most common adverse effects are constipation, nausea, and abdominal pain. It is contraindicated in persons who drink more than three alcoholic beverage per day because these patients are at increased risk for acute pancreatitis.[41] Eluxadoline should not be used in patients without a gallbladder because these patients are at increased risk of developing pancreatitis and/or sphincter of Oddi spasm. Eluxadoline is a Schedule IV controlled substance.

OUTCOME EVALUATION

- Monitor for adequate symptom relief. Patients whose pain does not respond to drug therapy may have a psychological comorbid condition requiring psychiatric intervention.
- Monitor for relief of pain if initially present. Monitor IBS-C or IBS-D patients for stool frequency, appearance, and size relative to normal characteristics. As stools normalize, associated symptoms such as bloating and abdominal distention should resolve.
- For IBS-C and IBS-M patients taking bulk producers, monitor for relief of constipation. Hard stools should soften within 72 hours.
- Monitor antidepressant and antispasmodic therapy for relief of abdominal pain and potential adverse effects.
- Assess 5-HT$_4$ receptor agonists for relief of crampy abdominal pain and bloating.
- Monitor linaclotide for treatment-limiting diarrhea in IBS-C.
- Evaluate 5-HT$_3$ receptor antagonists (alosetron) for relief of abdominal pain and fecal incontinence. Monitor for constipation.
- Expect antimotility agents to reduce stool frequency and control diarrhea within 18 to 36 hours unless severe.
- Monitor CBC, serum electrolytes and chemistries, stool guaiac, and erythrocyte sedimentation rate yearly for changes that might signal an overlapping organic problem.
- Refer for medical evaluation any patient presenting with red flag signs (eg, fever, weight loss, bleeding, anemia, persistent severe pain).

Patient Care Process for IBS

Collect Information:

- Determine the type, severity, and frequency of symptoms and possible exacerbating factors.
- Obtain a thorough current history of prescription, nonprescription, and dietary supplement use.

Assess the Information:

- Determine if any IBS treatments have been attempted and their effectiveness.
- Establish whether self-care is appropriate or a medical referral is needed.

Develop a Care Plan:

- Determine whether the patient has received prior education about IBS, lifestyle modifications, drug therapy for IBS, and symptom prevention measures. If necessary:
  - Explain medication use relative to symptom intensity
  - Describe potential adverse effects
  - List drugs that may interact with the therapy

Implement the Care Plan:

- Provide patient education about IBS and the treatment selected.

Follow-up: Monitor and Evaluate:

- Encourage patients to report every professional interaction since their last encounter to remain current with all treatment recommendations.
- Be vigilant for the occurrence of red flag symptoms.

Abbreviations Introduced in This Chapter

BSS	Bismuth subsalicylate
CBT	Cognitive behavioral therapy
CIC	Chronic idiopathic constipation
FBD	Functional bowel disorder
FGID	Functional gastrointestinal disorder
GMP	Guanosine monophosphate
IBS	Irritable bowel syndrome
IBS-C	Irritable bowel syndrome with constipation
IBS-D	Irritable bowel syndrome with diarrhea
IBS-M	Irritable bowel syndrome with constipation and diarrhea (mixed)
NTC	Normal-transit constipation
OIC	Opioid-induced constipation
ORS	Oral rehydration solution
STC	Slow-transit constipation
PAMORA	Peripherally acting μ-opioid receptor antagonist
TCA	Tricyclic antidepressant
TD	Traveler's diarrhea

REFERENCES

1. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology. 2016;150:1262–1279.
2. OTC Sales by Category 2013-2016. Consumer Healthcare Products Association. Available from: https://www.chpa.org/PR_OTCsCategory.aspx. Accessed August 16, 2017.
3. Lacy BE, Mearin F, Lin C, et al. Bowel disorders. Gastroenterology. 2016;150:1393–1407.
4. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology. 2006;130:1480–1491.
5. Wan Y, Corman S, Gao X, Liu S, Patel H, Mody R. Economic burden of opioid-induced constipation among long-term opioid users with noncancer pain. Am Health Drug Benefits. 2015;8(2):93–102.
6. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 2014;109(suppl 1):S2–S26.
7. Olufade T, Kong AM, Prinic N, et al. Comparing healthcare utilization and costs among Medicaid-insured patients with chronic noncancer pain with and without opioid-induced constipation: a retrospective analysis. Am Health Drug Benefits. 2017;10(2):79–86.
8. Bucharucha AE, Pemberton JH, Locke GR. American Gastroenterological Association technical review on constipation. Gastroenterolgy. 2013;144:218–238.
9. Bucharucha AE, Dorn SD, Lembo A, Pressman A. American Gastrological Association medical position statement on constipation. Gastroenterology. 2013;144:211–217.
10. Satish S, Rao C, Patcharatrakul T. Diagnosis and treatment of dyssynergic defecation. J Neurogastroenterol Motil. 2016;22:423–435.
11. Brenner DM, Chey WD. An evidence-based review of novel and emerging therapies for constipation in patients taking opioid analgesics. Am J Gastroenterol Suppl. 2014;2(1):38–46.
12. Camilleri M, Drossman DA, Becker G, et al. Emerging treatments in neurogastroenterology: a multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil. 2014;26:1386–1395.
13. Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. Aliment Pharmacol Ther. 2007;25(11):1351–1361.
14. Cuppoletti J, Chakrabarti J, Tewari K, Malinowska DH. Methadone but not morphine inhibits lubiprostone-stimulated Cl^- currents in T84 intestinal cells and recombinant human CIC-2, but not CFTR Cl^- currents. Cell Biochem Biophys. 2013;66:53–63.
15. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci. 2010;86:760–765.
16. Trulance® [package insert]. Synergy Pharmaceuticals, Inc., New York, NY; January 2017. Available from: http://pi.synergy.com/us-pi.pdf. Accessed November 21, 2017.
17. Webster L, Dhar S, Eldon M, et al. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain. 2013;154:1542–1550.
18. Poulsen JL, Brock C, Olesen AE, et al. Clinical potential of naloxegol in the management of opioid-induced bowel dysfunction. Clin Exp Gastroenterol. 2014;7:345–358.
19. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med. 2014;370:2387–2396.
20. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a

double-blind randomized, parallel group, dose-ranging study. J Pain Symptom Manage. 2008;35(5):458–468.
21. Movantik® [package insert]. Astra Zeneca Pharmaceuticals, L.P., Wilmington, DE; August 2017. Available from: https://pi.astrazeneca.com/us/movantik-pi.pdf. Accessed November 21, 2017.
22. Symproic® [package insert]. Purdue L.P., Stamford, CT. August 2017. Available from: https://purduepharma.com/us/symproic-pi.pdf. Accessed November 21, 2017.
23. Camilleri M, Sellin JH, Barrett KE. Pathophysiology, evaluation, and management of chronic watery diarrhea. Gastroenterology. 2017;152:515–532.
24. Camilleri M, Murray JA. Diarrhea and Constipation. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 19th ed. New York, NY: McGraw-Hill; 2014.
25. WHO methods and data sources for global burden of disease estimates 2000–2015. World Health Organization. Available from: https://www.who.int/healthinfo/global_burden_disease/GlobalDALY methods_2000_2015.pdf. Accessed October 20, 2017.
26. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clin Infect Dis. 2017;65(12):e45–e80.
27. Schiller LR, Pardi DS, Spiller R, et al. Gastro 2013 APDW/WCOG Shanghai working party report: chronic diarrhea: definition, classification, diagnosis. J Gastroenterol Hepatol. 2014;29:6–25.
28. Eggleston W, Clark KH, Marraffa JM. Loperamide abuse associated with cardiac dysrhythmia and death. J Ann Emer Med. 2017;69(1):83–86.
29. FDA Warns About Serious Heart Problems with High Doses of Antidiarrheal Medicine Loperamide (Imodium) Including from Abuse and Misuse. U.S. Food and Drug Administration. Available from: https://www.fda.gov/Drugs/DrugSafety/UCM505108.pdf. Accessed January 31, 2018.
30. Imodium (loperamide) for Over-the-Counter Use: Drug Safety Communication - FDA Limits Packaging To Encourage Safe Use. U.S. Food and Drug Administration. Available from: https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm594403.htm. Accessed January 31, 2018.
31. Imodium [package insert]. Janssen Pharmaceuticals, Inc. Titusville, New Jersey. Revised 2016. Available from: https://www.accessdata.fda.gov.pdf.4007556. Accessed February 2, 2018.
32. Endo Y, Shoji T, Fukudo S. Epidemiology of irritable bowel syndrome. Ann Gastroenterol. 2015;28:158–159.
33. Boeckxstaens G, Camilleri M, Sifrim D, et al. Fundamentals of neurogastroenterology: physiology/motility-sensation. Gastroenterol. 2016;150:1292–1304.
34. Staudacher HM, Lomer MCE, Farquharson FM, et al. A diet low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and a probiotic restores *Bifidobacterium* species: a randomized controlled trial. Gastroenterol. 2017;153:936–947.
35. Chang L, Lembo A, Sultan S. American Gastrointestinal Association Institute technical review on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;147:1149–1172.
36. Plecanatide Supplement Approval Letter. Food and Drug Administration/Center for Drug Evaluation and Research. Available from: https://www.fda.gov/cder/approval/4211838.pdf. Accessed January 30, 2018.
37. Trulance [package insert] Synergy Pharmaceuticals, Inc. New York, NY. January 2017. Available from: https://www.trulance.com/pdf. Accessed January 30, 2018.
38. Zelnorm Single Patient IND Packet. Food and Drug Administration/Drug Safety and Availability. Available from: https://www.fda.gov/Drugs/Drug Safety/UCM.103223.htm. Accessed January 30, 2018.
39. Xifaxan [package insert]. Salix Pharmaceuticals., Bridgewater, NJ. November 2015. Available from: https://www.rifaximin.com/hp-REF-XIF-0600.pdf. Accessed January 24, 2018.
40. Lembo A, Lacy B, Zuckerman M, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med. 2016;374(3):242–253.
41. Viberzi [package insert]. Allergan USA, Inc. Irvine, CA. Updated 2017. Available from: https://www.viberzi,com/pdf. Accessed February 2, 2018.

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22 Portal Hypertension and Cirrhosis

Laurajo Ryan

LEARNING OBJECTIVES

LO

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

1. Explain the pathophysiology of cirrhosis and portal hypertension.
2. Identify signs and symptoms of cirrhosis.
3. Identify laboratory abnormalities that result from liver disease and describe the associated pathophysiology.
4. Describe the consequences associated with decreased hepatic function.
5. Identify treatment goals for a patient with complications of cirrhosis.
6. Recommend a specific treatment regimen for a patient with cirrhosis that includes lifestyle changes, nonpharmacologic measures, and pharmacologic therapy.

INTRODUCTION

Cirrhosis involves replacement of normal hepatic architecture with fibrous scar tissue. Scarring is accompanied by loss of viable hepatocytes, which are the functional cells of the liver. Cirrhosis is characterized by progressive damage and deterioration of liver function, but even with extensive scarring some patients remain asymptomatic. KEY CONCEPT Advanced cirrhosis is irreversible and leads to portal hypertension, which in turn is responsible for the complications that define decompensated cirrhosis. Complications of cirrhosis include ascites, spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), hepatorenal syndrome (HRS), and variceal bleeding.[1] These complications all carry high mortality rates and are signs of disease progression.

EPIDEMIOLOGY AND ETIOLOGY

Cirrhosis is the 12th leading cause of death in the United States. It places an enormous economic and social burden on society from hospitalizations, lost wages, decreased productivity, and emotional strain of the disease on both patients and their families.

Cirrhosis is the result of long-term insult to the liver, and damage usually doesn't become clinically evident until the fourth decade of life. Infection with one or more strains of viral hepatitis causes acute, potentially reversible hepatic inflammation, whereas chronic infection with hepatitis B (HBV) or C (HCV) can lead to cirrhosis. Alcohol ingestion and HCV are the most common causes of cirrhosis in the United States, whereas HBV accounts for the majority of cases worldwide.[2] HCV therapies that provide sustained virologic response (SVR) essentially cure the disease, and are expected to dramatically decrease new cases of cirrhosis. Even patients who have already developed HCV cirrhosis can benefit from antiviral therapy, and recent guidelines recommend treatment for nearly all patients (see Chapter 24, Viral Hepatitis, for more details).[3]

Alcoholic cirrhosis usually develops only after decades of heavy drinking. It develops more quickly in women than men, even after taking body weight into account. Estimates vary, but alcoholic cirrhosis can develop after as few as two to three daily drinks in women and three to four drinks in men, although five to eight daily drinks is more typical.[4] Differences in metabolism may account for the gender disparity; women metabolize less alcohol in the gastrointestinal (GI) tract, allowing delivery of more ethanol (which is directly hepatotoxic) to the liver.[5] Genetic factors also play a role in disease progression; some patients develop cirrhosis with much less cumulative alcohol intake than is typical (either fewer drinks per day or faster disease onset), while others with much greater intake never develop cirrhosis.

Alcoholic Liver Disease

Alcoholic liver disease progresses through several distinct phases—from fatty liver to alcoholic hepatitis and finally to cirrhosis. Changes in metabolism account for the fatty liver, hypertriglyceridemia, and acidemia observed in alcoholic liver disease. Fatty liver and alcoholic hepatitis are often reversible with cessation of alcohol intake, and even though the scarring of cirrhosis is usually permanent, stopping drinking can decrease complications and slow progression to end-stage liver disease.[6]

Ethanol metabolism begins prior to absorption; alcohol dehydrogenase in the gastric mucosa oxidizes a portion of alcohol to acetaldehyde. The remaining alcohol is rapidly absorbed from the GI tract and readily enters body tissues because it is highly lipid soluble. KEY CONCEPT Alcohol dehydrogenase oxidizes ethanol to acetaldehyde primarily in the liver, which causes inflammation and fibrosis.[7] Acetaldehyde exerts direct toxic effects on the liver by damaging hepatocytes, inducing fibrosis, and directly coupling to proteins, interfering with their intended function. High ethanol levels saturate the alcohol dehydrogenase enzyme system. Once it is overwhelmed, the microsomal ethanol oxidizing system takes over the detoxification process. This is an inducible cytochrome P-450 (CYP450) enzyme system; it participates in

phase 1 metabolism, and like alcohol dehydrogenase, produces acetaldehyde as its end product.[8]

Less Common Causes of Cirrhosis

Genetics and metabolic risk factors mediate other less common causes of cirrhosis. These diseases vary widely in prevalence, disease progression, and treatment options.

Primary biliary cirrhosis is characterized by progressive inflammatory destruction of the bile ducts. This immune-mediated inflammation of the intrahepatic bile ducts causes remodeling and scarring, resulting in retention of bile in the liver, hepatocellular damage, and cirrhosis. The prevalence of primary biliary cirrhosis is difficult to estimate because it is often asymptomatic and patients are frequently diagnosed incidentally during routine health care visits.

Nonalcoholic fatty liver disease (NAFLD) begins with asymptomatic fatty liver but can progress to cirrhosis. NAFLD is a diagnosis of exclusion; viral, genetic, or environmental causes must be ruled out prior to making this diagnosis. NAFLD is directly related to several metabolic abnormalities—diabetes mellitus, dyslipidemia, obesity, insulin resistance, and other conditions associated with increased hepatic fat.[9]

Hereditary hemochromatosis is an autosomal recessive disease that causes increased intestinal iron absorption and subsequent deposition in hepatic, cardiac, and pancreatic tissue. Hepatic iron overload results in fibrosis, hepatic scarring, cirrhosis, and hepatocellular carcinoma. Repeated blood transfusions can also cause hemochromatosis, but this mechanism rarely leads to cirrhosis.

In Wilson disease (also an autosomal recessive disease), the protein responsible for facilitating copper excretion in the bile is faulty, so copper accumulates in hepatic tissue. High copper levels are toxic to hepatocytes, and fibrosis leading to cirrhosis can develop in untreated patients. Patients with Wilson disease usually present with symptoms of liver and/or neurologic disease while still in their teens.

A third autosomal recessive genetic disease is α_1-antitrypsin deficiency (AATD). Abnormalities in the α_1-antitrypsin protein cause it to deposit in the liver. AATD causes cirrhosis in children as well as adults; adults usually have concomitant pulmonary disease.

PATHOPHYSIOLOGY

Portal Hypertension and Cirrhosis

The portal vein is the primary vessel leading into the liver; it receives deoxygenated venous blood from the splanchnic bed (intestines, stomach, pancreas, and spleen) at a rate of 1 to 1.5 L/min (Figure 22–1). Portal flow accounts for approximately 75% of blood delivered to the liver; the hepatic artery provides the remaining 25% in the form of oxygenated blood from the abdominal aorta. Normal portal vein pressure is 5 to 10 mm Hg. Portal hypertension, defined as portal pressure greater than 10 to 12 mm Hg, is a consequence of increased resistance to hepatic blood flow.[10]

LO 1

The obstruction to flow that causes portal hypertension can develop from prehepatic, intrahepatic (sinusoidal), or posthepatic damage. Hepatic sinusoids are porous vessels within the liver that surround radiating rows of hepatocytes (Figure 22–2). Sinusoids transport systemic blood that contains ingested substances (eg, food, drugs, toxins) to the hepatocytes. The liver processes the nutrients (carbohydrates, proteins, lipids, vitamins, and minerals) for either immediate use or storage, while drugs and toxins are processed through a variety of metabolic steps.

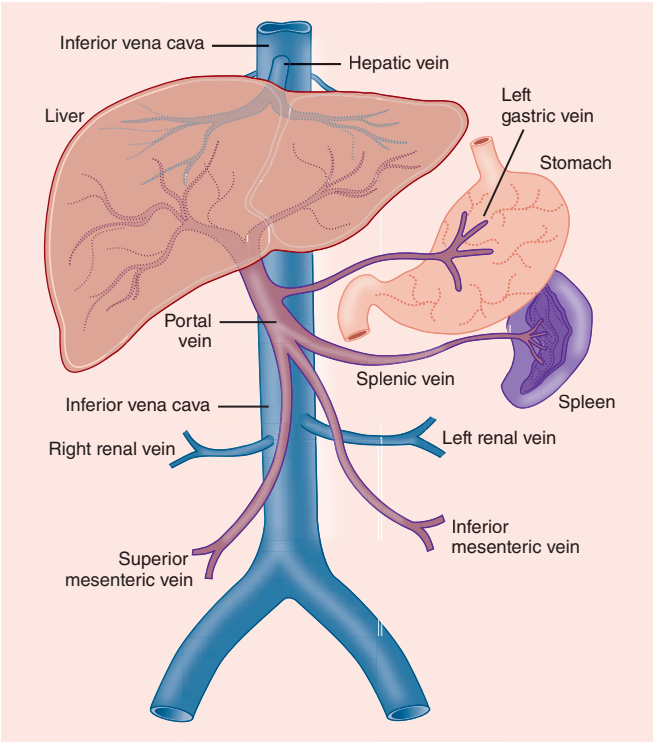

FIGURE 22–1. The portal venous system. (From Sease JM, Clements JN. Portal hypertension and cirrhosis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill, 2017. www.accesspharmacy.com, with permission.)

Progressive destruction of hepatocytes combined with an increase in fibroblasts and connective tissue culminates in cirrhosis. Fibrosis scar tissue nodules modify the basic architecture of the liver, disrupting hepatic blood flow and liver function.

Reduced hepatic blood flow significantly alters normal metabolic processes and decreases protein synthesis. Hepatic drug metabolism is reduced, which can result in higher systemic drug concentrations and toxicity by extending half-life of drugs normally eliminated by the liver (especially those with high first-pass metabolism). Decreased hepatic metabolism can also reduce or delay prodrug activation and cause therapeutic failure.

LO 1 LO 2

The liver processes metabolic waste products for excretion; in cirrhosis, bilirubin (from the enzymatic breakdown of heme) can accumulate, causing jaundice (yellowing of the skin), scleral icterus (yellowing of the sclera), and tea-colored urine (urinary bilirubin excreted as urobilinogen).

Changes in steroid hormone production, conversion, and handling are prominent features of cirrhosis. These changes manifest as decreased libido, gynecomastia (development of breast tissue in men), testicular atrophy, and feminization in men. Another effect of changes in sex hormone metabolism is development of palmar erythema and spider angiomata (nevi). Spider angiomata are vascular lesions found mainly on the trunk that have a central arteriole (body) surrounded by radiating "legs." When blanched, the lesions fill from the center body outward toward the legs. They are not specific to cirrhosis, but the number and size do correlate with disease severity, and their presence relates to risk of variceal hemorrhage.[10]

Increased intrahepatic resistance to portal blood flow increases pressure on the entire splanchnic bed; an enlarged spleen

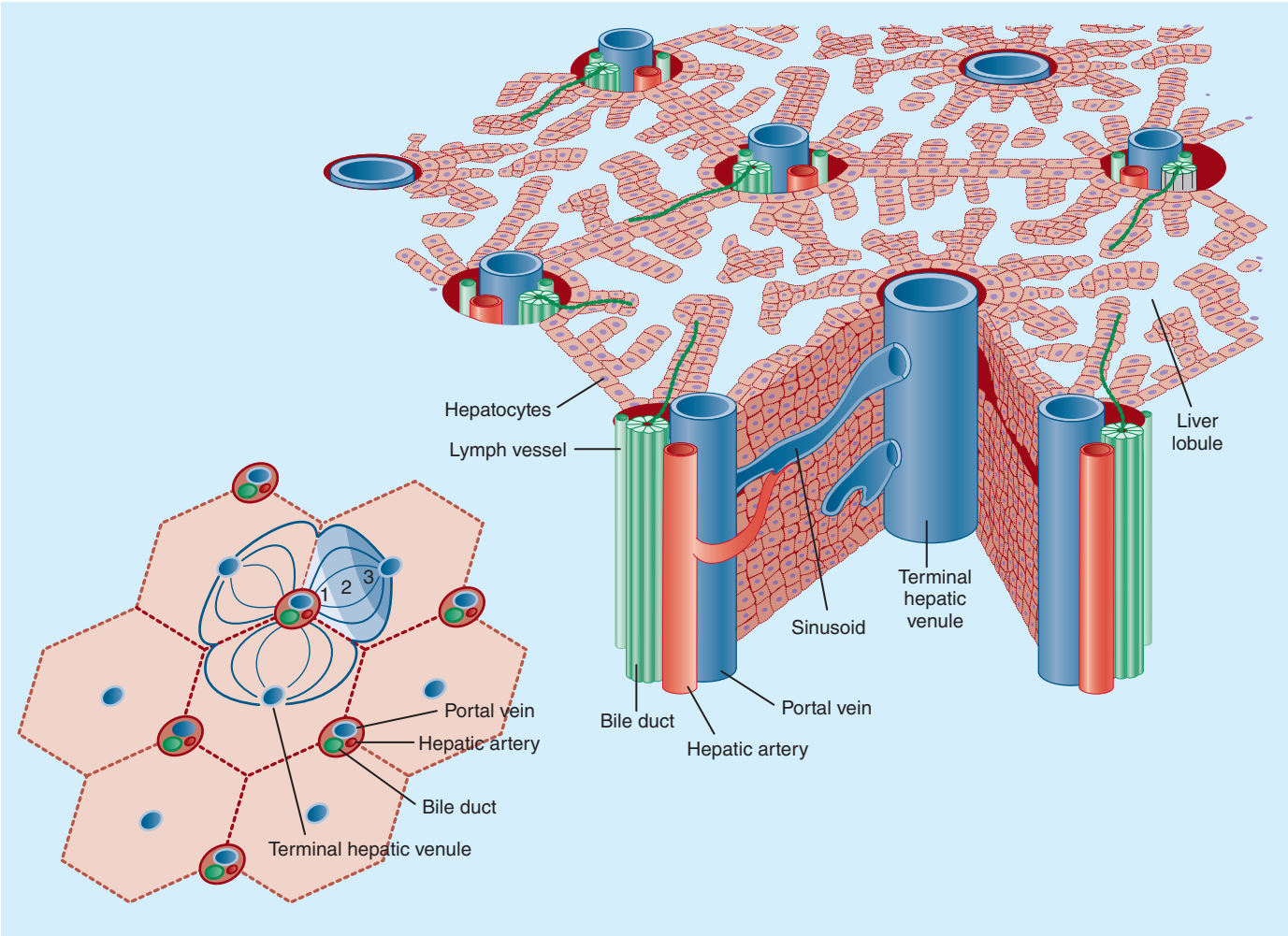

FIGURE 22–2. Relationship of sinusoids to hepatocytes and the venous system. (From Sease JM, Clements JN. Portal hypertension and cirrhosis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill, 2017. www.accesspharmacy.com, with permission.)

(splenomegaly) is a common finding in cirrhotic patients. Splenic platelet sequestration secondary to splenomegaly is one of the causes of thrombocytopenia in cirrhotic patients.

LO 1 Portal hypertension mediates systemic and splanchnic arterial vasodilation by increasing production of nitric oxide and other vasodilators in an attempt to counteract the increased pressure gradient. Nitric oxide causes a fall in systemic arterial pressure; this drop in pressure activates the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system, and increases antidiuretic hormone (ADH, vasopressin) production.[11] These systems are activated in an attempt to maintain arterial blood pressure and renal blood flow by increasing sodium and water retention. The excess sodium and water puts increased pressure on the vascular system. As a result, the umbilical vein, which LO 2 is usually eradicated in infancy, may become patent and cause prominent dilated veins that are visible on the surface of the abdomen. This phenomenon is called caput medusae because it resembles the head of the mythical Gorgon Medusa.

Ascites

LO 4 Ascites is the accumulation of fluid in the peritoneal space. It is the most common condition associated with decompensated cirrhosis and indicates a poor prognosis.[6]

The pathophysiology of ascites, portal hypertension, and cirrhosis are interrelated (Figure 22–3). Cirrhotic changes and subsequent decreases in synthetic function lead to decreased albumin production (hypoalbuminemia). Because albumin is the primary intravascular protein responsible for maintaining vascular oncotic pressure, low serum albumin levels, elevated hydrostatic pressure, and increased capillary permeability allow fluid to leak from the vascular space into body tissues. This results in ascites, peripheral edema, and fluid in the pulmonary system. Obstruction of hepatic sinusoids and hepatic lymph nodes also allows fluid to seep into the peritoneal cavity, further contributing to ascitic fluid formation.

The decrease in effective intravascular volume decreases renal perfusion; this activates the RAAS, increasing plasma renin activity, aldosterone production, and sodium retention. The subsequent increase in intravascular volume furthers the imbalance of intravascular oncotic pressure, allowing even more fluid to escape to the extravascular spaces, increasing ascites and peripheral edema. Unchecked, these combined effects enable the cycle of portal pressure and ascites to continue, creating a self-perpetuating loop of ascites formation.

Patients with ascites avidly retain sodium and water, not only through elevated aldosterone concentrations (from increased production and decreased clearance), but also through increases

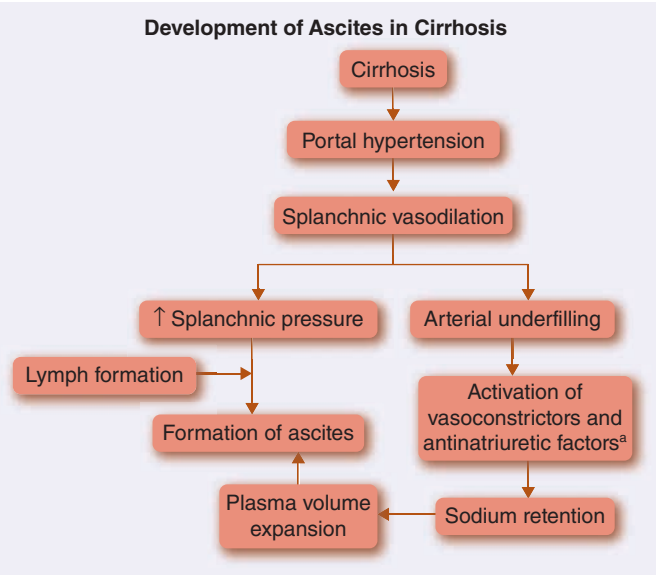

FIGURE 22–3. Development of ascites in cirrhosis. This flow diagram illustrates the importance of portal hypertension with splanchnic vasodilation in the development of ascites. [a]Antinatriuretic factors include the renin-angiotensin-aldosterone system and the sympathetic nervous system. (From Bacon BR. Cirrhosis and its complications. In: Kasper DL, Hauser SL, Jameson JL, et al., eds. Harrison's Principles of Internal Medicine, 19th ed. New York, NY: McGraw-Hill, 2015. www.accesspharmacy.com, with permission.)

in ADH and sympathetic nervous system activation. Patients become hyponatremic because of decreased free water excretion. This is not the result of too little sodium; it is a dilutional effect. Untreated, this combination of factors can lead to a decrease in renal function and HRS.[4,11]

Hepatorenal Syndrome

LO 4 HRS is a decline in renal function not caused by intrinsic renal disease in the setting of cirrhosis. Type 1 HRS is characterized by rapid deterioration of renal function (acute kidney injury [AKI]) that is not reversible with volume repletion. Untreated, it is rapidly fatal with a 50% mortality rate at 14 days. Renal artery vasoconstriction (stimulated by the sympathetic nervous system and RAAS) and decreased mean arterial pressure (mediated by nitric oxide) decrease renal perfusion and precipitate renal failure. Production of renin stimulates a cascade that causes fluid retention and peripheral vasoconstriction in an attempt to increase arterial pressure. Prostaglandin E_2 and prostacyclin production increase to stimulate renal vasodilation and maintain renal blood flow. HRS develops when these mechanisms are overwhelmed and renal perfusion drops acutely. SBP is a common trigger for HRS, as are nonsteroidal anti-inflammatory drugs (NSAIDs), which precipitate HRS by inhibiting prostaglandin production. Type 2 HRS has similar pathophysiology to type 1 HRS but is characterized by a less acute decline in renal function.

LO 3 The traditional laboratory parameters used to monitor renal function (serum creatinine, blood urea nitrogen [BUN]) tend to be deceptively low in cirrhotic patients because of reduced muscle mass and decreased hepatic urea production, respectively. Because of this, even minor changes in these laboratory values should be monitored closely; small changes can represent significant changes in renal function.

Varices

LO 4 The splanchnic system drains venous blood from the GI tract to the liver. Because portal hypertension increases resistance to drainage from the originating organ, collateral vessels (varices) develop in the esophagus, stomach, and rectum to compensate for the increase in pressure and blood volume. Varices divert blood meant for hepatic circulation back to the systemic circulation. This diversion decreases clearance of drugs and potential toxins through loss of first-pass (presystemic) metabolism. Varices are weak superficial vessels; any additional increase in pressure can cause them to rupture and bleed.[12]

Spontaneous Bacterial Peritonitis (SBP)

LO 4 SBP is an acute bacterial infection of peritoneal (ascitic) fluid in the absence of intraabdominal infection or intestinal perforation; up to 30% of patients with ascites develop SBP.[13] The peritoneal cavity is usually a sterile space. One proposed mechanism of bacterial contamination is translocation of intestinal bacteria to mesenteric lymph nodes, which then seed the ascitic fluid.[14] Bacterial translocation correlates with the delay in intestinal transit time and increased intestinal wall permeability observed in cirrhotic patients. Another possible mechanism of SBP is the hematogenous spread of bacteria into the peritoneal space.[15] Low protein ascites (< 1 g/dL [10 g/L]) is associated with increased rates of SBP; low protein is presumably correlated to low antibacterial activity.

Enteric gram-negative aerobes (*Escherichia coli*, *Klebsiella pneumoniae*) are the most common bacteria isolated from patients with SBP. *Streptococcus pneumoniae* is the most common gram-positive pathogen.[6]

Hepatic Encephalopathy

LO 4 Numerous factors, many of them poorly understood, are involved in the development of hepatic encephalopathy (HE). In severe hepatic disease, systemic circulation bypasses the liver; substances that are normally metabolized by the liver accumulate in the systemic circulation. These byproducts, especially nitrogenous waste, are neurotoxic.[16]

Ammonia (NH_3) is just one of the toxins implicated in HE. It is a metabolic byproduct of protein catabolism and is also generated by gut bacteria. In a normally functioning liver, hepatocytes degrade ammonia to form urea, which is renally excreted; in cirrhosis, conversion to urea is reduced and ammonia accumulates, causing encephalopathy. Patients with HE commonly have elevated serum ammonia concentrations, but ammonia levels do not correlate with the degree of CNS impairment.[16]

High levels of "false neurotransmitters" (aromatic amino acids, γ-aminobutyric acid, endogenous benzodiazepines) have also been implicated in HE. These substances bind to both the γ-aminobutyric acid and benzodiazepine receptors and act as agonists at the active receptor sites.[16]

HE is a clinical diagnosis; decreased cognition, confusion, and changes in behavior combined with physical signs such as asterixis (characteristic flapping of hands upon extension of arms with wrist flexion) indicate HE. A precipitating event associated with increased production and/or decreased elimination of toxins can often be identified in patients with previously stable cirrhosis who develop acute encephalopathy. Infections, variceal hemorrhage, renal insufficiency, electrolyte abnormalities, and increased dietary protein have all been associated with acute HE. Acute HE is often readily reversible, but changes of a more chronic, insidious nature are more difficult to treat; patients rarely recover fully from chronic HE.

Bleeding Diathesis and Synthetic Failure

LO 4

Coagulopathies signal end-stage liver disease. The liver manufactures both procoagulant and anticoagulant factors essential for blood clotting and maintenance of blood homeostasis. In advanced disease, the liver is unable to synthesize these proteins, resulting in extended clotting times (eg, prothrombin time) and bleeding irregularities.[17] These patients were previously thought to be "auto-anticoagulated," but better understanding of the spectrum of coagulation abnormalities has led to the understanding that these patients are at increased risk of venous thromboembolisms in addition to having extended clotting times.[18]

Thrombocytopenia is common in advanced liver disease as a result of both decreased hepatic thrombopoietin stimulation in the bone marrow and splenic sequestration of formed platelets.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to accompanying clinical presentation box for symptoms, signs, and laboratory abnormalities associated with cirrhosis.

Diagnosis of Cirrhosis

Cirrhosis may be diagnosed incidentally before the patient develops symptoms or acute complications, but many patients have decompensated disease (eg, ascites, SBP, variceal bleeding, HE) at initial presentation. Patients may have some, all, or none of the laboratory abnormalities and/or signs and symptoms of cirrhosis.[19]

Liver biopsy can definitively diagnose cirrhosis but is usually deferred in lieu of a presumptive diagnosis using noninvasive techniques such as ultrasound or computed tomography. A nodular liver with increased echogenicity is consistent with cirrhosis. The Model for End-Stage Liver Disease (MELD) score predicts 3-month mortality; it is used to classify disease severity and prioritize patients awaiting deceased-donor liver transplantation. The calculator is available at the Organ Procurement and Transplantation Network website (https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/).

Patients with ascites or known varices are presumed to have portal hypertension, but direct measurement is typically deferred because it requires invasive testing and increases the risk of bleeding.

Diagnosis of Ascites

Analysis of ascitic fluid obtained during **paracentesis** provides diagnostic clues to the etiology of fluid accumulation. Evaluation includes cell count with differential, albumin, total protein, Gram stain, and bacterial cultures. In patients without an established diagnosis of liver disease, the serum ascites–albumin gradient (SAAG) is used to determine the cause of ascites.[6] SAAG compares serum albumin concentration to ascitic fluid albumin concentration:

$$Alb_{serum} - Alb_{ascites} = SAAG$$

A value of 1.1 g/dL (11 g/L) or greater identifies portal hypertension as the cause of the ascites with 97% sensitivity.[6] In portal hypertension, low albumin in the peritoneal space balances the oncotic pressure gradient with the hydrostatic pressure gradient of portal hypertension. The differential diagnosis for SAAG values less than 1.1 g/dL (11 g/L) includes peritoneal carcinoma, peritoneal infection (tuberculosis, fungal, cytomegalovirus), and nephrotic syndrome. Serum albumin should be measured at the time of paracentesis for an accurate comparison.[6]

Clinical Presentation of Cirrhosis and Complications of Portal Hypertension

LO 2

General

- Signs and symptoms are specific to the complication the patient is experiencing at presentation.

Symptoms

- Patients with cirrhosis may be asymptomatic until acute complications develop.
- Nonspecific symptoms include anorexia, fatigue, weakness, changes in libido, and disturbances in sleep patterns. Patients may also bruise easily or bleed from minor injuries.
- Patients with ascites describe feelings of abdominal fullness and pain, nausea, shortness of breath, and early satiety.
- Hemorrhage from esophageal or gastric varices often presents as nausea, vomiting, and **hematemesis** and may be associated with melena, pallor, fatigue, and weakness from blood loss. Bleeding from rectal varices may present as **hematochezia**.
- In patients with bleeding varices, digestion of swallowed blood can cause nausea and precipitate symptoms of HE.
- Neurologic changes from HE can be overwhelming or so subtle that they are not apparent except during a targeted clinical evaluation.
- Patients with HE may complain of disruption of sleep patterns and day-to-night inversion; patients have delayed bedtime and wake times, which may progress to complete inversion of the normal diurnal cycle.
- SBP should be suspected in patients with symptoms of infection such as fever, chills, abdominal pain, and mental status changes.

Signs

- Nonspecific signs of liver disease include jaundice, scleral icterus, tea-colored urine, bruising, hepatomegaly, splenomegaly, spider angiomata, caput medusae, palmar erythema, gynecomastia, and testicular atrophy.
- Ascites can be detected by increased abdominal girth accompanied by shifting dullness and a fluid wave.
- Signs of variceal bleeding depend on the degree of blood loss and abruptness of onset. Rapid and massive blood loss is more likely to result in hemodynamic instability than slow, steady bleeding.
- Signs of acute bleeding may include pallor, hypotension, tachycardia, mental status changes, and hematemesis.
- Markers of hepatic encephalopathy (HE) include decreased cognition, confusion, changes in behavior, and asterixis.

(*Continued*)

Clinical Presentation of Cirrhosis and Complications of Portal Hypertension (Continued)

- Patients with SBP may present with fever, painful tympanic abdomen, and changes in mental status.
- Decreases in clotting factors may manifest as abnormal bruising and bleeding.
- Dupuytren's contracture is a contraction of the palmar fascia that usually affects the fourth and fifth digits. It is not specific to cirrhosis and can also be seen in repetitive use injuries.

Laboratory Abnormalities

LO 3

- Hepatocellular damage manifests as elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The degree of elevation does not correlate with remaining functional metabolic capacity of the liver. An AST level twofold higher than ALT suggests alcoholic liver damage.
- Elevated alkaline phosphatase is nonspecific and may correlate with liver or bone disease; it tends to be elevated in biliary tract disease; γ-glutamyl transferase (GGT) is specific to the bile ducts, and in conjunction with an elevated alkaline phosphatase, suggests hepatic disease. Extremely elevated GGT levels further indicate obstructive biliary disease.
- Increased total, direct, and indirect bilirubin concentrations indicate defects in transport, conjugation, or excretion of bilirubin.
- Lactate dehydrogenase (LDH) is a nonspecific marker of hepatocyte damage; a disproportionate elevation of LDH indicates ischemic injury.
- Thrombocytopenia may occur because of decreased platelet production and splenic sequestration of platelets.
- Anemia (decreased hemoglobin and hematocrit) occurs as a result of variceal bleeding, decreased erythrocyte production, alcohol use, and hypersplenism.
- Loss of hepatic synthetic function can manifest as elevated prothrombin time (PT) and international normalized ratio (INR).
- Decreased serum albumin and total protein occur in chronic liver damage due to loss of synthetic capacity within the liver.
- Portal hypertension causes serum albumin-to-ascites gradient of 1.1 g/dL (11 g/L) or greater.
- Increased blood ammonia concentration is characteristic of HE, but levels do not correlate to degree of impairment.
- Increased serum creatinine and blood urea nitrogen (BUN) signal a decline in renal function and may indicate hepatorenal syndrome.
- Signs and symptoms of infection (eg, mental status change, fever, abdominal pain) should prompt a diagnostic paracentesis in a patient with ascites (Figure 22–4). In SBP, there is decreased total serum protein, elevated white blood cell count (with left shift), and the ascitic fluid contains at least 250 cells/mm^3 (250 × 10^6/L) neutrophils. Bacterial culture of ascitic fluid may be positive, but lack of growth does not exclude the diagnosis.

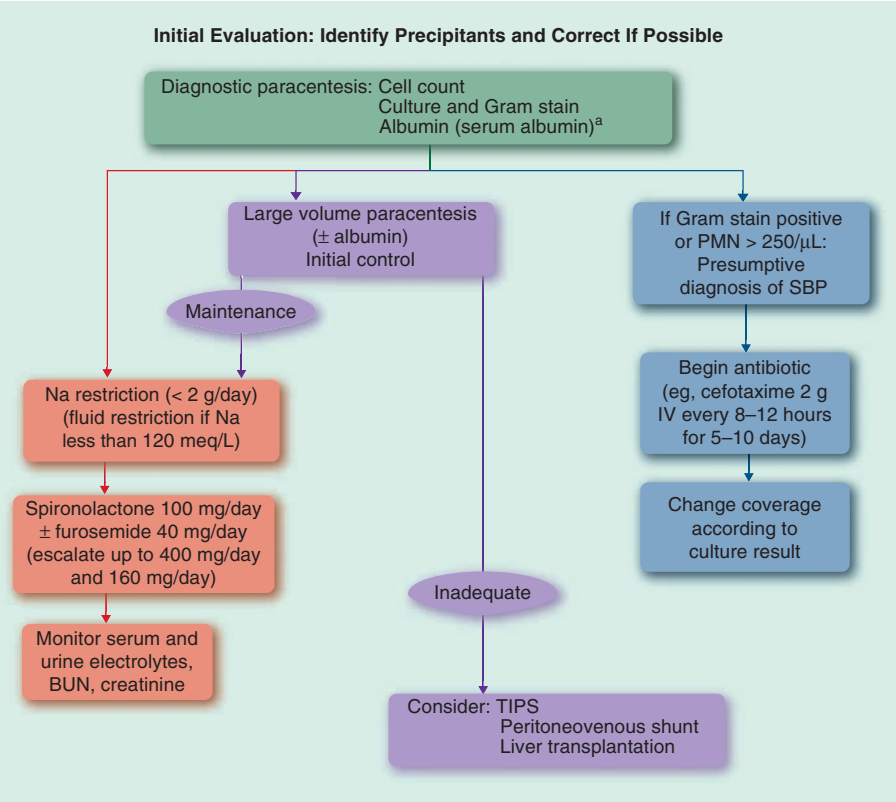

FIGURE 22–4. Approach to the patient with ascites and spontaneous bacterial peritonitis (SBP). [a]If PMN is greater than 250/μL (250 × 10^6/L) but culture is negative (culture-negative neutrocytic ascites), begin empiric antibiotics and retap after 48 hours. If culture is positive but PMN less than 250/μL (250 × 10^6/L), treat as if PMN greater than 250/μL (250 × 10^6/L) (presumed SBP). If polymicrobial infection exists, exclude SBP. (BUN, blood urea nitrogen; Na, sodium; PMN, polymorphonuclear leukocyte; TIPS, transjugular intrahepatic portosystemic shunt.) (Adapted from Chung RT, Podolsky DK. Cirrhosis and its complications. In: Kasper DL, Braunwald E, Fauci AS, et al., eds. Harrison's Principles of Internal Medicine, 17th ed. New York, NY: McGraw-Hill, 2005:1858–1869, with permission.)

TREATMENT OF PORTAL HYPERTENSION, CIRRHOSIS, AND COMPLICATIONS

Desired Outcomes

Recognizing and treating the underlying cause of cirrhosis is paramount. KEY CONCEPT Until recently, cirrhosis was considered irreversible, but treating the underlying cause in its early stages may reverse the damage. Eradication of HCV decreases mortality even with advanced disease. In patients without a reversible cause, cirrhosis treatment is directed at limiting disease progression and minimizing complications.[20] Immediate treatment goals are to stabilize acute complications such as variceal bleeding and prevent SBP. Once life-threatening conditions have stabilized, the focus shifts to preventing complications and further liver damage. The sections that follow concentrate on therapy to prevent and treat cirrhotic complications.

LO 5

Nonpharmacologic Therapy

Avoiding additional hepatic insult is critical for successful cirrhosis management. Lifestyle modifications can limit disease complications and slow further liver damage. The only proven treatment for alcoholic liver disease is immediate cessation of alcohol use, and because alcohol is hepatotoxic, all cirrhotic patients should abstain from alcohol to prevent further liver damage.

LO 6

Patients with ascites require dietary sodium restriction. Intake should be limited to less than 800 mg sodium (2 g sodium chloride) per day. More stringent restriction may cause faster mobilization of ascitic fluid, but adherence to such strict limits is very difficult. Ascites usually responds well to sodium restriction accompanied by diuretic therapy.[6]

Medications must be monitored carefully for potential adverse effects; hepatically metabolized drugs can accumulate in patients with liver disease. Unfortunately, little guidance is available on drug dosing in hepatic impairment because these patients have historically been excluded from drug trials. Daily acetaminophen use should not exceed 2 g. Dietary supplements, herbal remedies, and nutraceuticals have not been well studied in hepatic impairment and cannot be recommended.

LO 6

In patients with variceal bleeding, nasogastric (NG) suction reduces the risk of aspirating stomach contents; aspiration pneumonia is a major cause of death in patients with variceal bleeding. Because blood in the GI tract is very nauseating, NG suction during variceal bleeding can decrease vomiting by removing blood from the GI tract.

Endoscopic band ligation (EBL) involves application of a stricture around the varix to stop acutely bleeding varices. EBL is the preferred endoscopic treatment and is effective in up to 90% of patients.[21] It is also the standard of care for secondary prophylaxis of repeat bleeding in patients with a history of either esophageal or gastric variceal bleeding. Band ligation is best used in conjunction with pharmacologic treatment.[22,23]

During episodes of acute HE, temporary protein restriction to decrease ammonia production can be a useful adjuvant to pharmacologic therapy, but long-term protein restriction in cirrhotic patients is not recommended. Cirrhotic patients are already in a nutritionally deficient state, and prolonged protein restriction will exacerbate the problem.[16]

Hepatitis A and B vaccination is recommended in patients with cirrhosis to prevent additional liver damage from an acute viral infection.[24] Pneumococcal and influenza vaccination may also be appropriate and can reduce hospitalizations.

LO 6

Shunts are long-term solutions to decrease elevated portal pressure. Shunts divert blood flow through or around the diseased liver, depending on the location and type of shunt employed. Transjugular intrahepatic portosystemic shunts (TIPS) create a communication pathway between the intrahepatic portal

Patient Encounter Part 1

A 53-year-old woman was admitted to your unit overnight from the emergency department. She is a very poor historian and seems somewhat confused.

Chief Complaint: Abdominal pain and fullness; patient states, "I feel like I'm going to explode."

HPI: Increasing abdominal girth over the past 2 weeks; abdominal pain and intense tightness started yesterday afternoon

PMH: DVT "long time ago," and "bleeding ulcer" 2 years ago

Drug Allergies: NKDA

PSH: Cesarean section × 3

SH: Marital status unclear, at intake she stated she was not married, but later said her husband lives in Oklahoma. She works as a clerk at an elementary school. Denies tobacco, states she uses marijuana and alcohol on a "recreational" basis only. Cannot quantify intake.

FH: Mother with osteoporosis and hyperthyroidism; father with hypertension

Meds (Outpatient): OTC NSAIDs (ibuprofen, naproxen), antacids occasionally

ROS: Abdominal pain with nausea and early satiety

PE:

VS: BP 84/58 mm Hg, P 110 beats/min, T 101.7°F (38.7°C), RR 20 breaths/min, oxygen saturation 99% (0.99) on room air, Ht 67" (170 cm), Wt 56 kg, BMI 19.3 kg/m^2

General: Somnolent, ill-looking woman who appears older than stated age

HEENT: PERRL, EOMI, (+) scleral icterus, jaundiced skin with mild temporal wasting

CV: Tachycardic, no murmurs, rubs, or gallops

Chest: CTA bilaterally

Abd: Distended tense abdomen that is tender to palpation, hypoactive bowel sounds, hepatosplenomegaly, large ascites

Ext: 3+ pedal pulses, 2+ pitting edema

What signs and symptoms does she have that are consistent with cirrhosis?

Based on the current information, what is the most likely cause of her abdominal pain?

What risk factors does she have for cirrhosis?

Is there anything in her history that could indicate previous complications from cirrhosis?

Should this patient receive pharmacologic DVT prophylaxis?

vein and the hepatic vein. TIPS procedures may be preferred over surgically inserted shunts because they are placed through the vascular system rather than through more invasive surgical procedures, but they still carry a risk of bleeding and infection. TIPS placement can improve HRS but is associated with an increased incidence of HE.[16] The increased risk of HE results from decreased detoxification of nitrogenous waste products because the shunt allows blood to evade metabolic processing.

Hemodialysis is usually used only as a bridge for HRS patients awaiting liver transplantation. It can contribute to hemodynamic instability and does not correct the underlying liver disease.

Pharmacologic Therapy

Drug therapy directed at reducing portal hypertension can alleviate symptoms and prevent complications but cannot reverse cirrhosis.

▶ *Portal Hypertension*

LO 6 KEY CONCEPT Nonselective β-blockers (NSBB) such as propranolol and nadolol are first-line treatments for portal hypertension. They reduce bleeding and decrease mortality in patients with known varices.

Only nonselective β-blockers (those that block both β_1 and β_2 receptors) reduce bleeding complications in patients with known varices. Blockade of β_1 receptors reduces cardiac output and splanchnic blood flow, while β_2-adrenergic blockade prevents β_2-receptor–mediated splanchnic vasodilation while allowing unopposed α-adrenergic effects; this enhances vasoconstriction of the systemic and splanchnic vascular beds. The combination of β_1 and β_2 blockade makes the NSBB preferable to cardioselective (β_1 selective) agents in treating portal hypertension.[1,22,25] Although cardioselective β-blockers do lose β_1 selectivity at higher doses, most patients with cirrhosis cannot tolerate the high doses.

Because β-blockers decrease blood pressure and heart rate, they should be started at low doses to increase tolerability; cirrhotic patients often already have low blood pressure and heart rate. Propranolol is hepatically metabolized, so initial drug concentration, half-life, and pharmacologic effects are all increased in cirrhosis. A reasonable starting dose of propranolol is 10 to 20 mg once or twice daily.

LO 5 Doses should be titrated as tolerated with the goal of decreasing heart rate by 25% or to approximately 55 to 60 beats/min.[26] Heart rate reduction is not an accurate predictor of portal pressure reduction but is associated with maximally tolerated effect.

Carvedilol is a unique NSBB that also blocks α_1 receptors. The α_1 blockade induces intrahepatic vasodilation for a more potent decrease in portal pressure compared to other NSBB, but it also mediates greater decreases in mean arterial pressure.

The role of NSBB was called into question after observational trials suggested increased mortality in patients with a history of refractory ascites or SBP.[27,28] Later publications identified a complex dose–response relationship for NSBB in these patients; high doses (propranolol doses above 160 mg/day) are associated with increased mortality risk, while lower doses are associated with improved survival.[29,30] NSBB use should be carefully monitored in cirrhotic patients with tenuous blood pressure or other evidence of circulatory dysfunction, and discontinued in patients with acute decompensation (eg, variceal bleed, SBP, HRS). Carvedilol should be avoided in patients with refractory ascites to avoid additional vasodilation.[26]

Nitrates (eg, isosorbide mononitrate) have been shown in clinical trials to reduce portal pressure when used alone or in combination with β-blockers. However, they cause systemic vasodilation and increase mortality when used alone, and because patients treated with combination therapy have significantly more adverse events compared to β-blocker monotherapy, nitrates are seldom used in cirrhotic patients.[26]

▶ *Ascites*

LO 6 KEY CONCEPT The goals of treating ascites are to minimize acute discomfort, reequilibrate ascitic fluid, and prevent SBP. Treatment should modify underlying disease pathology; without directed therapy, fluid rapidly reaccumulates.

LO 6 Acute discomfort from ascites may be ameliorated by therapeutic paracentesis. Often removing just 1 to 2 L of ascitic fluid provides relief from pain and fullness. Volume resuscitation should be provided for large volume paracentesis; 6 to 8 g of IV albumin should be given per liter of fluid removed. Albumin 25% should be used because it has one-fifth the volume of the 5% product. Large-volume paracentesis without albumin administration can precipitate HRS through decreased perfusion. Albumin has not been shown to be beneficial in hemodynamically stable patients if less than 5 L of fluid is removed.[6]

LO 6 **Diuretics** Diuretics are usually required in addition to sodium restriction (see Nonpharmacologic Therapy). KEY CONCEPT Spironolactone (an aldosterone antagonist) with or without furosemide forms the basis of pharmacologic therapy for ascites. Cirrhosis is a high aldosterone state; spironolactone counteracts the effects of RAAS activation. Not only is aldosterone production increased, but decreased hepatic metabolism prolongs aldosterone half-life.

LO 6 A loop diuretic is typically added to spironolactone for more potent diuresis. A ratio of 40 mg furosemide (the most common loop diuretic) to 100 mg spironolactone usually maintains serum potassium within the normal range.

Doses should be titrated upward every 3 to 5 days. Because spironolactone is used for its antialdosterone effects, high doses (up to 400 mg/day) are used. If intolerable side effects such as painful gynecomastia occur with spironolactone, other potassium-sparing diuretics may be used, but clinical trials have not shown equivalent efficacy.[6]

Patient Encounter Part 2

Laboratory results for the patient showed the following:

Sodium 126 mEq/L (mmol/L)	Albumin 2.1 g/dL (21 g/L)
Potassium 3.2 mEq/L (mmol/L)	Total bilirubin 4.3 mg/dL (73.5 μmol/L)
Chloride 97 mEq/L (mmol/L)	Alk phos 174 IU/L (2.9 μkat/L)
Bicarbonate 19 mEq/L (mmol/L)	AST 68 IU/L (1.13 μkat/L)
BUN 6 mg/dL (2.1 mmol/L)	ALT 39 IU/L (0.65 μkat/L)
SCr 0.5 mg/dL (44 μmol/L)	INR 1.4
Glucose 89 mg/dL (4.9 mmol/L)	PT 17 seconds
Hemoglobin 8.4 g/dL (84 g/L; 5.21 mmol/L)	GGT 163 IU/L (2.72 μkat/L)
Hematocrit 28% (0.28)	LDH 187 IU/L (3.12 μkat/L)
WBC 11.3 × 10^3/mm^3 (10^9/L)	Serum NH_3 91 mcg/dL (53 μmol/L)
Platelets 63 × 10^3/mm^3 (10^9/L)	

Which laboratory values support a diagnosis of cirrhosis?

What test(s), if any, should be done to further investigate the source of abdominal pain?

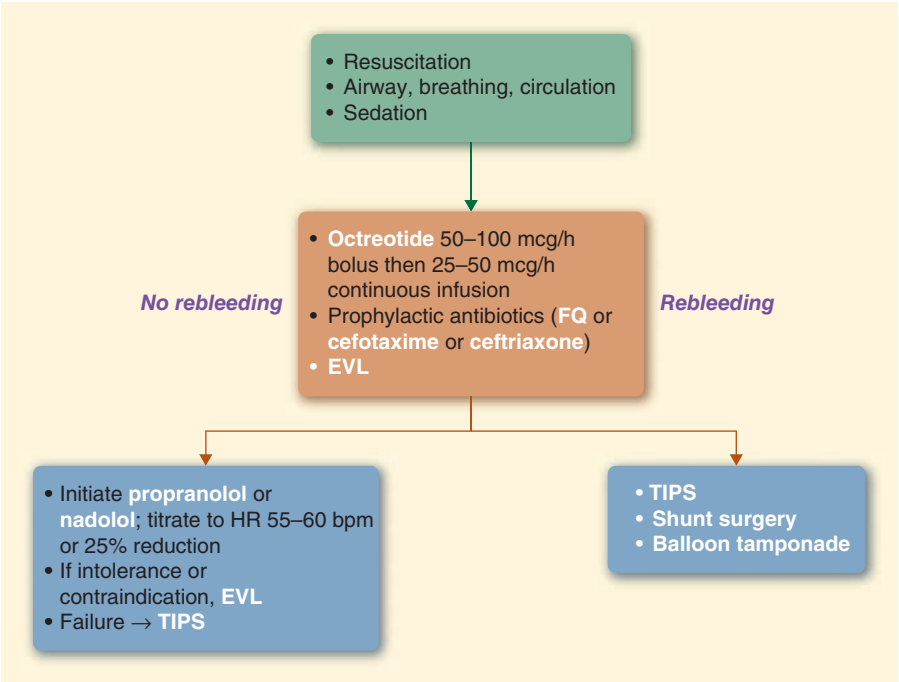

FIGURE 22–5. Treatment of acute variceal bleeding. (EVL, endoscopic variceal ligation; (FQ, fluoroquinolone; HR, heart rate; TIPS, transjugular intrahepatic portosystemic shunt.) (From Ryan L, Attridge RL, Moote R, Miller ML. Chapter 9. Portal Hypertension and Cirrhosis. In: Attridge RL, Miller ML, Moote R, Ryan L, eds. Internal Medicine: A Guide to Clinical Therapeutics, New York, NY: McGraw-Hill; 2013, with permission.)

Because ascites equilibrates with vascular fluid at a much slower rate than does peripheral edema, aggressive diuresis is associated with intravascular volume depletion rather than depletion of peritoneal fluid. The maximum amount of ascitic fluid that can be removed through diuresis is approximately 0.5 L/day.[6] Aggressive diuresis should be avoided unless patients have concomitant peripheral edema. These patients may require increasing furosemide doses until they are euvolemic; IV diuretics are often necessary. Diuretic therapy is typically lifelong.

▶ *Varices*

LO 5 Variceal bleeding is common in cirrhotic patients. KEY CONCEPT During acute variceal hemorrhage, it is crucial to control bleeding, prevent rebleeding, and avoid complications such as SBP. Mortality at 6 weeks is 15% to 25%.[26] A treatment algorithm for acute variceal bleeding is depicted in Figure 22–5.

LO 6 Octreotide (a synthetic somatostatin analog) causes selective vasoconstriction of the splanchnic bed, decreasing portal venous pressure with few serious side effects. The most common octreotide dose is a 50-mcg IV loading dose followed by a 50 mcg/hour continuous IV infusion. Therapy should continue for at least 24 to 72 hours after bleeding has stopped, but the optimal treatment duration has not been defined. Some clinicians continue octreotide for a full 5 days because this is the time frame with highest risk of rebleeding. Octreotide combined with endoscopic therapy results in decreased rebleeding rates and transfusion needs when compared with endoscopic treatment alone.[26] These patients are at high risk of developing SBP, and LO 6 prophylactic antibiotics provide both a morbidity and mortality benefit in this situation. Choice of specific agent should be based on local susceptibility data, but ceftriaxone (1 g IV every 24 hours) for 5 to 7 days has been proven effective.[26]

▶ *Spontaneous Bacterial Peritonitis*

LO 6 Prophylactic antibiotic therapy is recommended during acute variceal bleeding to prevent SBP; this is typically initiated with a third-generation cephalosporin. Prophylactic antibiotic therapy reduces in-hospital infections and mortality in patients hospitalized for variceal bleeding.[26]

LO 6 If SBP is suspected, empiric antibiotic therapy should be initiated with a broad-spectrum anti-infective agent after ascitic fluid collection, pending cultures, and susceptibilities (Figure 22–4). In the setting of presumed infection, delaying treatment while awaiting laboratory confirmation is inappropriate and may result in death. The preferred initial antibiotic should be an IV third-generation cephalosporin (eg, cefotaxime 2 g every 8 hours, ceftriaxone 1 g every 24 hours).[6,26] These agents cover the most common organisms implicated in SBP, but local resistance patterns must be taken into account when choosing empiric antibiotic therapy. Once a bacterial pathogen is identified, coverage should be narrowed to an agent that is highly active against that particular organism. SBP is rarely polymicrobial.

SBP is the primary cause of HRS. The risk of renal failure can be reduced with albumin therapy, 1.5 g/kg initially, followed by 1 g/kg on day 3 of SBP therapy for high-risk patients with SCr greater than 1 mg/dL (88 µmol/L), BUN above 30 mg/dL (10.7 mmol/L), or bilirubin higher than 4 mg/dL (68.4 µmol/L).[31]

LO 6 KEY CONCEPT Long-term SBP prophylaxis decreases mortality and is recommended in a select group of patients—those with a history of SBP, and those with low-protein ascites (ascitic fluid albumin less than 1.5 g/dL [15 g/L]) plus one of the following: SCr 1.2 mg/dL (106 µmol/L) or greater, BUN 25 mg/dL (8.9 mmol/L) or greater, serum sodium 130 mEq/L (mmol/L) or less, or Child–Pugh score of at least 9 (Child–Pugh classification estimates mortality from cirrhosis), with bilirubin of at least 3 mg/dL (51.3 µmol/L). Oral options are one trimethoprim–sulfamethoxazole double-strength daily or ciprofloxacin 500 mg daily.[6]

▶ *Hepatorenal Syndrome*

HRS is a life-threatening complication of cirrhosis. Targeted treatment increases central venous system volume. Peripheral vasoconstriction redistributes fluid from the periphery to the venous system; fluid is retained in the vascular space LO 5 by administering albumin (to increase oncotic pressure). The ultimate goal is to increase renal perfusion.

LO 6 A common regimen involves giving albumin 1 g/kg on day of diagnosis (day 1), followed by 20 to 40 g on subsequent treatment days. This regimen is used in combination with midodrine (an α-agonist) and octreotide. The initial midodrine dose is 7.5 mg orally three times daily; octreotide is usually administered subcutaneously (as opposed to IV during variceal bleeding) 100 mcg three times daily. Both drugs can be titrated as tolerated to achieve increases in mean arterial pressure of at least 15 mm Hg.

Terlipressin, a vasopressin analog available in Europe, has been used with success in patients with HRS, but it is not currently available in the United States.

▶ *Encephalopathy*

LO 6 **Lactulose** KEY CONCEPT Lactulose is the foundation of pharmacologic therapy to prevent and treat HE. It is a nondigestible synthetic disaccharide laxative; it is hydrolyzed in the gut to an osmotically active compound that draws water into the colon and stimulates defecation. Lactulose lowers colonic pH, which favors the conversion of ammonia (NH_3) to ammonium (NH_4^+), which cannot cross back from the gut into the systemic circulation because it is ionic. Lactulose is usually initiated at 15 to 30 mL two to three times per day and titrated to a therapeutic goal of two to three soft bowel movements daily.[16]

Antibiotic Therapy Rifaximin is a nonabsorbable antibiotic that decreases urease-producing gut bacteria, decreasing ammonia production. It is used extensively in Europe as first-line therapy for HE. Although rifaximin is both effective and well tolerated, its expense may prohibit long-term use. In the United States, it is reserved for use as add-on therapy after lactulose failure. The rifaximin dose is 550 mg twice daily to prevent HE recurrences and 400 mg three times a day for treatment.

LO 6

Metronidazole and neomycin have also been used to treat hepatic encephalopathy but are not generally recommended because of toxicity; prolonged metronidazole use is associated with peripheral neuropathy, and although neomycin is classified as a nonabsorbable aminoglycoside antibiotic, patients with cirrhosis do have detectable plasma concentrations. This is thought to be a result of decreased intestinal mucosa integrity, and it may lead to nephrotoxicity. Neomycin should not be used if other options exist.[16]

LO 6

Patient Encounter Part 3

An ultrasound-guided paracentesis was performed, and 7 L of fluid was removed. The analysis reveals clear yellowish fluid, total protein 0.8 g/dL (8 g/L), PMNs 255 cells/mm^3 (255 × 10^6/L), Gram stain was negative, sample sent for culture.

Should the patient receive fluids (crystalloid or colloid) after the paracentesis?

If so, what specific therapy would you initiate and why?

Because the Gram stain was negative, should you wait for the culture results to avoid potentially inappropriate antibiotic use?

If antibiotics are initiated, what is the most appropriate regimen?

Should any other therapy be considered at this time?

What are potential sources of her confusion?

How should her confusion be treated?

Patient Encounter Part 4

The next day, the patient's mental status has improved, she is less somnolent, and she states that her pain is much better, but feels like she has more fluid in her belly than immediately after the paracentesis. On physical examination, her abdomen is less tense than on admission, and she has decreased tenderness to palpation.

What pharmacologic and nonpharmacologic treatments are appropriate to reduce reaccumulation of ascitic fluid?

Does she require long-term prophylaxis to prevent recurrent SBP?

What is the best option for long-term SBP prophylaxis?

Flumazenil Evidence for false transmitters as the cause of encephalopathy has been demonstrated by functional improvement after administering flumazenil (a benzodiazepine antagonist). Unfortunately, long-term benefit has not been demonstrated, and because flumazenil can only be administered parenterally, it is not an appropriate choice for clinical use; flumazenil use is limited to the research setting.

▶ *Coagulation Abnormalities*

Vitamin K is essential for hepatic synthesis of coagulation factors. The elevated clotting time that results from decreased protein synthesis is indistinguishable from coagulopathy that is a result of malnutrition or poor intestinal absorption. When given subcutaneously (10 mg for 3 days), vitamin K_1 (phytonadione) can replete stores and establish if coagulation abnormalities are due to malabsorption alone. It is unusual to completely reverse clotting abnormalities, but INR decreases in most patients, conferring a decreased risk of bleeding. Because cirrhotic patients may have decreased bile production resulting in decreased absorption of fat-soluble vitamins, phytonadione should be given subcutaneously instead of orally to ensure absorption.

OUTCOME EVALUATION

- Reevaluate the pharmacotherapy regimen at each visit to assess adherence, effectiveness, adverse events, and need for drug titration.
- Determine adherence to lifestyle changes such as cessation of ethanol intake and avoidance of over-the-counter medications (particularly NSAIDs and acetaminophen) and dietary supplements that may exacerbate complications of cirrhosis.
- Assess dietary sodium intake by patient food recall. Measure dietary sodium adherence using spot urine sodium-to-potassium ratio to assess appropriate sodium excretion.
- Ask the patient specific, directed questions regarding adherence and adverse effects of β-blockers; inquire about symptoms of orthostatic hypotension (eg, lightheadedness, dizziness, or fainting).
- Evaluate effectiveness of diuretic therapy with regard to ascitic fluid accumulation and development of peripheral edema. Ask the patient directed questions regarding abdominal girth, fullness, tenderness, and pain. Weigh the patient at each visit, and ask the patient to keep a weight diary. Assess for peripheral edema at each visit.

Patient Care Process

Collect Information:

- Perform a medication history at each visit, and ask specifically about prescription, nonprescription, herbal products, and nutraceuticals as well as illicit substances. Be especially mindful of NSAID pain relievers and herbal remedies that can be hepatotoxic or affect renal function. Ask the patient how each medication is taken; this can provide insight into adherence.
- Ask about dietary compliance with sodium restriction; a 24-hour diet recall can help identify high-sodium intake.
- Complete a comprehensive review of systems and physical examination to identify subtle changes. Pay particular attention to fluid status and any GI complaints.

Assess the Information:

- Determine if the patient is taking any drugs that could adversely affect their liver disease or renal function.
- Identify drugs that can precipitate altered mental status or cause confusion.
- Identify medications that may have better alternatives, or are not crucial to continue.
- Identify any changes in health status that could signal decompensation: (1) changes in fluid status (peripheral edema or new or worsening ascites); (2) changes in GI habits that could signal hematochezia, melena, or hematemesis; and (3) changes in mentation such as confusion, changes in sleep patterns, or increased forgetfulness that could signal hepatic encephalopathy.
- Examine laboratory results for signs of worsening hepatic synthetic function or decompensation.

Develop a Care Plan:

- Identify methods to achieve and maintain lifestyle changes including avoiding alcohol and illicit drugs, and achieving a low-sodium diet.
- Choose drug therapies that do not worsen hepatic or renal function, and avoid drugs that may impair cognition or balance. A good resource for those (although targeted at the geriatric population) is the BEERS criteria medication list; a printable pocket card is available on the Internet.

Implement the Care Plan:

- Educate patient (and family as applicable) about lifestyle changes and pharmacotherapy regimens; make sure they understand the purpose of each.
- Select medications that are expected to be well tolerated as well as affordable, and choose the least burdensome dosing regimen.
- Educate the patient on potential adverse effects of drug therapy, how to identify and potentially mitigate those affects, and when to seek medical care.

Follow-up: Monitor and Evaluate:

- Follow up at regular intervals to assess both drug therapy and disease progression.
- Review adherence to lifestyle changes and medication regimens.
- Complete review of systems, physical and laboratory examinations as appropriate to assess changes in patient status.

- Obtain complete blood count (CBC) and PT/INR to assess for anemia, thrombocytopenia, or coagulopathy. Ask about bruising, bleeding, hematemesis, hematochezia, and melena to assess for bleeding.
- Review biopsy reports and laboratory data. Hepatic transaminases and blood ammonia levels do not correlate well with disease progression, but increased coagulation times are markers of loss of synthetic function.
- Evaluate for signs and symptoms of HE. Mental status changes may be subtle; questioning family members or caregivers about confusion or personality changes may reveal mild HE even if the patient is unaware of deficits. In patients taking lactulose therapy, titrate the dose to achieve two to four soft bowel movements daily.

Abbreviations Introduced in This Chapter

ADH	Antidiuretic hormone
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
CYP450	Cytochrome P-450 isoenzyme
GGT	γ-Glutamyl transferase
GI	Gastrointestinal
HE	Hepatic encephalopathy
HRS	Hepatorenal syndrome
INR	International normalized ratio
LDH	Lactate dehydrogenase
MELD	Model for End-Stage Liver Disease
NAFLD	Nonalcoholic fatty liver disease
NG	Nasogastric
NH_3	Ammonia
NH_4^+	Ammonium
NSAID	Nonsteroidal anti-inflammatory drug
PT	Prothrombin time
RAAS	Renin-angiotensin-aldosterone system
SAAG	Serum ascites–albumin gradient
SBP	Spontaneous bacterial peritonitis
TIPS	Transjugular intrahepatic portosystemic shunt

REFERENCES

1. Tsochatzis E, Bosch J, Burroughs A. Liver cirrhosis. Lancet. 2014;383:1749–1761.
2. Clearinghouse NDDI. Cirrhosis of the liver. NIH Publication No 14–1134 Bethesda, MD, 2014.
3. Recommendations for Testing, Managing, and Treating Hepatitis C. AASLD-IDSA. Available from: http://www.hcvguidelines.org/. Accessed November 1, 2017.

4. Rehm J, Taylor B, Mohapatra S. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug Alcohol Rev. 2010;29:437–445.
5. Soldin O, Mattison D. Sex differences in pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2009;48:143–157.
6. Runyon BA, AASLD. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology. 2013;57:1651–1653.
7. Seth D, Haber PS, Syn W-K, et al. Pathogenesis of alcohol-induced liver disease: classical concepts and recent advances. J Gastroenterol Hepatol. 2011;26:1089–1105.
8. Sakaguchi S, Takahashi S, Sasaki T, et al. Progression of alcoholic and non-alcoholic steatohepatitis: common metabolic aspects of innate immune system and oxidative stress. Drug Metab Pharmacokinet. 2011;26:30–46.
9. Chitturi S, Abeygunasekera S, Farrell GC. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology. 2002; 35:373–379.
10. Berzigotti A, Gilabert R, Abraldes J, et al. Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. Am J Gastroenterol. 2008;103:1159–1167.
11. Afzelius P, Bazeghi N, Bie P, et al. Circulating nitric oxide products do not solely reflect nitric oxide release in cirrhosis and portal hypertension. Liver Int. 2011;31:1381–1387.
12. Garcia-Tsao G, Sanyal A, Grace N, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology. 2007;46:922–938.
13. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol. 2000;32:142–153.
14. Steed H, Macfarlane G, Blackett K, et al. Bacterial translocation in cirrhosis is not caused by an abnormal small bowel gut microbiota. EMS Immunol Med Microbiol. 2011;63:346–354.
15. Eckmann C, Dryden M, Montravers P. Antimicrobial treatment of "complicated" intra-abdominal infections and the new IDSA guidelines—a commentary and an alternative European approach according to clinical definitions. Eur J Med Res. 2011;16:115–126.
16. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715–735.
17. Tripodi A, Primignani M, Chantarangkul V, Mannucci PM. Pro-coagulant imbalance in patients with chronic liver disease. J Hepatol. 2010;53:586–587.
18. Leonardi F, De Maria N, Villa E. Anticoagulation in cirrhosis: a new paradigm? Clin Mol Hepatol. 2017;23(1):13–21.
19. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med. 2001;344:495–500.
20. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA. 2012;308:2584–2593.
21. Runyon B, Montano A, Akriviadis E, et al. The serum ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med. 1992;117:215–220.
22. Sharara A, Rockey D. Gastroesophageal variceal hemorrhage. N Engl J Med. 2001;345:669–681.
23. Lo GH, Lai KH, Cheng JS, et al. Endoscopic variceal ligation plus nadolol and sucralfate compared with ligation alone for the prevention of variceal rebleeding: a prospective, randomized trial. Hepatology. 2000;32:461–465.
24. De La Pena J, Brullet E, Sanchez-Hernandez E, et al. Variceal ligation plus nadolol compared with ligation for prophylaxis of variceal rebleeding: a multicenter trial. Hepatology. 2005;41:572–578.
25. Pagliaro L, D'amico G, Sorensen T, et al. Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment. Ann Intern Med. 1992;117:59–70.
26. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2017; 65(1):310–335.
27. Serste T, Melot C, Francoz C, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. Hepatology. 2010;52:1017–1022.
28. Mandorfer M, Bota S, Schwabl P, et al. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 2014;146:1680–1690.
29. Bang UC, Benfield T, Hyldstrup L, et al. Effect of propranolol on survival in patients with decompensated cirrhosis: a nationwide study based Danish patient registers. Liver Int. 2016;36:304–1312.
30. Madsen BS, Nielsen KF, Fialla AD, Krag A. Keep the sick from harm in spontaneous bacterial peritonitis: dose of beta blockers matters. J Hepatol. 2016;64:1455–1456.
31. Ge PS, Runyon B. Treatment of patients with cirrhosis. N Engl J Med. 2016;375:67–77.

23 Pancreatitis

Janine E. Then and Heather M. Teufel

LEARNING OBJECTIVES

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

1. Describe the pathophysiology of acute pancreatitis and chronic pancreatitis.
2. Differentiate acute pancreatitis from chronic pancreatitis.
3. Formulate care plans for managing acute and chronic pancreatitis.
4. Choose appropriate pancreatic enzyme supplementation for patients with chronic pancreatitis.

INTRODUCTION

The pancreas is a gland in the abdomen lying in the curvature of the stomach as it empties into the duodenum. It functions primarily as an exocrine gland but also has endocrine function. The exocrine cells of the pancreas are called **acinar cells** that produce and store digestive enzymes that mix with a bicarbonate-rich solution released from duct cells to produce pancreatic juice. This juice is released through the **ampulla of Vater** into the duodenum to aid in digestion and buffer acidic fluid released from the stomach (Figure 23–1).[1]

Pancreatic enzymes are produced and stored as inactive proenzymes within **zymogen** granules to prevent autolysis and digestion of the pancreas. Amylase and lipase are released from the zymogen granules in the active form, whereas the proteolytic enzymes are activated in the duodenum by enterokinase. Enterokinase triggers the conversion of trypsinogen to the active protease **trypsin**, which then activates the other proenzymes to their active enzymes. The pancreas contains a trypsin inhibitor to prevent autolysis.

ACUTE PANCREATITIS

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT In the Western Hemisphere, acute pancreatitis (AP) is caused mainly by ethanol use/abuse and gallstones (**cholelithiasis**). Ethanol use accounts for about 30% of AP cases and gallstones about 30% to 40% of cases. Other common causes include hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (ERCP), pregnancy, and autodigestion due to early activation of pancreatic enzymes. Numerous medications have been implicated as causes of AP, but other causes should be ruled out before discontinuing a medication indefinitely (Table 23–1).[2]

PATHOPHYSIOLOGY

LO 1

Ethanol abuse may cause precipitation of pancreatic enzymes in pancreatic ducts, leading to chronic inflammation and fibrosis resulting in loss of exocrine function. Ethanol may be directly toxic to the pancreatic cells and may lead to an upregulation of enzymes that produce toxic metabolites leading to further damage.[3] Gallstones can obstruct the ampulla of Vater causing pancreatic enzymes or bile to move in a retrograde fashion into the pancreas. This retrograde movement may be responsible for pancreatic autolysis.[1]

Autolysis of the pancreas can occur when zymogens are activated in the pancreas before being released into the duodenum. AP can result from the initial injury to the zymogen-producing cells, which is followed by neutrophil, lymphocyte, and macrophage invasion of the pancreas and further activation of enzymes within the pancreas.

LO 2

AP can progress to peripancreatic fluid collections in or around the pancreas; they usually require no intervention and resolve spontaneously.[4,5] **Pancreatic pseudocysts** are walled-off fluid collections that form 4 weeks or longer after the onset of AP. Many pseudocysts resolve spontaneously, but some require surgical or percutaneous drainage. Rupture of a pancreatic pseudocyst is a serious complication and can lead to peritonitis and gastrointestinal (GI) bleeding.[4]

Pancreatic enzyme damage may lead to pancreatic necrosis, which is diffuse inflammation of the pancreas containing both necrotic tissue and fluid. KEY CONCEPT Pancreatic necrosis occurs within the first 2 weeks of AP and affects 10% to 20% of patients. Infected necrotic fluid collections occur in 16% to 47% of patients, usually due to bacteria normally present in the GI tract (*Escherichia coli*, Enterobacteriaceae, Enterococcal species, viridans group streptococci, and anaerobes). Disseminated infection may result from pancreatic necrosis.[4,6] Pancreatic abscess is pancreatic necrosis that is walled-off by granulation tissue and occurs weeks after AP.

CLINICAL PRESENTATION AND DIAGNOSIS

LO 2

Patients with AP may develop severe local and systemic complications. Multiorgan failure is a poor prognostic indicator. Disease severity can be predicted using the Ranson criteria, Glasgow severity scoring system, Acute Physiology and Chronic Health Evaluation II (APACHE II), and sequential organ failure assessment (SOFA). Awareness of risk factors for severe disease, including age greater than 55 years, comorbid conditions, laboratory findings, and presence of **systemic inflammatory response syndrome** (SIRS), may be more beneficial than scoring systems.[7]

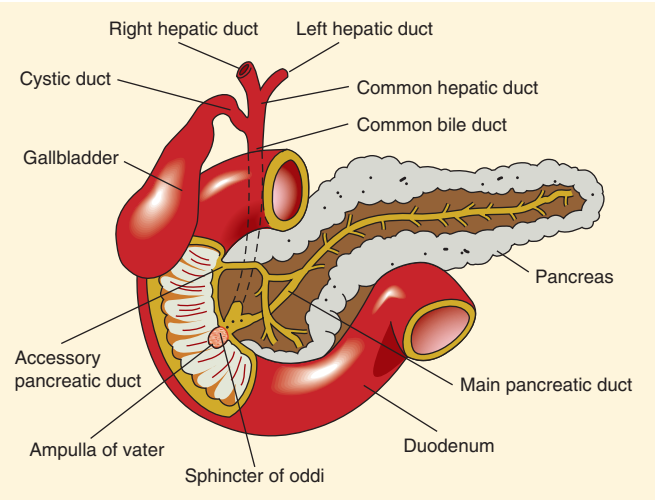

FIGURE 23–1. Anatomical structure of the pancreas and biliary tract. (From Bolesta S, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017; Figure 39–1, with permission. www.accesspharmacy.com.)

DIAGNOSIS

Diagnosis of AP is based on patient history, signs and symptoms, and laboratory values. The history can identify risk factors, such as alcohol abuse and medications. A serum lipase greater than three times the normal limit supports the diagnosis. The serum lipase has greater sensitivity and specificity for AP than does the serum amylase due to its duration of elevation.[2,8] Elevated hepatic enzymes may indicate gallstone pancreatitis, and triglycerides should be checked to rule out hypertriglyceridemia as the cause.[2,7]

Abdominal ultrasound can identify gallstones and sludge in the common bile duct but has limited sensitivity. Computed tomography (CT) may be more useful in staging pancreatitis or identifying complications. ERCP should be used early when patients have concurrent acute cholangitis. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are more costly options that can be used to evaluate severity and pancreatic abnormalities.[2,7]

Table 23–1

Selected Medications Associated with Acute Pancreatitis

Cardiovascular: Enalapril, lisinopril, ramipril, losartan, furosemide, hydrochlorothiazide, amiodarone, statins
Anti-infectives: Metronidazole, sulfonamides, tetracycline, tigecycline, pentamidine, isoniazid, lamivudine, didanosine, nelfinavir, interferon/ribavirin
Gastrointestinal: Omeprazole, mesalamine
Neurologic: Valproic acid, clozapine
Hormonal: Conjugated estrogens, tamoxifen
Oncologic: Ifosfamide, cytarabine
Analgesics: Sulindac, salicylates
Other: Propofol, mercaptopurine, azathioprine, corticosteroids, marijuana

Clinical Presentation of Acute Pancreatitis

Signs and Symptoms

- Sudden upper abdominal pain is the most common symptom.
- Pain may radiate to the back, and ecchymosis may be present in the flank and periumbilical areas.
- Nausea and vomiting are other common symptoms.
- Tachycardia, hypotension, fever, and abdominal distention may be present.

Laboratory Tests

- The serum amylase may be elevated to more than three times the upper limit of normal within the first 12 hours of the onset of AP. The degree of elevation does not correlate with disease severity, and levels may return to normal before the patient presents for care.
- Serum lipase rises within 4 to 8 hours of onset, peaks at 24 hours, and returns to normal within 8 to 14 days.
- Other laboratory abnormalities may include elevated white blood cell (WBC) count, hyperglycemia, hypocalcemia, hyperbilirubinemia, elevated serum lactate dehydrogenase (LDH), and hypertriglyceridemia.

TREATMENT

Desired Outcomes

The goals of treatment for AP include: (a) resolution of nausea, vomiting, abdominal pain, and fever; (b) ability to tolerate oral intake; (c) normalization of serum amylase, lipase, and WBC count; and (d) resolution of abscess, pseudocyst, or fluid collection as measured by CT scan.

Nonpharmacologic Therapy

KEY CONCEPT Therapy of AP is primarily supportive unless a specific etiology is identified (Figure 23–2). Supportive therapy involves fluid repletion, nutrition support, and analgesia. Patients are administered IV fluids to maintain hydration and blood pressure. Lactated Ringer's solution at a rate of 250 to 500 mL/hour should be used to provide aggressive hydration.[9] The total amount of fluids administered should be based on vital signs and urine output. Fluid requirements should be assessed carefully, especially in patients with concomitant cardiac, renal, and liver disease. Electrolytes such as potassium and magnesium may be added to the infusions if necessary. Hyperglycemia can be managed with insulin-containing IV infusions.[7]

LO 3

While it is common to discontinue oral feedings during AP, this does not prevent further damage because secretion of trypsin is already reduced.[6] In mild to moderate AP, diet should be advanced based on resolution of nausea, vomiting, and pain. In severe AP enteral nutrition should be started as early as possible and may include nasogastric or nasojejunal feedings. Early use of enteral nutrition (within 48 hours)[10] has been shown to decrease surgical interventions and infectious complications. Enteral nutrition is preferred, but if a patient is not meeting caloric goals, it may be supplemented with total parenteral nutrition.[6,7,10]

LO 3

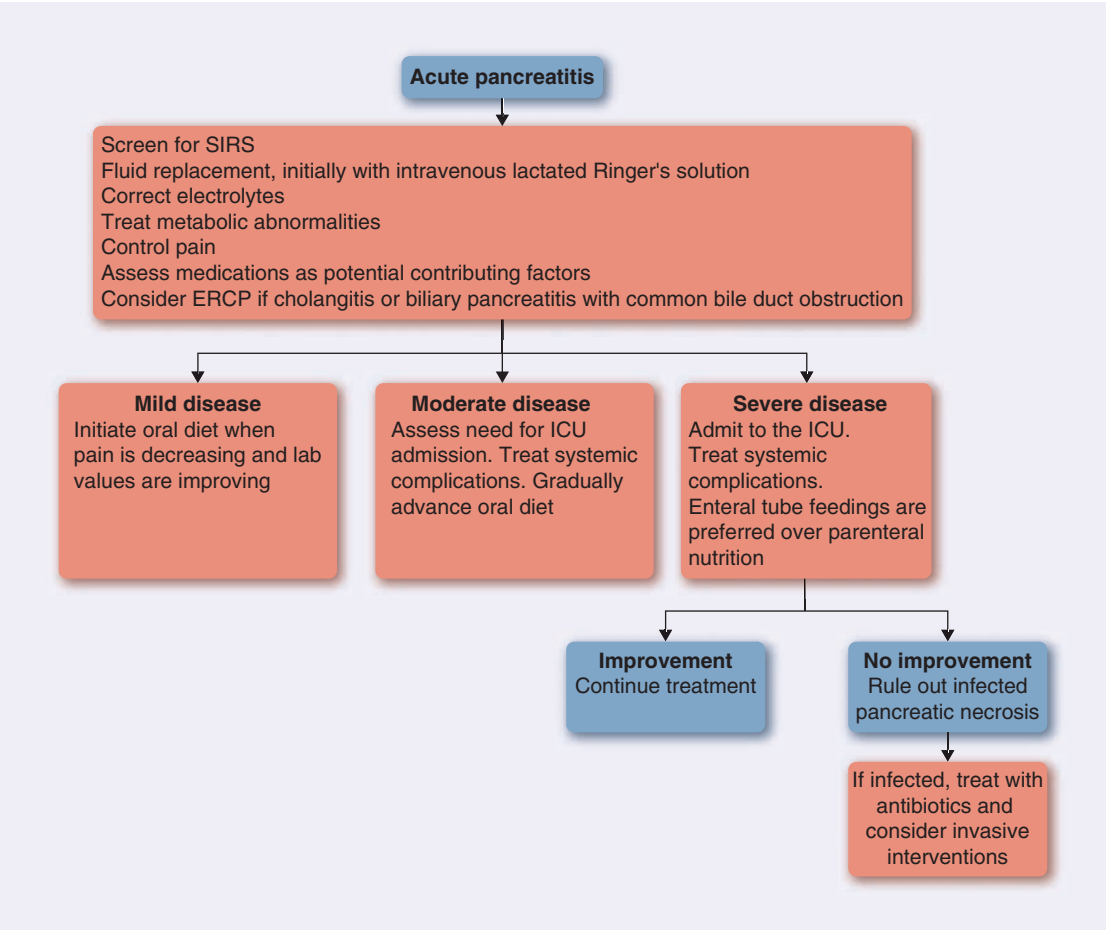

FIGURE 23–2. Algorithm for evaluation and treatment of acute pancreatitis. (ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome.) (From Bolesta S, Montgomery PA. Pancreatitis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017; Figure 39–3, with permission. www.accesspharmacy.com.)

If pancreatic necrosis or abscesses are present, surgical or interventional procedures may be necessary.

Pharmacologic Therapy

▶ *Analgesics*

No single opioid analgesic has proven to be superior to other opioids in treating pain associated with pancreatitis. Opioids should be titrated to the lowest effective dose. Consideration should also be given to nonopioid analgesic therapy based on current perioperative pain management strategies.[10] (See Chapter 34, Pain Management.)

Patient Encounter 1, Part 1

A 23-year-old man presents to the emergency department with a 2-day history of nausea and vomiting. He also complains of abdominal pain that is unrelieved and persistent. He has not eaten in the past 2 days because food exacerbates the pain. Upon examination, his abdomen is found to be distended.

What information about the patient presentation is consistent with acute pancreatitis?

What tests may be helpful in diagnosing acute pancreatitis?

▶ *Antibiotics*

Antibiotics do not prevent formation of pancreatic abscess or necrosis when given early in the course of AP.[2,7] Empiric antibiotics are not indicated if the patient has mild disease or a known noninfectious cause. In necrotizing pancreatitis, antibiotics may be appropriate for patients who fail to improve after 1 week, or deteriorate. The decision to use antibiotics should be guided by fine needle aspiration whenever possible. Stable patients with infected necrosis should be treated with antibiotics; surgical, radiologic, and/or endoscopic drainage would ideally be delayed by 4 weeks to allow for the area of necrosis to become walled off.[6,7,10] Consideration should be given to discontinuing antibiotics if no source of infection is confirmed.

Infections are usually polymicrobial, so broad-spectrum antibiotics with activity against enteric gram-negative bacilli are appropriate (Table 23–2). Patients may receive long courses of broad-spectrum antibiotics and may develop superinfections with resistant bacteria. Routine use of antifungal agents (eg, fluconazole) is not recommended but may be considered if peritonitis or GI perforation develops due to the presence of fungi such as *Candida albicans* in the GI tract.[1,7]

Patient Encounter 1, Part 2

PMH: None

Allergies: Amoxicillin (hives)

FH: Father—MI at 48 years of age, CHF, COPD; mother—osteoporosis, breast cancer, gallstones

SH: History of heavy drinking; tobacco 1 ppd; no recreational drugs

Meds: Bactrim DS twice daily for a skin lesion (started last week), naproxen 500 mg twice daily as needed for pain

ROS: Positive for sharp right upper quadrant (RUQ) abdominal pain that radiates to the right shoulder and back, nausea, vomiting; negative for substernal chest pain

PE:

VS: BP 105/60 mm Hg seated, 90/50 mm Hg standing, P 120 beats/min, RR 22 breaths/min, T 37.9°C (100.2°F), pain score 9/10, Wt 91 kg (200 lb), Ht 6′1″ (185 cm)

CV: Regular rate and rhythm, no murmurs

Abd: Distended, (+) rebound tenderness, (+) bowel sounds, (+) guarding

Labs:

WBC 15.8 × 10^3/mm^3 (10^9/L)	Amylase 90 IU/L (1.50 µkat/L)
Hgb 10.9 g/dL (109 g/L, 6.77 mmol/L)	Lipase 1250 IU/L (20.8 µkat/L)
Hct 30% (0.30)	AST 520 IU/L (8.67 µkat/L)
Platelets 250 × 10^3/mm^3 (10^9/L)	ALT 480 IU/L (8.0 µkat/L)
BUN 19 mg/dL (6.8 mmol/L)	Total bilirubin 2.7 mg/dL (46.2 µmol/L)
SCr 1.2 mg/dL (106 µmol/L)	
Glucose 220 mg/dL (12.2 mmol/L)	LDH 1050 IU/L (17.5 µkat/L)

Abdominal x-ray and ultrasound: Pending

What clinical signs are consistent with acute pancreatitis?

What additional information is needed at this point?

What treatment(s) would you initiate?

▶ *Ineffective Therapies*

KEY CONCEPT Therapies with no proven benefit on morbidity and mortality include reducing pancreatic secretion by administering somatostatin analogues or atropine, reducing gastric acidity and pancreatic secretion with histamine$_2$-receptor antagonists, probiotics, and immunomodulation.[11]

OUTCOME EVALUATION

- Monitor hydration and nutrition status closely; replace electrolytes as necessary.
- Provide analgesia and monitor pain severity using validated scales.
- Monitor patients with moderate to severe AP in an intensive care setting with frequent monitoring of vital signs.
- Continually assess patients for signs of infection, including fever, leukocytosis, and other signs of sepsis.

Table 23–2

Selected IV Antimicrobial Regimens for Pancreatic Necrosis

Drug	Usual Dose[a]	Notes
Meropenem	1 g every 8 hours	Risk of superinfection
Piperacillin/tazobactam	3.375–4.5 g every 6–8 hours	Avoid if allergic to penicillin
Cefepime + metronidazole	2 g every 12 hours + 500 mg every 8–12 hours	Will not cover enterococci
Aztreonam + vancomycin + metronidazole	1 g every 8 hours + 15 mg/kg every 8–12 hours + 500 mg every 6 hours	Option for penicillin-allergic patients

[a]Doses must be adjusted for the degree of renal impairment.

CHRONIC PANCREATITIS

EPIDEMIOLOGY AND ETIOLOGY

The incidence of chronic pancreatitis (CP) ranges from 5 to 12 per 100,000 persons, and is higher in men than women.[12] KEY CONCEPT The most common cause of CP in adults in Western countries is ethanol abuse. Other causes include genetic

Patient Care Process for Acute Pancreatitis

Collect Information:

- Assess fluid and nutritional status and abdominal pain severity using a pain scale.
- Review laboratory data: lipase and/or amylase; triglycerides.
- Review imaging results to determine potential causes (eg, obstruction) and extent of pancreatic damage.

Assess the Information:

- Review laboratory data, imaging and medication history for potential risk factors for pancreatitis (Table 23–1).

Develop a Care Plan:

- Determine the level of monitoring required based on the patient's location (eg, ICU, medical floor)
- Determine how to assess ongoing pain

Implement the Care Plan:

- Provide fluid resuscitation until the patient shows signs of adequate perfusion (monitor blood pressure and urine output).
- Provide analgesia using multimodal therapy.
- Initiate enteral nutrition early; consider parenteral nutrition if enteral nutrition is not tolerated within 1 week.

Follow-up: Monitor and Evaluate:

- Assess vital signs and pain frequently.
- Provide ongoing monitoring for potential infection.

predisposition, obstructive disease (secondary to ductal strictures or pseudocysts), autoimmune pancreatitis, abnormal cystic fibrosis transmembrane conductance regulator (CFTR) function as seen in cystic fibrosis (CF) patients, tropical pancreatitis, and idiopathic pancreatitis.[3,13] Cigarette smoking is an independent risk factor for CP.[14]

PATHOPHYSIOLOGY

LO 1

CP is an inflammatory process that occurs over time leading to impaired endocrine and exocrine function secondary to diffuse scarring and fibrosis. The pathogenesis of CP is not completely understood and varies depending on etiology. One theory is that protein-rich plugs form leading to ductal obstruction and inflammation, ultimately causing parenchymal fibrosis and ischemic injury to the acinar cells.[15]

KEY CONCEPT Long-term sequelae of CP include dietary malabsorption, impaired glucose tolerance, cholangitis, and potential addiction to opioid analgesics. As pancreatic exocrine function diminishes, patients have decreased ability to absorb lipids and protein with normal dietary intake, leading to weight loss and malnutrition. Fat- or protein-containing stools are common; carbohydrate absorption is usually unaffected.[13] Patients with CP are at risk and should be screened for deficiencies of vitamin B_{12} and fat-soluble vitamins (A, D, E, and K).[16,17]

LO 3

CLINICAL PRESENTATION AND DIAGNOSIS

The symptoms, signs, and laboratory abnormalities associated with CP are shown in the accompanying box. Several genetic mutations have been associated with CP (*PRSS1*, *SPINK1*, and *CFTR* genes) and may be useful in the diagnostic workup of CP.[15] Pancreatic biopsy with histologic examination is the gold standard for diagnosis of CP, but it is rarely performed. In the absence of histology, abdominal ultrasound, CT, MRCP, or ERCP can assist in the diagnosis.[3,13] Malabsorption and steatorrhea can be diagnosed using quantitative estimations of stool fat, including a 72-hour stool collection or the less cumbersome fecal elastase test.[18]

Patient Encounter 1, Part 3

The patient was discharged and presents again to the hospital 3 weeks later with similar pain and feeding intolerance. On this admission, his WBC count is elevated at $21.2 \times 10^3/mm^3$ ($10^9/L$), and he has a temperature of 38.7°C (101.6°F). He is hypotensive with a mean arterial pressure (MAP) of 60 mm Hg, and his HR is 115 beats/min. His RR is 28 breaths/min and SCr is 2.0 mg/dL (177 µmol/L).
A CT scan demonstrates pancreatic necrosis, and a fine needle aspiration is performed. His APACHE II score is calculated to be 13.

Should this patient be admitted to the ICU or general floor unit?

Does this patient meet criteria for antibiotics? If so, what agents should be considered?

Besides antibiotics, what other pharmacologic treatments may need to be optimized?

Clinical Presentation of Chronic Pancreatitis

General

- Presentation of CP can be similar to that of AP.

Symptoms

- Pain is the most common symptom, and it typically starts in the epigastrium and may radiate to the back or scapula. Pain can be sharp or dull, is not relieved by antacids, and can be provoked by ethanol ingestion or a fatty meal. Pain can be episodic with pain-free intervals, or prolonged and requiring hospitalization.
- Pain may be associated with nausea and vomiting, causing patients to avoid food.
- Weight loss can result from chronic fat and protein malabsorption.

Signs

- Steatorrhea (due to fat malabsorption), malnutrition, and glucose intolerance are often present in advanced CP.
- Chronic obstruction of the common bile duct by the inflamed pancreas can cause icterus (jaundice), cholangitis, and biliary cirrhosis.

Laboratory Tests

- Serum amylase and lipase concentrations may be normal to slightly elevated in CP and are not particularly useful in the diagnosis.
- Glucose intolerance may occur because of chronic destruction of pancreatic endocrine function.
- The serum bilirubin or alkaline phosphatase may be elevated due to inflammation near the common bile duct.
- Erythrocyte sedimentation rate (ESR), IgG4, rheumatoid factor, antinuclear antibody (ANA), and anti-smooth muscle antibody titer may be elevated in autoimmune pancreatitis.

TREATMENT

Desired Outcomes

Goals of pharmacotherapy for CP include: (a) relief of acute and chronic abdominal pain, (b) correction of dietary malabsorption with exogenous pancreatic enzymes, and (c) treatment of endocrine insufficiency and associated diabetes.

▶ *Nonpharmacologic Therapy*

LO 3

KEY CONCEPT Avoidance of ethanol, cigarette smoking, and fatty meals can decrease the pain of CP. Alcohol and cigarette abstainers may have slower disease progression and better response to pain therapy than nonabstainers.[3,13,14] Patients should consume a diet consisting of frequent small low-fat meals (< 20 g fat/day) or one with medium-chain triglycerides where absorption requires only minimal amounts of pancreatic enzymes.[3,19] Surgical procedures for CP include drainage procedures, partial pancreatic resection, and total pancreatectomy. Indications for surgery include poorly controlled pain, ductal obstruction, and symptomatic pseudocysts.[15] Most surgical procedures to reduce inflammation or remove strictures have not been studied in clinical trials and carry a high risk of morbidity and mortality.[3,13]

Pharmacologic Therapy

▶ *Analgesics*

LO 2 LO 3

KEY CONCEPT Pain management is an important component of therapy and similar to that of AP. Nonopioid analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]) are preferred, but the severe and persistent nature of the pain often requires opioid therapy. Patients can require chronic doses of opioid analgesics, with resulting risk of addiction.[3,20] Patients should also be assessed for neuropathic pain and treated accordingly (eg, tricyclic antidepressants, pregabalin).[20-22] Refer to Chapter 34 (Pain Management) for guidance in selecting an analgesic dose.

LO 3

▶ *Pancreatic Enzymes*

Pancreatic enzyme supplements (PES) are indicated in symptomatic patients with steatorrhea. The goal is to deliver exogenous enzyme to the duodenum without causing further GI side effects, risking noncompliance due to the large number of dosage units required, or causing undue medication expense.

LO 4

KEY CONCEPT Supplementation with pancreatic enzymes may reduce the pain and fatty diarrhea associated with CP. Common PES contain lipase, protease, and amylase in varying proportions. The half-life of endogenous lipase is based on the presence of its substrates (ie, triglycerides), and therefore dietary fat restriction should be reconsidered when pancreatic enzyme replacement is used.[18,19]

PES products approved by the US Food and Drug Administration are shown in Table 23–3.[23] Enteric-coated products are designed to release enzymes in the alkaline environment (pH > 5.5) of the duodenum, thus minimizing enzyme destruction in the stomach. However, in patients with delayed gastric emptying, the efficacy of the enteric-coated PES may be decreased due to early activation of the lipase enzymes. Addition of an H_2-blocker or proton pump inhibitor will decrease stomach acidity, thereby enhancing delivery of the PES to the site of action. The nonenteric-coated PES are deactivated immediately in an acidic

Table 23–3

FDA-Approved Pancreatic Enzyme Supplements

	Enzyme Content (Units)[a]		
Product	**Lipase**	**Protease**	**Amylase**
Creon 3000	3000	9500	15,000
Creon 6000	6000	19,000	30,000
Creon 12,000	12,000	38,000	60,000
Creon 24,000	24,000	76,000	120,000
Creon 36,000	36,000	114,000	180,000
Pancreaze 2600	2600	6200	10,850
Pancreaze 4200	4200	14,200	24,600
Pancreaze 10,500	10,500	35,500	61,500
Pancreaze 16,800	16,800	56,800	98,400
Pancreaze 21,000	21,000	54,700	83,900
Pertyze[b]	4000	14,375	15,125
Pertyze[b]	8000	28,750	30,250
Pertyze[b]	16,000	57,500	60,500
Viokace 10,440[c]	10,440	39,150	39,150
Viokace 20,880[c]	20,880	78,300	78,300
Zenpep 3000	3000	10,000	14,000
Zenpep 5000	5000	17,000	24,000
Zenpep 10,000	10,000	32,000	42,000
Zenpep 15,000	15,000	47,000	63,000
Zenpep 20,000	20,000	63,000	84,000
Zenpep 25,000	25,000	79,000	105,000
Zenpep 40,000	40,000	126,000	168,000

[a]All products are porcine derived.

[b]Bicarbonate-buffered enteric-coated microspheres.

[c]Nonenteric-coated tablets; must be administered with a proton pump inhibitor.

Patient Encounter 2

A 68-year-old man presents to the emergency department complaining of a chronic dull pain with a burning/tingling sensation in his abdomen for several months that is no longer relieved with over-the-counter analgesics. He has also had light-colored liquid stools for the past month and has lost 10 pounds (4.5 kg) because of decreased appetite and worsening abdominal pain with meals.

PMH: Hypertension, coronary artery disease, hypothyroidism, depression, recurrent acute pancreatitis, GERD

SH: Consumes a six-pack of beer per day and has a 35 pack–year history of cigarette smoking

Meds: Aspirin 81 mg once daily, enalapril 20 mg once daily, hydrochlorothiazide 25 mg once daily, metoprolol 25 mg twice daily, levothyroxine 150 mcg every morning, sertraline 100 mg once daily, omeprazole 20 mg once daily, and recent use of ibuprofen 400 mg every 4 to 6 hours without pain relief

ROS: (+) for RUQ abdominal pain that radiates to his back, decreased appetite, 10-lb (4.5-kg) weight loss and diarrhea for the past month. (–) for chest pain or shortness of breath

PE:

VS: BP 148/86 mm Hg, HR 75 beats/min, RR 15 breaths/min, T 37.1°C (98.8°F), Wt 77.3 kg (170 lb), Ht 5′10″ (178 cm)

Pain Assessment: Ranges from 6–8 out of 10 (numerical rating scale); currently 8/10 pain. Describes as dull aching pain and tingling, needle-like pain

CV: Regular rate and rhythm, no murmurs

Abd: Distended, (+) rebound tenderness, (+) bowel sounds

Labs:

Amylase 50 IU/L (0.83 µkat/L)	BUN 19 mg/dL (6.8 mmol/L)
Lipase 100 IU/L (1.7 µkat/L)	SCr 0.75 mg/dL (66 µmol/L)
AST 32 IU/L (0.53 µkat/L)	Glucose 248 mg/dL (13.8 mmol/L)
ALT 29 IU/L (0.48 µkat/L)	Triglycerides 180 mg/dL (2.03 mmol/L)

CT Scan Abdomen: Diffuse pancreatic scarring and calcifications

What signs and symptoms are consistent with chronic pancreatitis?

Why are the serum amylase and lipase normal?

What lifestyle modifications would you recommend for this patient?

What, if any, treatment regimens would you initiate, and how would you monitor their effects?

Patient Care Process for Chronic Pancreatitis

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review the medical history and physical assessment findings to identify signs/symptoms of abdominal pain, steatorrhea, decreased appetite secondary to abdominal pain, and/or signs of glucose intolerance.
- Speak with the patient and review lifestyle and dietary habits, specifically any significant alcohol or smoking history.
- Ask the patient to rate the pain, if any, and relate factors that exacerbate and relieve the pain.

Assess Information:

- Determine whether the patient is receiving any medication(s) that may cause or exacerbate pancreatitis.
- Using validated pain scales, determine whether the pain is currently controlled.
- Review relevant laboratory tests (eg, amylase, lipase, basic metabolic panel, liver panel, complete blood count, lipid panel, fasting glucose, fat-soluble vitamin levels) and imaging (eg, ultrasound, CT, MRI, MRCP).
- If the patient is already receiving pharmacotherapy, assess efficacy, safety, and patient adherence.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- If the patient has signs of malnutrition or nutritional deficiencies, determine if PES or supplemental vitamins are indicated.
- If the patient has elevated fasting blood glucose or A1C, consider starting insulin therapy (see Chapter 43, Diabetes Mellitus).
- Develop an analgesic plan to control and prevent pain (see Chapter 34, Pain Management).

Implement the Care Plan:

- Provide resources for alcohol and smoking abstinence, if applicable.
- Address any patient concerns about pancreatitis and its management.
- Initiate PES in patients with steatorrhea.
- Discuss importance of diet, medication adherence, and lifestyle modifications to reduce complications of AP and/or CP.

Follow-up: Monitor and Evaluate:

- Adjust PES dosage based on nutritional status and pain with meals on a monthly basis until adequate control is achieved. Once stable doses of PES and analgesia are established, monitor the patient once or twice yearly.
- Evaluate the patient's Vitamin A, D, E, K, and B_{12} levels, fasting blood glucose, and A1C at least annually.
- Reassess analgesia and adjust medication and dosages as indicated.

environment and therefore must be administered with a proton pump inhibitor.[18,19]

PES should be taken immediately prior to or portioned throughout meals and snacks to aid in the absorption and digestion of food. KEY CONCEPT Dosing is initiated on body weight and adjusted based on clinical symptoms and stool fat content. The usual starting dose is 500 units/kg/meal of lipase with half of the mealtime dose administered with snacks. Doses of lipase more than 10,000 units/kg/day should be used with caution because they may be associated with colonic stricture and fibrosis.[18,19] LO 4

► *Endocrine*

Patients with CP can develop glucose intolerance, but it usually does not progress to overt diabetes mellitus until late in the disease. Fasting blood glucose should be monitored annually, and ensuing diabetes should be treated with insulin. Patients with CP are at increased risk of hypoglycemia due to dysfunction of the pancreatic alpha cells, which are responsible for glucagon secretion.[3,13,24] LO 2 LO 3

► *Other Therapies*

In patients with autoimmune pancreatitis, prednisolone 30 to 40 mg/day tapered over a 3-month period may provide rapid relief of symptoms.[25] Antioxidants such as methionine, ascorbic acid, and selenium may reduce the number of painful days per month in patients with CP.[3,26,27] LO 3

OUTCOME EVALUATION

- Monitor pain control and adjust analgesics accordingly.
- Encourage lifestyle modifications such as abstinence from ethanol and cigarettes.
- Counsel patients to monitor for weight gain or loss and fatty stool output as markers of malabsorption.
- Educate patients that adherence with PES is key to improved outcomes.

Abbreviations Introduced in This Chapter

ANA	Antinuclear antibody
AP	Acute pancreatitis
APACHE II	Acute Physiology and Chronic Health Evaluation II
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CP	Chronic pancreatitis
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
GI	Gastrointestinal
LDH	Lactate dehydrogenase

MAP	Mean arterial pressure
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
PES	Pancreatic enzyme supplements
RUQ	Right upper quadrant
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
WBC	White blood cell

REFERENCES

1. Hegyi P, Pandol S, Venglovecz V, Rakonczay Z Jr. The acinar-ductal tango in the pathogenesis of acute pancreatitis. Gut. 2011;60:544–552.
2. Forsmark CE, Vege SS, Wilcox CM. Acute pancreatitis. N Engl J Med. 2016;375:1972–1981.
3. Braganza JM, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. Lancet. 2011;377:1184–1197.
4. Brun A, Agarwal N, Pitchumoni CS. Fluid collections in and around the pancreas in acute pancreatitis. J Clin Gastroenterol. 2011;45:614–625.
5. Whitehead DA, Gardner TB. Evidence-based management of necrotizing pancreatitis. Curr Treat Options Gastroenterol. 2014;12(3):322–332.
6. Srinivasan G, Venkatakrishnan L, Sambandam S, et al. Current concepts in the management of acute pancreatitis. J Family Med Prim Care. 2016;5:752–758.
7. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology Guideline: Management of Acute Pancreatitis. Am J Gastroenterol. 2013;108:1400–1415.
8. Frank B, Gottlieb K. Amylase normal, lipase elevated: is it pancreatitis? A case series and review of the literature. Am J Gastroenterol. 1999;94(2):463–469.
9. Singh VK, Gardner TB, Papachristou GI, et al. An international multicenter study of early intravenous fluid administration and outcome in acute pancreatitis. United European Gastroenterol J. 2017;5:491–498.
10. Stigliano S, Sternby H, de Madaria E, Capurso G, Petrov MS. Early management of acute pancreatitis: a review of the best evidence. Dig Liver Dis. 2017;49:585–594.
11. Moggia E, Koti R, Belgaumkar AP, et al. Pharmacological interventions for acute pancreatitis. Cochrane Database Syst Rev. 2017 Apr 21;4:CD011384. doi: 10.1002/14651858.CD011384.pub2.
12. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterol. 2013;144:1252–1261.
13. Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis and therapy. Gastroenterology. 2007;132:1557–1573.
14. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. Nat Rev Gastroenterol Hepatol. 2010;7:131–145.
15. Majumder S, Chari ST. Chronic pancreatitis. Lancet. 2016;387:1957–1966.
16. Duggan SN, Smyth ND, O'Sullivan M, et al. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. Nutr Clin Pract. 2014;29(3):348–354.
17. Sikkens EC, Cahen DL, Koch AD, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. Pancreatology. 2013;13(3):238–242.
18. Berry AJ. Pancreatic enzyme replacement therapy during pancreatic insufficiency. Nutr Clin Pract. 2014;29(3):312–321.
19. Domínquez-Muňoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. J Gastroenterol Hepatol. 2011;26(suppl2): 12–16.
20. Puylaert M, Kapural L, Van Zundert J, et al. Pain in chronic pancreatitis. Pain Pract 2011;11(5):492–505.
21. Olesen SS, Bouwense SA, Wilder-Smith OH, Van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Gastroenterology. 2011;141:536–543.
22. Drewes AM, Bouwense SAW, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. Pancreatology. 2017;17(5):720–731.
23. Giuliano CA, Dehoorne-Smith ML, Kale-Pradhan PB. Pancreatic enzyme products: digesting the changes. Ann Pharmacother. 2011;45:658–666.
24. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. World J Gastroenterol. 2013;19(42):7276–7281.
25. Hirano K, Tada M, Isayama H, et al. Long-term prognosis of autoimmune pancreatitis with and without corticosteroid treatment. Gut. 2007;56(12):1719–1724.
26. Bhardwaj P, Garg PK, Maulik SK, et al. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. Gastroenterology. 2009;136:149–159.
27. Zhou D, Wang W, Cheng X, Wei J, Zheng S. Antioxidant therapy for patients with chronic pancreatitis: a systematic review and meta-analysis. Clin Nutr. 2015;34:627–634.

24 Viral Hepatitis

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LEARNING OBJECTIVES

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

1. Differentiate the five types of viral hepatitis by epidemiology, etiology, pathophysiology, clinical presentation, and natural history.
2. Identify modes of transmission and risk factors among the major types of viral hepatitis.
3. Evaluate hepatic serologies to understand how the type of hepatitis is diagnosed.
4. Create treatment goals for a patient infected with viral hepatitis.
5. Recommend appropriate pharmacotherapy for prevention of viral hepatitis.
6. Develop a care plan for treatment of chronic viral hepatitis.
7. Formulate a monitoring plan to assess adverse effects of pharmacotherapy for viral hepatitis.

INTRODUCTION

The most common types of viral hepatitis include hepatitis A (HAV), B (HBV), C (HCV), D (HDV), and E (HEV). Acute hepatitis may be associated with all five types of hepatitis and rarely exceeds 6 months in duration. Chronic hepatitis (disease lasting longer than 6 months) is usually associated with hepatitis B, C, and D. KEY CONCEPT Chronic viral hepatitis may lead to the development of **cirrhosis** and may result in **end-stage liver disease** (ESLD) and **hepatocellular carcinoma** (HCC). Complications of ESLD include **ascites**, edema, **hepatic encephalopathy**, infections (eg, spontaneous bacterial peritonitis), hepatorenal syndrome, and **esophageal varices**. *Therefore, prevention and treatment of viral hepatitis may prevent ESLD and HCC.*

Viral hepatitis may occur at any age and is one of the most common causes of liver disease in the world. The true prevalence and incidence may be underreported because most patients are asymptomatic. The epidemiology, etiology, and pathogenesis vary depending on the type of hepatitis and are considered separately below.

EPIDEMIOLOGY AND ETIOLOGY

Hepatitis A (HAV)

LO 1 HAV affects 1.4 million people yearly worldwide.[1] The prevalence is highest in economically challenged and underdeveloped countries, including Central and South America, Africa, the Middle East, Asia, and the Western Pacific.[2] The numbers of acute HAV infections and hospitalizations have decreased since the introduction of the HAV vaccine in 1995.[3] However, outbreaks may still occur, as observed in 292 confirmed HAV cases in Hawaii in 2016 that was linked to scallops.[4]

LO 2 HAV is primarily detected in contaminated feces and infects people via the fecal–oral route.[1,2] Outbreaks occur in areas of poor sanitation.[2] About 45% of the cases reported have no identifiable risk factors; individuals at greatest risk of acquiring HAV are listed in Table 24–1.[2]

There are no documented cases of chronic hepatitis A.[2] Death from HAV is rare and mostly associated with fulminant hepatitis; approximately 100 people in the United States die each year from HAV-related causes.[2]

Hepatitis B (HBV)

LO 1 Approximately 2 billion people worldwide have evidence of past or present HBV infection, and more than 240 million people have chronic hepatitis B (CHB).[5] Globally, more than 680,000 deaths are associated with HBV annually.[5] Despite having an effective vaccine against HBV since 1982, it is estimated that there were 21,900 new HBV infections in 2015 in the United States.[3] Fewer than 1% of individuals in North America and Western Europe are chronically infected, compared with greater than 5% in developing areas in parts of Africa, South America, East Asia, and Pacific Islands.[5]

LO 2 The primary modes of transmission of HBV are by blood and body fluids through perinatal, sexual, or percutaneous exposure (Table 24–1).[5,6] Infants born to mothers who are infected with actively replicating HBV have a 90% risk of becoming infected.[6]

Hepatitis C (HCV)

LO 1 Up to 3.9 million Americans and 80 million people worldwide have chronic HCV.[5,7] The prevalence is highest in injection drug users, who account for 60% of newly diagnosed acute HCV infections.[8] HCV is categorized by genotypes, which are geographically specific. There are seven genotypes (numbered 1–7) and 67 subtypes (eg, genotypes 1a, 1b, 2a, 3b), with the newest genotype recently identified, genotype 7.[9] Genotype 1 is the most common in the United States, whereas genotype 4 is most common in the Middle East and North Africa.[10] Approximately 75% of patients with HCV in the United States have genotype 1, and about 15% and 9% have genotypes 2 and 3, respectively.[11] Genotype does not indicate disease severity but is used to determine the duration of therapy and the likelihood of therapeutic response.[12]

Table 24–1

Risk Factors for Acquiring Viral Hepatitis

Hepatitis A
International travelers to endemic areas (eg, Africa, Asia, and parts of South America)
Sexual contact with infected persons (eg, men having sex with other men)
Day care centers or household contacts with people infected with HAV
IV drug users using unsterilized needles
Workers involved with nonhuman primates
Patients with clotting factor disorders

Hepatitis B and D
Infants born to infected mothers
International travelers to endemic areas
Men having sex with other men
Individuals with multiple heterosexual partners
IV drug users using unsterilized needles
Recipients of blood products
Household contacts with acute hepatitis B
Health care providers and public safety workers in contact with infected blood
Residents and staff of facilities for developmentally disabled persons
Patients undergoing dialysis

Hepatitis C
Current or former injection drug users
Recipients of blood products (clotting factor concentrates made before 1987, blood transfusions or solid organ transplants before July 1992)
Health care providers in contact with infected needles
Chronic hemodialysis
Individuals having multiple sexual partners
HIV infection
Perinatal transmission (< 5%)
Unprofessional body piercing and tattooing
Person born from 1945 through 1965

Hepatitis E
International travelers to endemic areas (eg, parts of Asia, Africa, and Mexico)
Ingestion of foods and drinks contaminated with bodily waste

LO2 Contaminated needles and syringes with or without paraphernalia (eg, containers, filters) used by intravenous drug users (IVDU) are the primary source of HCV transmission.[8] As many as 70% to 90% of IVDUs have HCV infection.[12] The risk of HCV transmission via blood transfusion is very low (0.001% per unit transfused).[13] Approximately 10% of individuals with HCV have no identifiable risk factors[13] (Table 24–1).

Hepatitis D (HDV)

LO1 Hepatitis D affects up to 20 million people worldwide.[14] Areas with the highest prevalence include the Middle East, parts of Africa and Central Asia, and parts of South America.[15]

LO2 HDV infection is unique because it can only occur in people who are also infected with the HBV.[14,15] The most likely modes of transmitting HDV are similar to those of HBV (Table 24–1).[15]

Hepatitis E (HEV)

LO1 An estimated 20 million individuals worldwide are infected annually with HEV, and the disease was associated with about 44,000 deaths in 2015.[16] The highest prevalence is found in East and South Asia.[16] HEV infection primarily occurs in underdeveloped countries with poor sanitation. The HEV is transmitted mainly by the fecal–oral route (eg, contaminated drinking water).[16]

LO2

PATHOPHYSIOLOGY

Hepatitis A

Hepatitis A is a nonenveloped single-stranded RNA virus classified as the *Hepatovirus* genus under the Picornaviridae family.[2] The primary host for the HAV is humans, with hepatic cells as the main site for viral replication. As part of the viral degradation process, the HAV is released into the biliary system causing elevated HAV concentrations in the feces. Hepatitis A infections are usually self-limiting and do not lead to chronic disease; rarely it may result in fulminant hepatitis.[1,2]

LO1

Hepatitis B

The HBV belongs to the Hepadnaviridae family.[6] It is a partially double-stranded DNA virus with a phospholipid layer containing hepatitis B surface antigen (HBsAg) that surrounds the nucleocapsid. The nucleocapsid contains the core protein that produces hepatitis B core antigen (HBcAg), which is undetectable in the serum. Hepatocellular injury from HBV is thought to be due to a cytotoxic immune reaction that occurs when HBcAg is expressed on the surface of hepatic cells. Fortunately, antibodies against hepatitis B core antigen (anti-HBc) are measurable in the blood, where anti-HBc to immunoglobulin M (IgM) indicates active infection, and anti-HBc to IgG indicates either chronic infection or possible immunity against HBV.

LO1

Viral replication usually occurs when the hepatitis B envelope antigen (HBeAg) is present and circulating in the blood. The serum HBV DNA concentration is a measure of viral infectivity and quantifies viral replication. Once the HBV infection resolves, antibodies against the hepatitis B envelope (anti-HBe) and antibodies against hepatitis B surface antigen (anti-HBs) develop, and HBV DNA levels become undetectable. However, if these antibodies do not develop, the likelihood of developing CHB increases. This depends primarily on the host's immune system at the time of infection. In immunocompetent individuals, the disease resolves spontaneously and does not lead to further complications. In immunocompromised persons, the HBV is less likely to be eradicated, thus causing persistent infection leading to hepatic cell damage and inflammation.[5,6]

Approximately 90% of adults infected with the HBV develop anti-HBs, which results in lifelong immunity. Unfortunately, about 90% of infants born to mothers with active HBV infection will go on to develop CHB.[5] About 50% of adults with acute HBV infections are asymptomatic, and those with symptoms may experience jaundice or fatigue.[6]

Hepatitis C

Hepatitis C, first known as non-A, non-B hepatitis, is a bloodborne infection caused by a single-stranded RNA virus belonging to the Flaviviridae family and the *Hepacivirus* genus.[17]

Antibodies against HCV (anti-HCV) in the blood indicate infection. If the infection persists for more than 6 months and viral replication is confirmed by HCV RNA levels, the person has chronic hepatitis C, which occurs in 55% to 85% of cases.[5,7]

About 15% of patients have acute hepatitis C that resolves without further complications.[7] Chronic disease may be due to an ineffective host immune system, with cytotoxic T lymphocytes unable to eradicate the HCV, thereby allowing persistent damage to hepatic cells. The most common risk factors for developing

LO1

Patient Encounter Part 1

A 53-year-old white woman presents to the doctor's office for a yearly check-up. Her complaints include fatigue and itching for past few years. Over the past week she had eaten store-bought fish that gave her an upset stomach.

PMH: Diet-controlled hypertension, osteoporosis, arthritis, hemodialysis on Tuesday, Thursday, and Saturday

PSH: None

FH: Father with HTN; mother with NASH; married with a 24-year-old daughter

SH: Never smoked tobacco. One time use of IV cocaine at age 16. Drinks alcohol socially (drank heavily in her 20s when she was in college). Professor in business administration at a local university

Meds: Multivitamin daily, acetaminophen as needed, calcium and vitamin D

ROS: Complains of fatigue and itching; no nausea, vomiting, diarrhea, abdominal pain, or anorexia; never experienced an episode of jaundice, pale stools, or tea-colored urine

PE:

VS: BP 130/85 mm Hg, P 82 beats/min, RR 20/minute, T 37.0°C (98.6°F), Wt 76 kg (167 lb), Ht 5'10" (178 cm)

Abd: Soft, nontender, normal liver span; no hepatosplenomegaly, no ascites

The remainder of the examination was within normal limits.

Labs:

Sodium 141 mEq/L (mmol/L)
Potassium 5.1 mEq/L (mmol/L)
Chloride 99 mEq/L (mmol/L)
CO_2 21 mEq/L (mmol/L)
BUN 20 mg/dL (7.1 mmol/L)
SCr 4.1 mg/dL (362 µmol/L)
Glucose 122 mg/dL (6.8 mmol/L)
Hgb 10.1 g/dL (101g/L; 6.26 mmol/L)
Hct 30.1% (0.301)
Plt 119 × 10^3/mm^3 (119 × 10^9/L)
WBC 5.1 × 10^3/mm^3 (5.1 × 10^9/L)

AST 40 IU/L (0.67 µkat/L)
ALT 42 IU/L (0.70 µkat/L)
T. bilirubin 1.0 mg/dL (17.1 µmol/L)
Alk phos 164 IU/L (2.73 µkat/L)
Albumin 3.1 g/dL (31 g/L)
Anti-HAV IgM (–)
Anti-HAV IgG (–)
Anti-HCV (+), genotype 1b
HCV RNA 3,188,750 IU/mL (kIU/L)
TSH 1.3 µIU/mL (mIU/L)

FibroScan: Moderate fibrosis, F3

What information is suggestive of viral hepatitis?

What risk factors does she have for viral hepatitis?

What additional information do you need before creating a treatment plan for this patient?

hepatic fibrosis include obesity, diabetes, heavy alcohol use, male sex, and coinfections with HIV or HBV.[8]

From 55% to 85% of chronic cases progress to mild, moderate, or severe hepatitis. Cirrhosis and its complications may take several decades to develop in 15% to 30% of patients infected with HCV. Once cirrhosis is confirmed, the risk of developing HCC is 2% to 4% per year.[5]

Hepatitis D

LO 1

The HDV belongs to the genus *Delta virus* of the Deltaviridae family. The HDV is a defective single-stranded circular RNA virus that requires the presence of HBV for HDV viral replication, causing either coinfection (both hepatitis B and D infection occurring simultaneously) or superinfection (acquiring HDV after having long-standing HBV disease).[14] This occurs because the HDV antigen (HDVAg) is coated by the HBsAg.[14]

Hepatitis E

LO 1

Hepatitis E is a nonenveloped single-stranded messenger RNA virus of the Hepeviridae family, with at least 4 different genotypes; genotypes 1 and 2 are found in humans, and genotypes 3 and 4 occur in animals.[16,18] The HEV is similar to HAV in that the virus is found in contaminated feces, thus infecting people via the fecal–oral route. HEV infections are usually self-limiting and rarely result in hepatic complications. Chronic infections occur rarely but may lead to cirrhosis; they are more common in immunocompromised individuals (eg, HIV infection) and organ transplant recipients.[18]

CLINICAL PRESENTATION AND DIAGNOSIS

See box for the clinical presentation of viral hepatitis.

Diagnosis of Viral Hepatitis

Diagnosing viral hepatitis may be difficult because most infected individuals are asymptomatic.[2,5,15,18] Because symptoms alone cannot identify the specific type of hepatitis, laboratory serologies

Clinical Presentation of Viral Hepatitis

Symptoms

- Most patients infected with any type of viral hepatitis have no symptoms.
- Symptomatic patients may experience a flu-like syndrome, fevers, fatigue/malaise, anorexia, nausea, vomiting, diarrhea, dark urine, pale-appearing stools, pruritus, and abdominal pain.

Signs

Jaundice may be evident in the whites of the eyes (scleral icterus) or skin.

- An enlarged liver (hepatomegaly) and spleen (splenomegaly) may be present.
- In fulminant hepatitis with hepatic encephalopathy, patients may have asterixis and coma.
- In rare instances, extrahepatic symptoms may develop (arthritis, postcervical lymphadenopathy, palmar erythema, cryoglobulinemia, and vasculitis).

Laboratory Tests

- See Table 24–2.

LO 3

Table 24–2

Interpretation of Viral Hepatitis Serology Panels

Type	Laboratory Test	Result	Interpretation of Panel
Hepatitis A	IgM anti-HAV IgG anti-HAV	Negative Negative	Susceptible to infection
	IgM anti-HAV IgG anti-HAV	Positive Positive	Acutely infected Immune due to either natural infection or HAV vaccine
Hepatitis B[a]	HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible to infection
	HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection
	HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination
	HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
	HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
	HBsAg anti-HBc Anti-HBs	Negative Positive Negative	Four interpretations possible: (a) Resolved infection (most common); (b) false-positive anti-HBc, thus susceptible; (c) low-level chronic infection; (d) resolving acute infection
Hepatitis C	anti-HCV	Negative	Susceptible to infection
	anti-HCV	Positive	Acutely or chronically infected
Hepatitis D[b]	IgM anti-HDV HDVAg HBsAg HBeAg anti-HBc	Positive Positive Positive Positive Positive	Acute HBV-HDV coinfection
Hepatitis E	IgM anti-HEV IgG anti-HEV	Negative Negative	Susceptible to infection
	IgM anti-HEV	Positive	Acutely infected
	IgG anti-HEV	Positive	Immune due to natural infection

[a]Centers for Disease Control and Prevention. Hepatology [Internet]. http://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf.

[b]Hepatitis D should be suspected in those who have HBsAg positivity. Hepatitis D may present as either coinfection where both HDV and HBV serologies appear simultaneously, whereas for superinfection, HBV has been present for some time and later HDV develops.

anti-HAV, hepatitis A antibody; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; anti-HCV, hepatitis C antibody; anti-HDV, hepatitis D antibody; anti-HEV, hepatitis E antibody; HAV, hepatitis A virus; HBV, hepatitis B virus; HDV, hepatitis D virus; HDVAg, hepatitis D antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

must be obtained (Table 24–2). A liver biopsy may be obtained to determine the severity of the liver disease, but this is an invasive test that may be associated with complications such as severe pain, bleeding, and death.[19] Therefore, several patented blood tests (FibroTest®, HepaScore®) have been developed that use a panel of serum biomarkers (eg, ALT, AST, platelet count) along with the age and sex of the patient to determine the degree of hepatic fibrosis. A noninvasive imaging test that uses ultrasound vibration-controlled transient elastography (VCTE) is now recommended to assess the severity of liver disease.[19] These invasive and noninvasive tests are imperfect and are usually only able to identify mild and severe disease. Therefore, it is important to monitor laboratory values over time to assess the severity of liver fibrosis (eg, AST, ALT, serum albumin, platelet counts, prothrombin time/INR).

► *Hepatitis A*

LO 3

Hepatitis A is diagnosed by detecting immunoglobulin antibodies to the capsid proteins of the HAV. Detectability of IgM anti-HAV in the serum indicates acute infection. IgM appears approximately 3 weeks after exposure and becomes undetectable within 6 months. In contrast, IgG anti-HAV appears in the serum at approximately the same time that IgM anti-HAV develops but indicates protection and lifelong immunity against hepatitis A.[2]

► *Hepatitis B*

LO 3

Hepatitis B is diagnosed when HBsAg is detectable in the serum, but it does not distinguish between acute and chronic HBV. The presence of IgM antibodies to HBcAg indicates active infection.

IgG anti-HBc indicates either chronic infection or possible immunity against HBV.[6]

In most cases, detectable HBeAg indicates active viral replication. Measurement of HBV DNA determines viral infectivity and quantifies viral replication. Once HBV viral replication ceases, anti-HBe is detectable in the serum. However, a minority of patients may develop anti-HBe and still have elevated HBV DNA levels because of a mutation in the HBV.[20] Therefore, CHB infections may be differentiated as either HBeAg-positive or HBeAg-negative.[20,21] Hepatitis B serologies are evaluated to assess HBV treatment response and determine whether to vaccinate.

▶ *Hepatitis C*

LO 3

Hepatitis C is diagnosed by testing for anti-HCV in the serum and confirmed by the presence of HCV RNA. HCV RNA levels quantify viral replication and are used to determine if antiviral treatment for HCV is effective. Undetectable HCV RNA levels indicate past infection or that the infection is resolved. An HCV genotype should be obtained to determine the likelihood of response to anti-HCV therapy and the duration of treatment required.[8]

▶ *Hepatitis D*

LO 3

Hepatitis D infection requires the presence of HBV for HDV viral replication. Measuring HDV RNA levels confirms hepatitis D infection and is the most accurate diagnostic test. The presence of IgM anti-HD indicates active disease, and IgG anti-HD also becomes detectable if the infection does not resolve spontaneously. HDV antibodies do not confer immunity.[15]

▶ *Hepatitis E*

LO 3

Diagnosis of acute hepatitis E is based on the presence of IgM anti-HEV. IgG anti-HEV emerges when the HEV infection resolves.[16] HEV RNA levels can be obtained from either blood or stool and are usually tested if chronic HEV infection is suspected.[16]

PREVENTION AND TREATMENT OF VIRAL HEPATITIS

Desired Outcomes

LO 4

Treatment outcomes for viral hepatitis are to (a) prevent the spread of infection, (b) prevent and treat symptoms, (c) suppress viral replication, (d) normalize hepatic aminotransferases, (e) improve liver histology, and (f) decrease morbidity and mortality by preventing cirrhosis, HCC, and ESLD.

For hepatitis B, additional treatment goals include seroconversion or loss of HBsAg, and seroconversion or loss of HBeAg.[20] The primary goal of treating chronic HCV is to achieve undetectable HCV RNA for at least 12 weeks after completing hepatitis C therapy, known as achieving a sustained virologic response (SVR).[8]

General Approach

LO 5

Managing viral hepatitis involves both prevention and treatment. Prevention of hepatitis A and B (and indirectly for hepatitis D) can be achieved with immune globulin (IG) or vaccines. KEY CONCEPT Acute viral hepatitis is primarily managed with supportive care. Mild to moderate symptoms rarely require hospitalization, but hospital admission is recommended in individuals experiencing significant nausea, vomiting, diarrhea, and encephalopathy. Liver transplantation may be required rarely if fulminant hepatitis develops. Treatment is available for chronic HBV, HCV, and HDV.

Hepatitis A Prevention

LO 5

KEY CONCEPT Good personal hygiene and proper disposal of sanitary waste are required to prevent HAV fecal–oral transmission.[1,2] This includes frequent hand washing with soap and water after using the bathroom and prior to eating meals. Drinking bottled water and avoiding fruits, vegetables, and raw shellfish harvested from sewage-contaminated water may minimize the risk of becoming infected with the HAV. Individuals at risk of acquiring HAV (Table 24–1) should receive serum IG and/or the hepatitis A vaccine.[2, 22]

▶ *Immune Globulin*

IG is a solution containing antibodies from sterilized pooled human plasma that provides passive immunization against HAV.[2] IG is available as an IV (IGIV) or intramuscular (IGIM) formulation, but only IGIM is used for prevention of HAV. IGIM does not confer lifelong immunity but is effective in providing pre- and postexposure prophylaxis against HAV.[2]

IGIM should be injected into a deltoid or gluteal muscle. It does not affect the immune response of inactivated or live-virus vaccines; however, administrating live vaccines concomitantly with IGIM may decrease the immune response significantly.[2]

Preexposure Prophylaxis IGIM administration is indicated for individuals at high risk of acquiring the HAV who (a) are younger than 12 months, (b) elect not to receive the hepatitis A vaccine, or (c) cannot receive the hepatitis A vaccine (eg, because of allergic reaction). Because active immunity takes several weeks to develop, travelers who are older than 40 years, immunocompromised, or have chronic liver disease or other chronic medical conditions who plan to depart for endemic areas within 2 weeks *and* have not received the hepatitis A vaccine should receive IGIM. If the duration of travel is 1 month or less, the dose of IGIM should be 0.1 mL/kg. However, if travel will be 2 months or longer, then a dose of 0.2 mL/kg should be administered and repeated every 2 months during the stay.[2,24]

Postexposure Prophylaxis Individuals in contact with people infected with acute HAV (Table 24–1) may be candidates for postexposure prophylaxis. IGIM is recommended for individuals younger than 12 months or older than 40 years of age, immunocompromised, diagnosed with chronic liver disease, or have contraindications to the hepatitis A vaccine.[2,22]

The risk of infection may be decreased by 90% if IGIM 0.02 mL/kg is given within 2 weeks of exposure to the HAV. IGIM may still be beneficial if given more than 2 weeks after exposure to a known case of HAV.[22]

▶ *Hepatitis A Vaccine*

Persons at risk of acquiring HAV should receive the hepatitis A vaccine to provide pre- and postexposure prophylaxis. Two inactivated hepatitis A vaccines are available in the United States: HAVRIX and VAQTA. The recommended regimen is to administer two injections 6 months apart (at months 0 and 6).[2,22] These vaccines are considered interchangeable, and doses depend on age (Table 24–3).[2]

Efficacy is defined by measuring antibody response. Protective levels are greater than 20 mIU/mL (IU/L) for HAVRIX and greater than 10 mIU/mL (IU/L) for VAQTA.[23] Within 4 weeks

Table 24–3

Recommended Intramuscular Doses of Hepatitis A Vaccines

Product	Recipient Age (years)	Dose (Units)	Volume (mL)	No. of Doses	Schedule (months)
VAQTA	1–18	25	0.5	2	0, 6–18
	19 or more	50	1	2	0, 6–18
HAVRIX	1–18	720 ELISA	0.5	2	0, 6–12
	19 or more	1440 ELISA	1	2	0, 6–12

ELISA, enzyme-linked immunosorbent assay.

From: Centers for Disease Control and Prevention. Hepatitis A FAQs for Health Professionals [Internet]. http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#vaccine.

of administering the first vaccine dose, more than 95% of adults and 97% of children and adolescents develop protective antibody concentrations. All recipients receiving the second dose in clinical trials had 100% antibody coverage; therefore, postvaccination measurement of antibody response is not required.[2]

For preexposure prophylaxis, the hepatitis A vaccine is recommended for travelers to endemic hepatitis A countries. It should be administered to healthy travelers 40 years of age and younger regardless of the scheduled dates for departure. Adults who are older than age 40 or are immunocompromised should receive both the hepatitis A vaccine and IGIM (0.02 mL/kg) if travel will occur in less than 2 weeks.[22]

For postexposure prophylaxis, the hepatitis A vaccine is effective in preventing clinical infection in healthy individuals between 12 months and 40 years of age when administered within 14 days after exposure.[22] Individuals outside these age ranges or with significant comorbid conditions should receive IGIM rather than the hepatitis A vaccine because this population has not been studied.[22]

The hepatitis A vaccine may provide immunity for about 25 years in adults and 14 to 20 years in children.[24] The most common and often self-limiting adverse effects in adults include injection site reactions (eg, tenderness, pain, and warmth), headaches, fatigue and flu-like symptoms. Infants and children may have feeding disturbances. Local reactions may be minimized by using an age-appropriate needle length and injecting into the deltoid muscle. Hepatitis A vaccine given during pregnancy has not been evaluated; however, the risk of fetal complications should be minimal because both vaccines are made from inactivated HAV.[2,24]

Hepatitis B Prevention

LO 5

KEY CONCEPT The risk of acquiring the HBV may be minimized by avoiding contaminated blood products and high-risk behavior (Table 24–1) and by receiving the hepatitis B vaccine.[6] Screening pregnant women for HBV and providing universal hepatitis B vaccinations to all newborns is effective in preventing hepatitis B infections.[25,26] In some cases, postexposure prophylaxis with hepatitis B immune globulin (HBIG) may be recommended to prevent the development of acute infection and complications associated with HBV.

▶ *Hepatitis B Immune Globulin (HBIG)*

HBIG is a sterile solution containing antibodies prepared from pooled human plasma that has a high concentration of anti-HBs. A single dose intramuscular of HBIG 0.06 mL/kg provides passive immunization to prevent CHB infections.[25]

The most common side effects of HBIG include erythema at the injection site, headaches, myalgia, fatigue, urticaria, nausea, and vomiting. Serious adverse effects are rare and may include abnormal liver function tests, arthralgias, and anaphylactic reactions. HBIG should be used with caution in individuals who have experienced hypersensitivity reactions to IG or have immunoglobulin A deficiency. Concomitant administration of HBIG and live vaccines should be avoided because the efficacy of the immunization may decrease significantly.

▶ *Hepatitis B Vaccine*

Two single-antigen hepatitis B vaccines are available in the United States: Recombivax HB and Engerix-B. KEY CONCEPT Persons at high risk of acquiring the HBV (Table 24–1) should be vaccinated at months 0, 1, and 6. The vaccine dose depends on the person's age. A third HBV vaccine, Heplisav-B, has a unique adjuvant that stimulates direct immune response to the HBsAg. This product requires only two doses versus three doses for Recombivax HB and Engerix-B (Table 24–4).

The hepatitis B vaccine is also indicated for postexposure prophylaxis to prevent CHB. Individuals exposed to HBV should receive the hepatitis B vaccine with or without HBIG, preferably within 24 hours of exposure based on the source of exposure and the vaccination status of the exposed person (Table 24–5).[6] Postexposure prophylaxis for perinatal exposure depends on several factors, including maternal HBsAg status and the newborn's weight (Table 24–6).[6]

For optimal response, the hepatitis B vaccine should be administered intramuscularly (the anterolateral thigh in neonates and infants and the deltoid region in older children and adults) and not IV or intradermally. Intragluteal IM injections should be avoided because they may result in lower rates of immunity.[25]

The hepatitis B vaccine is effective when antibody concentrations are greater than 10 mIU/mL (IU/L), but postvaccination antibody testing is not routinely recommended because most people completing the vaccination series obtain adequate antibody levels. It may be advisable to determine if immunity has been achieved in infants born to HBsAg-positive mothers and immunocompromised persons.[6]

Effective immunity may last for more than 20 years in healthy individuals. However, patients with poor immune systems may have an anamnestic response that requires titers to be checked periodically with booster doses given.[6]

The most frequent adverse effects are local injection site reactions, flu-like symptoms, dizziness, and irritability.[6] Anaphylaxis, serum sickness-like hypersensitivity syndrome, chronic fatigue syndrome, Guillain-Barré syndrome, and neurologic diseases (leukoencephalitis, optic neuritis, and transverse myelitis) have been reported rarely.[6] Hepatitis B vaccine is not contraindicated during pregnancy and should be safe to the fetus because it is an inactivated vaccine.[6,25]

Table 24–4

Recommended Intramuscular Dosing Regimens for Hepatitis B Vaccines

Product	Patient Categories	Dose (mcg)	Volume (mL)	No. of Doses	Schedule (months)
Recombivax HB	0–19 years of age	5	0.5	3	0, 1, 6
	11–15 years of age[a]	10	1	2	1, 4–6
	≥ 20 years of age	10	1	3	0, 1, 6
	Hemodialysis[b] < 20 years of age	5	0.5	3	0, 1, 6
	Hemodialysis ≥ 20 years of age	40	1	3	0, 1, 6
Engerix-B	0–19 years of age	10	0.5	3	0, 1, 6
	≥ 20 years of age	20	1	3	0, 1, 6
	Hemodialysis[b] < 20 years of age	10	0.5	3	0, 1, 6
	Hemodialysis ≥ 20 years of age	40[c]	2	4	0, 1, 2, 6
Heplisav-B	≥ 18 years of age	20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant	0.5	2	0, 1

[a]Adolescents 11 through 15 years of age may receive either the 5-mcg three-dose pediatric formulation or a 10-mcg two-dose regimen using the adult formulation.

[b]Higher doses might be more immunogenic, but no specific recommendations have been made.

[c]Two 1.0-mL doses administered at one site.

Centers for Disease Control and Prevention. Hepatitis B FAQs for Health Professionals [Internet]. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#vaccFAQ

LOS

Table 24–5

Recommendations for Prophylaxis after Exposure to the Hepatitis B Virus

	Treatment to Administer If Serology Test of Source Person Is:	
Exposed Person's Vaccination Status	HBsAg-Positive	Unknown HBsAg Status
Unvaccinated	HBIG × 1 and initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated[a]	Administer HB vaccine booster dose	No treatment

[a]A person who has written documentation of a complete hepatitis B vaccine series and did not receive postvaccination testing.

HB, hepatitis B; HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin.

LOS

Table 24–6

Recommendations for Hepatitis B Prophylaxis to Prevent Perinatal Transmission

	Mother's HBsAg Status		
Treatment	Positive	Negative	Unknown
HBIG[a]	Given within 12 hours of birth	None	Test HBsAg. If positive, give within 7 days; if negative, give none. For infants weighing < 2000 g, administer within 12 hours of birth
AND			
Hepatitis B vaccine[b]			
Dose 1	Within 12 hours of birth	Within 12 hours of birth[c]	Within 12 hours of birth
Dose 2	At month 1–2	At month 1–2	At month 1–2
Dose 3[d]	At month 6	At month 6–18	At month 6

[a]0.5 mL intramuscularly in a different site from vaccine.

[b]See Table 24–4 for appropriate hepatitis B vaccine dose.

[c]Full-term infants who are medically stable and weigh 2000 g or more born to HBsAg-negative mothers should receive the hepatitis B vaccine within 24 hours of birth. Preterm infants weighing less than 2000 g born to HBsAg-negative mothers should receive the first dose of hepatitis B vaccine 1 month after birth or at hospital discharge.

[d]The final dose in the vaccine series should be administered at least 8 weeks after the second dose and at least 16 weeks after the first dose. The final dose should not be administered before age 24 weeks (164 days).

From Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005; 54(RR-16):1–31. https://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html

▶ *Hepatitis A and B Combination Vaccine*

KEY CONCEPT Twinrix combines both inactivated HAV and HBV and is approved for individuals older than 18 years who are at risk for HAV and HBV infections.[6] A 1-mL dose of Twinrix may be administered at either months 0, 1, and 6 or in an accelerated schedule on days 0, 7, between 21 and 30, and with a fourth dose at month 12.[6] The accelerated schedule is intended for patients who start the vaccination series but are unable to complete the standard three-dose schedule in time to develop adequate immunity before embarking on travel that will put them at risk of exposure to hepatitis A and B.[27] The side-effect profile of Twinrix is similar to giving each vaccine separately.

Chronic Hepatitis B Treatment

The American Association for the Study of Liver Diseases (AASLD) recommends treatment for CHB patients with persistently elevated ALT (more than two times the upper limit of normal) or significant histological disease and elevated HBV DNA levels greater than 20,000 IU/mL (kIU/L) to delay progression to cirrhosis and prevent the development of ESLD.[20] Similar treatment criteria apply to patients infected with HBeAg-negative CHB except that therapy should be initiated when HBV DNA levels exceed 2000 IU/mL (kIU/L).[20]

The primary treatment endpoint is to suppress HBV replication to achieve undetectable serum levels. The ideal treatment should induce a biochemical response (normalize ALT levels), histological response (decrease liver inflammation documented by liver biopsy scores), and serological conversion (loss of HBeAg and HBsAg and detectable antiHBe).[20]

LO 6

KEY CONCEPT The drug of choice for CHB depends on the patient's past medical history, ALT, HBV DNA level, HBeAg status, severity of liver disease, and history of previous HBV therapy. There were eight approved HBV agents: two formulations of interferon (IFN) alfa and six nucleoside/nucleotide analogs. Telbivudine as an oral agent is no longer available in the United States as of December 2016, but it may still be available in other parts of the world.[20,28] All HBV therapies are effective with no agent showing superiority to others in reducing the risk of developing HBV complications.[20]

Entecavir, tenofovir, and pegylated (peg) IFN-α_{2a} are recommended first-line therapies due to profound HBV DNA suppression; the latter agent should be considered in patients with compensated liver disease because of its finite treatment duration and lack of drug resistance.[20]

Adefovir, lamivudine, and telbivudine are not recommended due to high rates of resistance.[20,21] Patients who are responding should continue therapy, but adding or switching to a more potent HBV agent should be considered if there is inadequate virologic response or drug resistance develops.

For all oral HBV agents, patients should be monitored for lactic acidosis and severe hepatomegaly because some cases have been fatal. Hepatic function tests should be monitored if treatment is to be discontinued, because severe acute hepatitis exacerbations have been reported. Dosage adjustments are required in patients with renal dysfunction for all oral HBV regimens. With all oral HBV agents, HIV resistance may develop if given as monotherapy; therefore, test for HIV prior to starting a single anti-HBV agent. Patients coinfected with HIV and HBV should receive concomitant highly active antiretroviral therapy (HAART) with an HBV agent. Each HBV agent is described briefly in the sections that follow.

▶ *Interferon and Pegylated Interferon*

IFN-α_{2b} and pegIFN-α_{2a} are the only IFN therapies approved for HBV. PegIFN is IFN attached to a polyethylene glycol molecule that increases the drug's half-life, thereby allowing once-weekly dosing rather than thrice-weekly administration of unmodified IFN. IFN is effective in suppressing, and in some cases ceasing, viral replication without inducing resistance.[20]

Approximately one-third of HBeAg-positive patients achieve HBeAg seroconversion after 48 weeks of pegIFN therapy.[28] HBeAg-negative hepatitis B may require more than 48 weeks of therapy to attain undetectable HBV DNA levels.[28] Factors associated with a greater chance of HBeAg seroconversion include low baseline HBV DNA concentrations and high pretreatment ALT levels.[30]

PegIFN-α_{2a} (Pegasys) 180 mcg subcutaneously once weekly for 48 weeks is well tolerated and recommended for compensated CHB.[20,29,30] The same dose is recommended for HBeAg-negative CHB; however, the treatment duration may exceed 48 weeks to increase sustained virological response rates.[20,30]

Although pegIFN has lack of resistance and possible HBsAg loss or seroconversion (development of anti-HBs), its disadvantages include the need for subcutaneous injections and a pronounced adverse-effect profile that may require dosage reductions or treatment discontinuation (see Table 24–7). PegIFN is contraindicated with telbivudine due to potential neuropathy.[29]

▶ *Entecavir*

Entecavir (Baraclude) is a guanosine nucleoside analog approved for patients over 2 years of age with either HBeAg-positive

Table 24–7

Adverse Effects of Pegylated Interferon and Ribavirin

Adverse Effect	Therapeutic Intervention
Pegylated interferon	
Flu-like symptoms (eg, fevers, chills, rigors, myalgias)	Premedicate with acetaminophen or nonsteroidal anti-inflammatory drugs. Administer at bedtime.
Psychiatric abnormalities (eg, irritability, depression, and rarely, suicidal, or homicidal ideations)	Seek mental health specialist, antidepressants, anxiolytics. If symptoms are severe, discontinue treatment.
Neutropenia	Obtain a complete blood count with differential and monitor ANC. If less than 1.0×10^9/L, consider reducing dose.
Thrombocytopenia	Obtain a complete blood count and monitor platelet count. Consider reducing dose if platelet count is significantly low.
Elevated ALTs	Obtain LFTs and monitor. Only use pegylated interferon in patients with compensated liver disease.
Ribavirin	
Dermatological (rash, itching, dry skin)	Recommend creams, lotions, oral antihistamines
Hemolytic anemia	Monitor hemoglobin, shortness of breath, chest pain. Reduce dose if hemoglobin less than 10 g/dL (100 g/L; 6.21 mmol/L) or significant symptoms

or HBeAg-negative CHB.[20] Resistance rates are low (1%–2%) in lamivudine-naive patients treated with entecavir for up to 5 years.[29,30] For patients previously treated with lamivudine and switched to entecavir, the resistance rate is approximately 28% at 1 year and up to 51% at 5 years.[31]

The dose of entecavir is 0.5 mg orally once daily for patients 16 years or older with compensated liver disease and naïve to lamivudine therapy. Entecavir 1 mg once daily is recommended for lamivudine or telbivudine resistance or decompensated liver disease. Entecavir should be given on an empty stomach (at least 2 hours before or after a meal). The side-effect profile of entecavir is similar to lamivudine and adefovir dipivoxil.

▶ *Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide*

Tenofovir disoproxil fumarate (TDF; Viread) is an acyclic adenine nucleotide reverse transcriptase inhibitor similar in structure to adefovir dipivoxil that inhibits HIV and HBV replication. It is indicated for HBV patients older than 12 years of age with either HBeAg-positive or HBeAg-negative CHB and/or HIV when prescribed with other HAART therapies.

TDF 300 mg orally once daily (taken on an empty stomach) has high efficacy with almost no development of resistance and is generally well tolerated. However, rare but significant adverse effects include nephrotoxicity and Fanconi syndrome, decreased bone mineral density, and osteomalacia.[20,29,32] TDF is a prodrug that is converted to tenofovir in the plasma and is then phosphorylated to tenofovir diphosphate. High concentrations of the diphosphate compound in cells increase risk of kidney and bone toxicity. Creatinine clearance (CrCl), serum phosphate, liver function tests, and bone mineral density should be monitored prior to initiating treatment and during therapy. The TDF dose must be reduced with CrCl less than 50 mL/min (0.84 mL/s).

Tenofovir alafenamide (TAF; Vemlidy) was subsequently approved for compensated CHB. The recommended TAF dose is 25 mg orally once daily taken with food. TAF offers antiviral activity similar to TDF but with a safer side-effect profile. TAF delivers the prodrug tenofovir directly to hepatic cells intracellularly, resulting in lower concentrations in the kidneys and bone.[32] TAF may be administered at full doses until the CrCl is less than 15 mL/min (0.25 mL/s).

▶ *Adefovir Dipivoxil*

Adefovir dipivoxil (Hepsera) is a prodrug of adefovir, an adenosine nucleotide analog that inhibits DNA polymerase; it is indicated for CHB in patients older than 12 years. Resistance to adefovir is minimal for the first few years of treatment but increases to approximately 30% after 5 years of therapy.[29]

The dose of adefovir is 10 mg orally once daily taken with or without food. The most common side effects include asthenia, abdominal pain, diarrhea, dyspepsia, headaches, nausea, and flatulence. Adefovir is associated with nephrotoxicity at higher doses (30 mg/day). Renal function should be monitored during treatment in all patients, especially those with preexisting or risk factors for renal impairment.

▶ *Lamivudine*

Lamivudine (Epivir-HBV) is an oral synthetic cytosine nucleoside analog with antiviral effects against HIV and HBV. Lamivudine is effective in suppressing HBV replication, normalizing ALT levels, and improving liver histology. Patients may have a similar or a superior response in achieving these endpoints when compared with pegIFN. Prolonged lamivudine therapy (up to 5 years) may be needed to sustain seroconversion, but this leads to lamivudine resistance rates as high as 70% at 5 years.[29] Due to the high rate of resistance, lamivudine is no longer recommended as first-line therapy for CHB.[20,29]

The adult dose of lamivudine is 100 mg orally once daily for CHB without HIV coinfection. Lamivudine 3 mg/kg once daily up to a maximum dose of 100 mg is approved for pediatric patients (2–17 years of age). It may be taken with or without food. Adverse effects are minimal and include fatigue, diarrhea, nausea, vomiting, and headaches. ALT levels should be monitored during therapy because a two- to threefold increase may be observed; levels should also be monitored when therapy is discontinued because increased levels may indicate a disease flare leading to liver failure.

▶ *Telbivudine*

Telbivudine (Tyzeka) is an L-nucleoside analog that inhibits HBV replication. It was commercially available in the United States until December 2016 for patients 16 years or older with HBeAg-positive or HBeAg-negative CHB. Telbivudine offers a slightly more effective reduction in HBV DNA levels and normalization of aminotransferases than lamivudine. Telbivudine resistance is lower than lamivudine, but rates are significant with continued treatment. Also, there is a higher rate of telbivudine treatment failure in patients who have lamivudine resistance.[23] Telbivudine is not highly recommended but may be considered if adefovir or tenofovir resistance is present.

Where commercially available in the world, the dose of telbivudine is 600 mg orally once daily with or without food. Adverse effects are similar to other HBV oral agents. Patients should also be monitored for myopathy characterized by elevated creatine kinase levels and muscle weakness.[20] Peripheral neuropathy has also occurred when used together with pegIFN, so the combination is contraindicated.[20,29] Elevated LFTs occur at rates similar to lamivudine.

Hepatitis C Prevention

Avoiding high-risk behaviors such as sharing needles among IV drug users is the primary means of avoiding infection with the HCV. The risk of acquiring HCV through a blood transfusion is 1 in 2 million since 1992, when widespread screening of blood products and universal precautions took effect. More than 75% of individual infected with the HCV were born during the "baby boomer" generation. Although the reasons for these high infection rates are not completely understood, HCV had not yet been identified and there was no method for detecting it in blood products. The CDC recommends that everyone born between 1945 and 1965 be tested at least once in their lifetime for HCV. There are currently no vaccines to prevent HCV, but several are under development.[33] Therefore, high-risk individuals (Table 24–1) should be tested for HCV because most people are asymptomatic and unaware they are infected.[5]

LO 6 Chronic Hepatitis C Treatment

Treatment for HCV has been revolutionized over the past decade, with efficacy rates above 90% compared to 50% to 80% before 2011. The primary goal of HCV treatment is to achieve an SVR, also known as a "virological cure," defined as undetectable HCV RNA levels at 12 weeks or longer after treatment completion.

Patient Encounter Part 2: Creating a Care Plan

Based on the information presented, create a care plan for this patient's hepatitis. Your plan should include:

(a) a statement of the drug-related needs and/or problems;

(b) the goals of therapy;

(c) a patient-specific detailed therapeutic plan;

(d) a follow-up plan to determine whether the goals have been achieved; and

(e) a follow-up plan to identify potential adverse effects of therapy.

Normalization of liver function tests and improvement of histology are additional treatment outcomes, but the primary goal is to prevent progression and development of cirrhosis, HCC, and ESLD.[8] Patients who achieve SVR do not cure the existing liver disease; those with advanced disease and cirrhosis continue to have liver disease progression; thus, cirrhotic surveillance must be performed (eg, ultrasound to evaluate for HCC). Initiating HCV treatment early before development of advanced liver disease may minimize the risk of developing cirrhosis and the complications associated with ESLD.

KEY CONCEPT Treatment for chronic hepatitis C depends on the patient's past medical history, previous HCV treatment history, severity of liver disease, and HCV genotype.[8]

▶ *Interferon/Pegylated Interferon and Ribavirin*

IFN and pegIFN are no longer recommended for chronic HCV because SVR rates are suboptimal, only 10% to 40% with genotype 1 and 30% with genotype 2 or 3. PegIFN-α_{2a} (Pegasys) and pegIFN-α_{2b} (PEG-Intron) have extended half-lives allowing for once-weekly administration compared to thrice-weekly with unpegylated IFN. The SVR rates with pegIFN can be increased to 50% to 80% by adding ribavirin, a synthetic guanosine analog that inhibits viral polymerase. From 2002 to 2011, pegIFN plus ribavirin was considered standard-of-care for HCV.[8]

As described in the CHB treatment section, pegIFN has frequent and sometimes severe adverse effects (Table 24–7). In addition, up to 35% of patients require either a dosage reduction or drug discontinuation due to hematologic complications (thrombocytopenia, neutropenia, anemia).[34] Ribavirin causes a dose-related hemolytic anemia that may require dosage reductions or discontinuation.[34] Dermatological effects (eg, rash, pruritus, dry skin) occur commonly with ribavirin. Because ribavirin can be teratogenic and embryocidal, all women of childbearing age and men who are able to father a child must use two forms of contraception during HCV therapy containing ribavirin and for 6 months after completion of treatment.

▶ *Direct-Acting Antiviral Agents—First Generation*

Since 2011, a new category of drugs for HCV known as direct-acting antivirals (DAAs) have emerged. The first-generation DAAs approved were the protease inhibitors boceprevir and telaprevir, which resulted in higher SVR rates of 63% to 66% when coadministered with pegIFN and ribavirin.[32] Despite higher SVR rates, first-generation DDAs are no longer commercially available in the United States or recommended due to significant adverse effects (ie, blood dyscrasias, dermatological effects), increased pill burden (11–22 pills daily), complicated dosing regimens, significant and multiple drug interactions, and increased rates of viral resistance.[8]

▶ *Direct-Acting Antiviral Agents—Second Generation*

Drug development for HCV continues to evolve, resulting in higher SVR rates (well above 90%), fewer adverse effects, and shorter treatment durations with less complex regimens compared to pegIFN and ribavirin with or without a first-generation DAA. Selection of a DAA regimen is based on HCV genotype, previous HCV treatment history, severity of liver disease, current medical conditions and medications, and presence or absence of resistance-associated substitutions (RAS). Prior to administering any second-generation DAA regimen, presence of HBV should be excluded because cases of HBV reactivation have occurred, leading to fulminant hepatitis or death. Patents positive for HBV should be treated for it either prior to or concomitantly with HCV therapy. HCV patients who do not have immunity against HBV should receive the HBV vaccine.[8] Selected DAAs require RAS testing before starting HCV therapy (Table 24–8). If RAS are present, the options are to choose a drug from a different DAA class, add ribavirin, and/or treat for longer than 12 weeks. Many of the current regimens require addition of ribavirin (see Table 24–7 for adverse effect monitoring). The approved DAAs for HCV are described below; however, refer to www.hcvguidelines.org for the most up-to-date treatment recommendations.[8]

Simeprevir (Olysio) This agent is an NS3/4A serine protease inhibitor indicated for HCV genotype 1 without cirrhosis or with compensated (Child-Pugh A) cirrhosis when administered with sofosbuvir. Simeprevir is also indicated for genotype 1 or 4 when administered with pegIFN and ribavirin. The simeprevir triple therapy SVR rate varies depending on the patient's genotype 1 subtype. In clinical trials the overall SVR rate was about 80%, but the rate was lower in patients with genotype 1a (24% to 43%) than genotype 1b (78% to 84%).[8,34] The lower SVR rate with genotype 1a may be due to the baseline presence of NS3 Q80K polymorphism, a naturally occurring variation of the HCV virus. Therefore, baseline screening for NS3 Q80K polymorphism is recommended if prescribing simeprevir with PegIFN and ribavirin; if positive for the polymorphism, then an alternative HCV therapy should be used. Triple therapy with simeprevir, pegIFN, and ribavirin is not recommended due to its significant adverse effect profile, long treatment duration, and low SVR rates compared to newer IFN-free HCV regimens.[8]

Sofosbuvir (Sovaldi) This is the first agent of the NS5B polymerase inhibitor class approved for treatment of HCV genotypes 1, 2, 3, and 4; it also has efficacy in genotypes 5 and 6.[8] Sofosbuvir is commonly administered with other DAAs to achieve SVR rates above 90%. Treatment durations range from 8 to 24 weeks with the most common being 12 weeks.[8] Sofosbuvir plus PegIFN and ribavirin is no longer recommended for genotype 1 disease.[8] Sofosbuvir has fewer drug interactions than other DAAs; however, some may be significant because sofosbuvir is a substrate of intestinal P-glycoprotein. Agents that should be avoided with sofosbuvir include amiodarone, St. John's wort, certain anticonvulsants (carbamazepine, phenytoin), some HIV protease inhibitors (tipranavir/ritonavir), and some antimycobacterials (rifampin).

Sofosbuvir and Ledipasvir (Harvoni) This product is the first fixed-dose combination tablet and the first FDA-approved all-oral HCV regimen that does not require administration with pegIFN or ribavirin. Ledipasvir has a different mechanism of action than sofosbuvir; it inhibits the HCV NS5A protein,

Table 24–8

Direct-Acting Antiviral Agents for Treatment of Hepatitis C

Brand Name	Generic Name	Date of Approval	Cost per 28 Days (US$)[a]	Dosage (mg)	Regimen[e]	Drug Interactions	Resistance Testing Required	Indication	Warnings[f,g] and Contraindications
Olysio	Simeprevir	11/22/13	22,120	150	1 daily with sofosbuvir[e]	CYP3A2 CYP3A4 OATP1B1/3 P-gp[b] BCRP[h]	NS3 Q80K	GT 1 without cirrhosis or with compensated cirrhosis GT 4 when used with PegIFN and ribavirin HIV-1 co-infection	Assess and monitor for decompensated liver disease Amiodarone Photosensitivity, rash
Sovaldi	Sofosbuvir	12/06/13	28,000	400	1 daily with other DAA ± ribavirin[e]	P-gp[b]		GT 1,2,3,4 without cirrhosis or with compensated cirrhosis[e] GT 2,3[e] HIV-1 co-infection	Amiodarone Severe renal impairment, end stage renal disease
Harvoni	Ledipasvir/ sofosbuvir FDC[c]	10/10/14	31,500	90/400	1 daily ± ribavirin[e]	P-gp[b] BCRP[h] Acid suppressing agents		GT 1,4,5,6 without or with compensated cirrhosis[e] GT 1 with decompensated cirrhosis[e] GT 1,4 who are liver transplant recipients HIV-1 co-infection	Amiodarone Severe renal impairment, end-stage renal disease
Viekira XR[d]	Dasabuvir/ ombitasvir/ paritaprevir/ ritonavir FDC[c]	07/25/16	27,773	200/8.33/ 50/33.33	3 daily ± ribavirin[e]	CYP3A CYP2C8 UGT11A1 OATP1B1/3 P-gp[b] BCRP[h] Acid suppressing agents		GT 1 without cirrhosis and with compensated cirrhosis HIV-1 co-infection Liver transplant recipients with mild fibrosis	Avoid in patients with severe hepatic impairment (Child-Pugh B and C) Known hypersensitivity to ritonavir Discontinue ethinyl estradiol-containing medications
Daklinza	Daclatasvir	07/24/15	21,000	30, 60, 90	1 daily with other DAA ± ribavirin[e]	CYP3A P-gp[b] BCRP[h] OATP1B1/3	NS5A RAS	GT 1,3[e]	Strong inducers of CYP3A (phenytoin, carbamazepine, rifampin, St. John's wort) Amiodarone
Zepatier	Elbasvir/ grazoprevir FDC[c]	01/28/16	18,200	50/100	1 daily ± ribavirin[e]	OATP1B1/3 CYP3A	NS5A RAS	GT 1,4 HIV-1 co-infection Renal impairment, including hemodialysis	Avoid in patients with severe hepatic impairment (Child-Pugh B and C) Efavirenz
Technivie	Ombitasvir/ paritaprevir/ ritonavir FDC[c]	01/28/16	25,551	12.5/75/50	2 daily	P-gp[b] BCRP[h] OATP1B1/3 CYP3A Acid suppressing agents		GT 4 without cirrhosis or with compensated cirrhosis	Avoid in patients with severe hepatic impairment (Child-Pugh B and C) Known hypersensitivity to ritonavir Discontinue ethinyl estradiol-containing medications

(*Continued*)

Table 24–8

Direct-Acting Antiviral Agents for Treatment of Hepatitis C (*Continued*)

Brand Name	Generic Name	Date of Approval	Cost per 28 Days (US$)[a]	Dosage (mg)	Regimen[e]	Drug Interactions	Resistance Testing Required	Indication	Warnings[f,g] and Contraindications
Epclusa	Sofosbuvir/ velpatasvir FDC[c]	06/28/16	24,920	400/100	1 daily	P-gp[b] BCRP[h] OATP1B1/3 OATP2B1 CYP2B6 CYP2C8 CYP3A4 Acid suppressing agents		GT 1,2,3,4,5,6 with or without compensated cirrhosis and decompensated cirrhosis[e] HIV-1 co-infection	Amiodarone Severe renal impairment, end-stage renal disease
Vosevi	Sofosbuvir/ velpatasvir/ voxilaprevir FDC[c]	07/18/17	24,920	400/100/100	1 daily	P-gp[b] BCRP[h] OATP1B1/3 OATP2B1 CYP1A2 CYP2B6 CYP2C8 CYP3A4 Acid suppressing agents		GT 1,2,3,4,5,6 with or without compensated cirrhosis who had been treated with an NS5A inhibitor or with sofosbuvir without an NS5A inhibitor[e]	Avoid in patients with severe hepatic impairment (Child-Pugh B and C) Rifampin Amiodarone Severe renal impairment, end-stage renal disease
Mavyret	Glecaprevir/ pibrentasvir[c]	08/03/17	13,200	100/40	3 daily	P-gp BCRP[h] OATP1B1/3 CYP3A CYP1A2 UGT1A1[i]		GT 1,2,3,4,5,6 with or without compensated cirrhosis[e] GT 1 who had been treated with an NS5A inhibitor without an NS3/4A protease inhibitor or with an NS3/4A protease inhibitor without an NS5A inhibitor GT 1,2,3,4,5 PRS[j] HIV-1 co-infection	Avoid in patients with severe hepatic impairment (Child-Pugh C). Use with caution in Child-Pugh B. Atazanavir, rifampin

[a]Wholesale acquisition cost

[b]P-glycoprotein

[c]Fixed-dose combination tablet

[d]Prior to Viekira XR, the product was Viekira pak (dasabuvir 250 mg tablet and ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg FDC[c]), approved on 12/19/2014.

[e]Refer to www.hcvguidelines.org for the most up-to-date HCV treatment regimen.

[f]All patients should be evaluated for HBV and be vaccinated if not yet immune. If HBV is positive, then treat before initiating HCV therapy with any DAA.

[g]If coadministered with ribavirin, then refer to the warnings and contraindications associated with ribavirin.

[h]Breast cancer resistance protein

[i]Uridine glucuronosyltransferase

[j]PRS = Prior treatment experience with interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment with an HCV NS3/4A protease inhibitor or NS5A inhibitor

which is required for viral replication. The product is indicated for chronic HCV genotype 1, 4, 5, and 6 infection in patients older than age 12 or weighing at least 35 kg. See Table 24–8 for additional approved indications. The dose is one tablet (sofosbuvir 400 mg/ledipasvir 90 mg) daily (with or without food) for 8, 12, or 24 weeks depending on prior HCV treatment history, cirrhosis status, and baseline viral load.[8] Adverse effects are minimal, and drug interactions are similar to those receiving sofosbuvir alone. Use of high-dose acid suppressing agents with Harvoni decreases efficacy of ledipasvir; if these medications are required, doses should not exceed the equivalent of famotidine 40 mg twice daily or omeprazole 20 mg once daily.

Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir (Viekira XR) *and* Ombitasvir, Paritaprevir, and Ritonavir (Technivie) These two fixed-dose combination products are indicated for patients with HCV infections with or without Child-Pugh A compensated cirrhosis. Viekira XR is indicated for genotype 1 and Technivie is for genotype 4. See Table 24–8 for additional approved indications. The duration of treatment and the decision to add ribavirin are based on genotype and whether cirrhosis is present. The drugs have different mechanisms of action to inhibit HCV viral replication. Ombitasvir is an NS5A inhibitor, paritaprevir is an NS3/4A protease inhibitor, and dasabuvir is a nonnucleoside NS5B polymerase inhibitor with ritonavir, a CYP3A inhibitor. The SVR rate (80% to 100%) is affected by certain patient factors, including treatment experience, genotype, and presence of cirrhosis. Patients without cirrhosis and naïve to treatment are more likely to achieve an SVR rate greater than 90%.

Viekira XR and Technivie are contraindicated in patients with decompensated liver disease (Child-Pugh B and C) because fulminant hepatitis, need for liver transplant, or death may occur. Patients with cirrhosis should be monitored for hepatic decompensation. These agents may be used in patients with renal impairment including dialysis. However, renal dosage adjustments are required when used with ribavirin.

Treatment is well tolerated with minimal side effects; however, elevated ALT greater than 5 times the upper limit of normal may be seen in about 1% of patients. If it occurs, this effect is usually seen within the first 4 weeks of therapy. Elevated ALT levels are more pronounced in females using contraceptives contacting ethinyl estradiol, so these products should be discontinued before initiating Viekira XR or Technivie. Additional adverse effects may occur if given with ribavirin (Table 24–7).[8] Ritonavir is also an HIV-1 protease inhibitor, and patients coinfected with HCV and HIV may develop ritonavir resistance; HCV/HIV-1 coinfected patients should be started on a suppressive antiretroviral drug regimen before starting Viekira XR or Technivie to reduce the risk of HIV-1 protease inhibitor drug resistance. Drugs utilizing the CYP3A and/or CYP2C8 metabolic pathway are contraindicated with both products.

Daclatasvir (Daklinza) This NS5A inhibitor is approved for HCV genotype 1 or 3 and is co-administered with sofosbuvir for 12 weeks. Patients with decompensated (Child-Pugh B or C) disease require addition of ribavirin and perhaps a longer treatment duration of 24 weeks.[8] Daclatasvir has several significant drug interactions requiring dosage modifications. Because daclatasvir is co-administered with sofosbuvir with or without ribavirin, refer to those sections for additional adverse effects and drug interactions. The usual dose is 60 mg daily; patients taking CYP3A inducers should take 90 mg daily, and those using CYP3A inhibitors should use 30 mg daily.

Elbasvir and Grazoprevir (Zepatier) This fixed-dose combination tablet is approved for HCV genotype 1 or 4. Elbasvir is an NS5A inhibitor and grazoprevir is a NS3/4A protease inhibitor; these mechanisms inhibit different parts of the virus to halt viral replication. Patients with genotype 1a disease should be tested for the NS5A RAS; if NS5A polymorphism is absent, monotherapy with Zepatier for 12 weeks results in a SVR rate above 90%. If the polymorphism is present, ribavirin is added and treatment is extended to 16 weeks. Zepatier is a safe and well-tolerated option for patients with renal insufficiency including patients on hemodialysis because the drugs are primarily eliminated via the feces. Zepatier is contraindicated in patients with decompensated liver disease (Child-Pugh B and C) because fulminant hepatitis, need for liver transplant, or death may occur. All patients with cirrhosis should be monitored for hepatic decompensation while on treatment. Drug–drug interactions with elbasvir/grazoprevir should be evaluated prior to administration.

Sofosbuvir and Velpatasvir (Epclusa) This is the first fixed-dose combination tablet approved for all 6 HCV genotypes (known as a pangenotypic DAA). Sofosbuvir (400 mg), an NS5B polymerase inhibitor, is combined with velpatasvir (100 mg), an NS5A inhibitor that does not require administration of pegIFN or ribavirin to achieve a SVR well above 90% for all HCV genotypes. This is especially important for patients with genotype 3, which is more difficult to treat. Epclusa (one tablet daily with or without food for 12 weeks) is indicated for adult patients with or without compensated cirrhosis. Patients with decompensated Child-Pugh B or C cirrhosis should take Epclusa for 12 weeks with weight-based ribavirin, if tolerated, to increase the likelihood of achieving SVR. Adverse effects are minimal, and drug interactions are similar to those associated with Harvoni.[8]

Sofosbuvir, Velpatasvir, and Voxilaprevir (Vosevi) This pangenotypic fixed-dose combination tablet contains drugs targeting three different sites to inhibit HCV viral replication. Similar to the components of Epclusa, Vosevi also includes a NS3/4A protease inhibitor, voxilaprevir. The dose is one tablet (sofosbuvir 400 mg/velpatasvir 100 mg/voxilaprevir 100 mg) daily (with food) for 12 weeks for adult patients with or without compensated cirrhosis (Child-Pugh A) who have been previously treated with a HCV regimen that included an NS5A inhibitor or sofosbuvir. Patients with decompensated Child-Pugh B or C should not be treated with Vosevi because hepatic decompensation may be associated with the protease inhibitor. This triple therapy has SVR rates above 95%, particularly in DAA-experienced patients. Vosevi is approved for all genotypes and is well tolerated, with adverse effect and drug interaction profiles similar to Epclusa. However, the protease inhibitor voxilaprevir has potential interactions with drugs metabolized via the OATP1B1 and OATP1B3 pathways. There are no dosage recommendations for patients with renal insufficiency or end-stage renal disease.

Glecaprevir and Pibrentasvir (Mavyret) This is the first pangenotypic fixed-dose combination tablet containing an NS3/4A protease inhibitor (glecaprevir) and an NS5A inhibitor (pibrentasvir). It is approved for adults with or without compensated cirrhosis (Child-Pugh A) or patients who are treatment experienced with either an HCV NS3/4A or NS5A inhibitor. This is the first 8-week DAA treatment that is effective for all HCV genotypes in: (1) noncirrhotic patients, (2) patients co-infected with HIV, and (3) patients with renal insufficiency.

The dose is three tablets (glecaprevir 300 mg/pibrentasvir 120 mg) daily (with a moderate- to high-fat meal) in adults without cirrhosis. Patients with compensated Child-Pugh A cirrhosis require 12 weeks of therapy. Treatment-experienced patients require either 12 or 16 weeks of treatment. Patients with decompensated Child-Pugh B cirrhosis should not be treated with Mavyret, and Child-Pugh C cirrhosis is considered a contraindication because hepatic decompensation associated with the protease inhibitor may occur.

The 8-week dual therapy has SVR rates greater than 98% for genotypes 1, 2, 5, and 6 and approximately 95% for genotype 3 noncirrhotic patients. Mavyret is well tolerated; the most common adverse effects are headache and fatigue. There are numerous drug interactions, especially with drugs metabolized via the P-gp, OATP1B1/3, CYP3A, and UGT1A1 pathways.

▶ *Cost of HCV Treatment*

The new generation of HCV agents is associated with improved SVR rates and side-effect profiles. However, their high cost may prohibit some patients from receiving HCV treatment. Typically, 12 weeks of DAA therapy has a wholesale acquisition price of $72,000 to $95,000 (Table 24–8). For example, the cost of the first PegIFN-free DAA regimen with sofosbuvir was $1000 per day, or $84,000 to $168,000 for a 12- or 24-week treatment regimen, excluding the cost of other coadministered medications. The price has steadily declined as more DAA regimens became available. In August 2017, Mavyret (glecaprevir plus pibrentasvir) was approved for an 8-week course of therapy costing $26,400. Extending treatment to 12 or 16 weeks adds an additional $13,200 or $26,400, respectively, making this treatment the least expensive of all DAAs. In an ideal world, all patients infected with HCV would be treated. The unfortunate reality is that the high cost of HCV regimens strains health care resources, making it infeasible to treat everyone. The AASLD recommends that all patients be treated regardless of severity of the liver disease, except those with short life expectancies.[8] Despite this recommendation, insurers have restricted access to treatment due to cost and have used stage of fibrosis as one of the criteria to prioritize approval of treatment.[36,37] It is hoped that HCV medications will someday be affordable so all infected individuals may receive treatment.

Hepatitis D Prevention and Treatment

Hepatitis D infection is possible only if the patient is also infected with HBV; therefore, hepatitis B vaccination can indirectly prevent hepatitis D infections. The recommended treatment for HDV is pegIFN for 48 weeks.[10] For patients with mild liver disease, treatment should be withheld with HDV RNA and ALT levels monitored every 12 to 24 weeks. Treatment should be considered for individuals with advanced liver disease.[10] First-line oral agents for treating HBV infections (eg, tenofovir) may be co-administered with pegIFN; however, studies have shown no additional benefit in achieving viral clearance.[10] Monotherapy with nucleoside/nucleotide analogs is ineffective in reducing HDV DNA levels but may decrease hepatitis B viral loads.[10]

Hepatitis E Prevention and Treatment

Because hepatitis E is transmitted via the fecal–oral route, good personal hygiene and proper disposal of sanitary waste are the most effective ways to prevent viral acquisition. There are no commercially available vaccines in the United States to prevent hepatitis E. However, a hepatitis E vaccine has been licensed in China since 2011 and may become available for countries with high HEV infection incidence rates.[16]

Patient Encounter Part 3

The patient received treatment for hepatitis C for 4 weeks, and the following laboratory test results have just been obtained:

Sodium 138 mEq/L (mmol/L)
Potassium 5.7 mEq/L (mmol/L)
Chloride 98 mEq/L (mmol/L)
CO_2 19 mEq/L (mmol/L)
BUN 52 mg/dL (18.6 mmol/L)
SCr 4.7 mg/dL (415 µmol/L)
Glucose 103 mg/dL (5.7 mmol/L)
Hgb 10.8 g/dL (108 g/L; 6.70 mmol/L)
Hct 32.1% (0.321)
WBC 4.1 × 10^3/mm^3 (10^9/L)
Plt 114 × 10^3/mm^3 (10^9/L)
AST 18 IU/L (0.30 µkat/L)
ALT 19 IU/L (0.32 µkat/L)
T. bilirubin 1.7 mg/dL (29.1 µmol/L)
Albumin 3.1 g/dL (31 g/L)
Alk phos 168 IU/L (2.80 µkat/L)
HCV RNA level: undetectable

What questions should you ask the patient?

What action should you take to treat any complaints the patient may have?

What action should you take based on the patient's week 4 HCV RNA level?

OUTCOME EVALUATION

LO 7

Monitoring for efficacy in patients treated for chronic hepatitis B or C includes evaluating aminotransferase levels and hepatitis B or C viral levels and serologies.

Hepatitis B

- Obtain an ALT at baseline and then every 3 to 6 months during hepatitis B treatment.
- Monitor HBV DNA levels every 3 to 6 months to determine treatment response.
- Monitor HBeAg and anti-HBe every 6 months to determine if seroconversion to anti-HBe occurred or HBeAg was lost in HBeAg-positive CHB patients.[20]
- Monitor HBsAg every 6 to 12 months to determine if HBsAg was lost or anti-HBs developed in CHB HBeAg-negative patients with persistently undetectable serum HBV DNA levels.[20]
- Continue treatment in CHB HBeAg-positive patients until HBeAg seroconversion has been attained along with undetectable HBV DNA levels. Once anti-HBe appears, complete an additional 12 months of hepatitis B therapy.[20]
- Continue treatment in CHB HBeAg-negative patients until HBsAg is lost.[20]
- Monitor ALT, HBV DNA levels, seroconversion, and signs and symptoms of hepatic decompensation monthly for 6 months then every 3 months for patients with confirmed cirrhosis. Monitor for hepatitis flare and viral relapse when discontinuing hepatitis B therapy.[20]
- Monitor ALT, HBV DNA levels, seroconversion, and signs and symptoms of hepatic decompensation every 3 months for at least 1 year for all patients who discontinued HBV therapy.[20]
- Obtain a CBC with differential every 4 weeks and thyroid-stimulating hormone (TSH) and fasting lipid panel every 12 weeks when receiving pegIFN therapy for hepatitis B.[20]

Patient Encounter Part 4

The patient has now been treated for a total of 12 weeks and the HCV RNA level is undetectable.

What action should you take based on the week 12 HCV RNA level?

What other information should you counsel the patient about in addition to the side effects associated with the hepatitis C therapy?

- For patients receiving tenofovir or adefovir, monitor serum creatinine, phosphorus, urine glucose, and urinary protein for nephrotoxicity at baseline then periodically (more frequently in patients with baseline renal insufficiency).[20]
- For patients taking telbivudine, monitor creatine kinase at baseline and periodically (eg, every 12 weeks) because muscle weakness and myopathy have occurred.[20]

Hepatitis C

- Evaluate the patient's HBV status. If not yet immune to HBV, then vaccinate. If positive for CHB, then have hepatologist evaluate the patient for HBV treatment.
- Evaluate for signs and symptoms of decompensated liver disease prior to initiating DAA therapies containing an HCV NS3 protease inhibitor. Patients with Child-Pugh B or C should not receive NS3 protease inhibitors (Table 24–8).
- Evaluate for the presence of RAS prior to initiating HCV therapy (Table 24–8).
- The ultimate goal of HCV therapy is to achieve SVR, defined as having undetectable HCV RNA levels for at least 3 months posttreatment; this indicates virological cure.[8]

Patient Encounter Part 5

The patient's daughter was recently found to be positive for hepatitis B. She is pregnant and ready to give birth. She has a history of irritability. She has no surgical history. She is taking a neonatal vitamin with iron.

All laboratory test results are normal except for the following:

AST 84 IU/L (1.4 µkat/L)	HBeAg (–)
ALT 87 IU/L (1.45 µkat/L)	Anti-HBc IgG (+)
Anti-HAV IgM (–)	Anti-HBc IgM (–)
Anti-HAV IgG (+)	Anti-HBe (–)
Anti-HBs (–)	Anti-HCV (–)
HBsAg (+)	HBV DNA 109,134 IU/mL (kIU/L)

Based on the information presented:

(a) what additional information do you need before creating a treatment plan for this patient?

(b) create a detailed care plan for the patient;

(c) discuss adverse effects to monitor;

(d) discuss a follow-up plan to determine whether the treatment goals have been achieved.

- Obtain HCV RNA level at week 4 of therapy to assess for efficacy. If detectable, repeat at week 6. If HCV RNA level has increased greater than 1 $\log_{10}$ IU/mL (1 $\log_{10}$ kIU/L), then discontinue all HCV medications.
- End of treatment response (ETR or EOT) is defined as having undetectable HCV RNA levels at the end of treatment.
- Monitor ALT levels every 4 weeks. Biochemical response is defined as normalization of ALT.
- Histologic response is defined as improving inflammation and fibrosis as documented by liver biopsy scores.

Patient Care Process

Collect Information:

- Speak with the patient to identify risk factors for acquiring viral hepatitis (Table 24–1).
- Review social history to determine if any practices may contribute to or worsen the severity of liver disease (ie, alcohol, high-fat food intake).
- Review past medical history focusing on hepatic and renal disorders.
- Review physical assessment findings focusing on mental status changes, edema, and color of skin and eyes (ie, jaundice).
- Perform a medication history (prescription, over-the-counter drugs, dietary supplements) to identify drug interactions (may refer to hep-druginteraction.org) or drug-induced liver toxicity.
- Review use of any drugs in the past for the treatment of hepatitis B or C.
- Obtain a vaccination history to determine which vaccines have been given.
- Review laboratory tests to determine severity of liver disease. Review hepatitis serologies to determine if vaccination is needed (Tables 24–3 and 24–4).
- Speak with the patient and review insurance coverage records for medical and medication history.

Assess the Information:

- Determine if treatment is indicated by reviewing laboratory values, liver serologies, and liver biopsy report (if available) or imaging (CT, Fibroscan, ultrasound).
- If the patient does not qualify for hepatitis therapy, then schedule return visits every 3 to 6 months to monitor health condition and laboratory tests.
- If the patient qualifies for treatment, assess for uncontrolled medical conditions, and if present, treat or refer to an appropriate medical specialty for evaluation (eg, HIV, diabetes, renal disease, HBV).
- Determine which vaccines need to be administered.
- For patients with HCV, assess severity of liver disease to recommend appropriate anti-HCV regimen (Table 24–9).

(*Continued*)

Patient Care Process (*Continued*)

- Document, trend, and review laboratory values to determine severity of liver disease (platelet counts, AST, ALT, INR, albumin).
- Assess the efficacy, safety, and patient adherence of current pharmacotherapy.
- Assess current medications before initiating hepatitis therapy to identify potential drug–drug interactions and ensure that doses are appropriate based on organ function.
- Assess laboratory values, and medications with potential for drug interactions or adherence problems for patients currently on treatment.

LO 6

Develop a Care Plan:

- Refer to AASLD HBV guidelines for CHB treatment recommendations.
- Refer to www.hcvguidelines.org for HCV treatment guidelines.
- Refer to https://www.hepatitisc.uw.edu/ for HCV treatment regimens.
- Obtain a pregnancy test in women of childbearing potential who are prescribed ribavirin-based therapies.

Implement the Care Plan:

- Educate the patient about the hepatitis drug regimen, potential side effects, and duration of therapy.
- Inform the patient about the importance of drug adherence to minimize the risk of developing resistance.
- Educate the patient to avoid alcohol and illicit drug use during treatment and after completion of therapy.
- Work with the local specialty pharmacy to ensure that medications are covered by insurance and continued without disruption in treatment.
- Educate all men and women who are of childbearing age and are receiving ribavirin to use two forms of birth control during treatment and for 6 months after treatment.
- Address any patient concerns about the liver disease and its management.
- Discuss the importance of lifestyle modification to reduce the progression of liver disease.

LO 7

Follow-up: Monitor and Evaluate:

- At each clinic visit, review the medication list, assess for medication adverse effects and drug interactions, and review laboratory tests to assess efficacy and toxicity.
- Confirm adherence and number of missed doses to minimize drug resistance.
- Obtain laboratory test results every week to every 2 to 4 weeks until complete treatment if ribavirin is prescribed.
- Assess for decompensated liver disease while on HCV therapy (Table 24–9).
- Follow up with a hepatologist every 6 months for cirrhosis surveillance.

- Monitor WBC, absolute neutrophil count (ANC), and platelets either weekly or biweekly during the first month of therapy and monthly thereafter if stable while on pegIFN (Table 24–7).
- Monitor WBC with platelet count, creatinine, and LFTs after 4 weeks of initiating DAA therapy, then monthly until treatment is completed.
- Monitor TSH and fasting lipid panel every 12 weeks while receiving pegIFN.
- Monitor hemoglobin weekly or biweekly during the first month and monthly thereafter if stable while on ribavirin (Table 24–7).
- Monitor for fatigue, shortness of breath, chest pain, and dermatological complications while on ribavirin; discontinue treatment if complaints are significant.
- Monitor serum creatinine in patients receiving ribavirin to detect renal insufficiency that may result in ribavirin accumulation and toxicity (eg, hemolytic anemia).
- Conduct a thorough medication reconciliation of prescription, over-the-counter, and dietary and herbal supplements prior to and during HCV therapy.

Table 24–9

Child-Turcotte-Pugh (CTP) Classification of the Severity of Cirrhosis

	Points		
Parameter	**1**	**2**	**3**
Albumin (g/dL [g/L])	> 3.5 [35]	2.8–3.5 [28–35]	< 2.8 [28]
Bilirubin (mg/dL [μmol/L])	< 2 [34]	2–3 [34–51]	> 3 [51]
Prothrombin time (sec prolonged)	< 4	4–6	> 6
OR			
International normalized ratio	< 1.7	1.7–2.3	2.3
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Encephalopathy	None	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory)

Calculation of CTP score: Add the points for each parameter. CTP Class A: 5–6 points; Class B: 7–9 points; Class C: 10–15 points.

Abbreviations Introduced in This Chapter

ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-HAV	Hepatitis A virus antibody
Anti-HBc	Hepatitis B core antibody
Anti-HBe	Hepatitis B envelope antibody
Anti-HBs	Hepatitis B surface antibody
Anti-HCV	Hepatitis C antibody
Anti-HDV	Hepatitis D antibody
Anti-HEV	Hepatitis E antibody
AST	Aspartate aminotransferase
CHB	Chronic hepatitis B infection
CrCl	Creatinine clearance
DAA	Direct-acting antiviral
ETR	End of treatment response
ESLD	End-stage liver disease
HAV	Hepatitis A virus
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B envelope antigen
HBIG	Hepatitis B immunoglobulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B deoxyribonucleic acid
HCV	Hepatitis C virus
HCV RNA	Hepatitis C virus ribonucleic acid
HDV	Hepatitis D virus
HDVAg	Hepatitis D antigen
HDV RNA	Hepatitis D virus ribonucleic acid
HEV	Hepatitis E virus
IgG	Immunoglobulin G
IgG anti-HD	IgG antibodies to hepatitis D virus antigen
IgM	Immunoglobulin M
IgM anti-HD	IgM antibodies to hepatitis D virus antigen
IG	Immune globulin
IGIM	Immune globulin for intramuscular administration
IGIV	Immune globulin for IV administration
pegIFN	Pegylated interferon
RAS	Resistance-associated substitutions
RVR	Rapid virologic response
SVR	Sustained virologic response
WBC	White blood cell counts

REFERENCES

1. Hepatitis A and Hepatitis A vaccine. National Vaccine Information Center. Available from: http://www.nvic.org/vaccines-and-diseases/Hepatitis-A.aspx. Accessed August 10, 2017.
2. Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington D.C. Public Health Foundation, 2015. Available from: http://www.cdc.gov/vaccines/pubs/pinkbook/hepa.html. Accessed August 10, 2017.
3. Surveillance for Viral Hepatitis—United States, 2015. Available from: https://www.cdc.gov/hepatitis/statistics/2015surveillance/commentary.htm. Accessed August 9, 2017.
4. Disease Outbreak Control Division. Hepatitis A Outbreak 2016. State of Hawaii, Department of Health. Available from: http://health.hawaii.gov/docd/hepatitis-a-outbreak-2016/. Accessed August 11, 2017.
5. WHO Guidelines on Hepatitis B and C Testing. World Health Organization. Available from: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0096180/pdf/PubMedHealth_PMH0096180.pdf. Accessed August 10, 2017.
6. Centers for Disease Control and Prevention. Hepatitis B. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S., eds. 13th ed., Washington D.C.: Public Health Foundation, 2015. Available from: http://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html. Accessed August 10, 2017.
7. Hepatitis C FAQ for Health Professionals. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1. Accessed August 17, 2017.
8. Recommendations for Testing, Managing, and Treating Hepatitis C. AASLD-IDSA. Available from: http://www.hcvguidelines.org. Accessed August 17, 2017.
9. Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology. 2014;59(1):318–327.
10. Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014 November;61:S45–S57.
11. Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. Gastroenterology. 2006;131(2):478–484.
12. Hepatitis C FAQs for Health Professionals. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/hepatitis/HCV/index.htm. Accessed August 17, 2017.
13. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998;47(RR-19):1–39.
14. Elazar M, Koh C, Glenn JS. Hepatitis delta infection: current and new treatment options. Best Pract Res Clin Gastroenterol. 2017;31(3):321–327.
15. Hepatitis D Fact Sheet. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/hepatitis-d/en/. Accessed August 17, 2017.
16. Hepatitis E Fact Sheet. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs280/en/. Accessed August 17, 2017.
17. Zingaretti C, De Francesco R, Abrignani S. Why is it so difficult to develop a hepatitis C virus preventive vaccine? Clin Microbiol Infect. 2014;20(suppl 5):103–1099.
18. Pérez-Gracia MT, García M, Suay B, et al. Current knowledge on hepatitis E. J Clin Transl Hepatol. 2015;3(2):117–126.
19. Singh S, Muir AJ, Dieterich DT, Falck-Ytter YT. American Gastroenterological Association Institute technical review on the role of elastography in chronic liver diseases. Gastroenterology. 2017 May;152(6):1544–1577.
20. Terrault NA, Bzowej NH, Chang KM, et al; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 January;63(1):261–283.
21. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. J Hepatol. 2017 July 21. pii: S0168–8278(17)32017-2.
22. Centers for Disease Control and Prevention (CDC). Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2007;56(41):1080–1084.
23. Advisory Committee on Immunization Practices (ACIP); Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006 May 19;55(RR-7):1–23.

24. Hepatitis A FAQs for Health Professionals. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/hepatitis/HAV/HAVfaq.htm#vaccine. Accessed August 22, 2017.
25. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: Immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54(RR-16):1–31.
26. Mavilia MG, Wu GY. Mechanisms and prevention of vertical transmission in chronic viral hepatitis. J Clin Transl Hepatol. 2017 June 28;5(2):119–129.
27. Centers for Disease Control and Prevention. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press; 2017. https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/hepatitis-b. Accessed August 20, 2017.
28. Scott LJ, Chan HLY. Tenofovir alafenamide: a review in chronic hepatitis B. Drugs. 2017 June;77(9):1017–1028.
29. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 August;67(2):370–398.
30. Trépo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet. 2014 June 18. pii: S0140–6736(14)60220–60228.
31. Jeon HJ, Jung SW, Park NH, et al. Efficacy of tenofovir-based rescue therapy for chronic hepatitis B patients with resistance to lamivudine and entecavir. Clin Mol Hepatol. 2017;23(3):230–238.
32. Scott LJ, Chan HLY. Tenofovir alafenamide: a review in chronic hepatitis B. Drugs. 2017 June;77(9):1017–1028.
33. Abdelwahab KS, Ahmed Said ZN. Status of hepatitis C virus vaccination: recent update. World J Gastroenterol. 2016 January 14;22(2):862–873.
34. Kohli A, Shaffer A, Sherman A, Kottilil S. Treatment of hepatitis C: a systematic review. JAMA. 2014;312(6):631–640.
35. Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2014 June 3. pii: S0140–6736(14)60538–9.
36. Lo Re V 3rd, Gowda C, Urick PN, et al. Disparities in absolute denial of modern hepatitis C therapy by type of insurance. Clin Gastroenterol Hepatol. 2016;14(7):1035–1043.
37. Lynch SM, Wu GY. Hepatitis C virus: a review of treatment guidelines, cost-effectiveness, and access to therapy. J Clin Transl Hepatol. 2016;4(4):310–319.

25 Acute Kidney Injury

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LEARNING OBJECTIVES

LO

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

1. Assess a patient's kidney function based on clinical presentation, laboratory results, and urinary indices.
2. Identify pharmacotherapeutic outcomes and endpoints of therapy in a patient with acute kidney injury (AKI).
3. Apply knowledge of the pathophysiology of AKI to development of a treatment plan.
4. Develop strategies to minimize the occurrence of drug- and radiocontrast-induced AKI.
5. Monitor and evaluate the safety and efficacy of the therapeutic plan.

INTRODUCTION

Acute kidney injury (AKI) is a potentially life-threatening syndrome that occurs primarily in hospitalized patients and frequently complicates the course of those who are critically ill. It is characterized by a rapid decrease in glomerular filtration rate (GFR) and the resultant accumulation of nitrogenous waste products (eg, creatinine), with or without a decrease in urine output.

The term acute kidney injury has replaced the name acute renal failure because it more completely encompasses the entire spectrum of acute injury to the kidney, from mild changes in kidney function to end-stage kidney disease requiring renal replacement therapy (RRT).

KEY CONCEPT AKI is defined as an increase in serum creatinine (SCr) of at least 0.3 mg/dL (27 μmol/L) within 48 hours, a 50% increase in baseline serum creatinine within 7 days, or a urine output of less than 0.5 mL/kg/h for at least 6 hours. Only one criterion needs to be met for diagnosis of AKI.[1]

EPIDEMIOLOGY AND ETIOLOGY

Approximately 7% to 18% of all hospitalized patients develop AKI.[2] More than half of those who are critically ill develop AKI,[3] and 30% to 40% of survivors of AKI develop chronic kidney disease (CKD).[3] Despite improvements in the medical care of individuals with AKI, mortality remains high. About 4% of hospital admissions are community-acquired AKI[4] with an incidence of 20 to 200 cases per million population.[2]

PATHOPHYSIOLOGY

There are three categories for the causes of AKI: prerenal, intrinsic, and postrenal AKI. The pathophysiologic mechanisms differ for each of the categories.

Prerenal AKI

Prerenal AKI occurs in approximately 10% to 25% of patients diagnosed with AKI and is characterized by reduced blood delivery to the kidney. A common cause is intravascular volume depletion due to conditions such as hemorrhage, dehydration, or gastrointestinal (GI) fluid losses. Early volume restoration can prevent progression and improve recovery because it can restore renal blood flow before structural damage to the kidney has occurred.[5] Conditions of reduced cardiac output (eg, congestive heart failure [CHF], myocardial infarction), septic shock, and hypotension can also reduce renal blood flow, resulting in decreased glomerular perfusion and prerenal AKI. With a mild to moderate decrease in renal blood flow, intraglomerular pressure is maintained by dilation of afferent arterioles (arteries supplying blood to the glomerulus), constriction of efferent arterioles (arteries removing blood from the glomerulus), and redistribution of renal blood flow to the oxygen-sensitive renal medulla.

Drugs may cause a functional AKI when they interfere with these autoregulatory mechanisms. Nonsteroidal anti-inflammatory drugs (NSAIDs) impair prostaglandin-mediated dilation of afferent arterioles. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) inhibit angiotensin II–mediated efferent arteriole vasoconstriction and cause prerenal AKI in 6% to 38% of treated patients.[6] The calcineurin inhibitors cyclosporine and tacrolimus, particularly in high doses, are potent renal vasoconstrictors. All of these agents can reduce intraglomerular pressure, with a resultant decrease in GFR. Prompt discontinuation of the offending drug can often return kidney function to normal.

Other causes of prerenal AKI are renovascular obstruction (eg, renal artery stenosis), hyperviscosity syndromes (eg, multiple myeloma), and systemic vasoconstriction (eg, hepatorenal syndrome).

Intrinsic AKI

Intrinsic renal failure is caused by diseases that can affect the structure of the nephron, such as the tubules, glomerulus, interstitium, or blood vessels. Acute tubular necrosis (ATN) is a term that is often used synonymously with intrinsic AKI, but ATN relates more specifically to necrosis of tubular epithelial cells resulting from nephrotoxins (eg, aminoglycosides, contrast agents, amphotericin B), sepsis, or ischemia. ATN accounts for

50% of all cases of AKI.[7] In addition, prerenal AKI can progress to ATN if the underlying cause of it is not promptly corrected.

Glomerular, interstitial, and blood vessel diseases may also lead to intrinsic AKI but occur with a much lower incidence. Examples include **glomerulonephritis**, systemic lupus erythematosus, **interstitial nephritis**, and vasculitis.

Postrenal AKI

Postrenal AKI is due to obstruction of urinary outflow. Causes include benign prostatic hypertrophy, pelvic tumors, and precipitation of renal **calculi**.[7] Rapid resolution of postrenal AKI without structural damage to the kidney can occur if the underlying obstruction is corrected. Postrenal AKI accounts for less than 10% of cases of AKI.

CLINICAL PRESENTATION AND DIAGNOSIS

The definition and categorization of AKI has evolved over the past decade. The first AKI classification system was *RIFLE* (Risk, Injury, Failure, Loss, and End stage), which defined and stratified the severity of kidney disease.[1]

The Acute Kidney Injury Network (AKIN) modified the *RIFLE* definition and staging for AKI. The AKIN staging system is based on changes in SCr and uses three stages (stages 1 to 3); stage 1 also includes an absolute increase in SCr of 0.3 mg/dL (27 μmol/L) or greater.[1] This highlights the association of even small increases in SCr concentration with morbidity and mortality, making early detection critical. It also categorizes all patients receiving RRT as stage 3.[8] Studies have validated both RIFLE and AKIN criteria in identifying hospitalized patients at risk of mortality associated with AKI.[9] A common classification and definition of AKI is advocated by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury (**Table 25–1**).[1]

LO 1 Decreased urine output may be a more sensitive marker than increases in SCr in early AKI; however, decreased urine output is not universally present in AKI. **Oliguria** and **anuria** are defined as daily urine outputs of less than 400 mL and 50 mL, respectively. Reduced urine output is associated with increased mortality and may represent a more severe form of AKI. Nonoliguric AKI is defined as urine output greater than 400 mL/day. It may still represent severe AKI but is associated with better patient outcomes.[10]

LO 1 As kidney function declines, SCr and blood urea nitrogen (BUN) rise. Monitoring SCr and BUN and comparing them to baseline can assist in determining if a patient's kidney function is worsening or improving. BUN is a less sensitive marker for evaluation of AKI compared to SCr. Urea is a product of amino acid metabolism, and although it is eliminated via glomerular filtration, it also undergoes reabsorption in the proximal tubules. Increased blood urea reabsorption occurs at lower urine flow rates within the kidney, such as that which occurs in prerenal AKI. Thus, an elevated BUN to SCr ratio can indicate prerenal AKI. Other conditions that can result in an elevated BUN are excessive protein intake and GI bleeding (because of blood breakdown to amino acids in the gut).

LO 1 Although some clinical and laboratory findings assist in the general diagnosis of AKI, others are used to differentiate among prerenal, intrinsic, and postrenal AKI. For example, patients with prerenal AKI typically demonstrate enhanced sodium reabsorption, which is reflected by a low urine sodium concentration and a low fractional excretion of sodium (FENa). The FENa is calculated by the following equation:

$$\text{Fractional excretion of sodium (FENa)} = 100 \times \frac{(\text{Urinary sodium concentration} \times \text{Plasma creatinine concentration})}{(\text{Plasma sodium concentration} \times \text{Urinary creatinine concentration})}$$

FENa is a measure of the percentage of sodium excreted by the kidney. Ordinarily, 1% to 2% of sodium intake is excreted by the kidneys. A FENa less than 1% may indicate prerenal AKI because it represents the response of the kidney to decreased renal perfusion by decreasing sodium excretion. Loop diuretics such as furosemide enhance sodium excretion and increase FENa, confounding the interpretation of the test.

LO 1 Urine is typically more concentrated with prerenal AKI, and there is a higher urine osmolality and urine-to-plasma creatinine ratio (> 20:1 for units of mg/dL) compared to intrinsic and postrenal AKI. Other factors, such as patient symptoms, laboratory test results, urinary indices, and results of diagnostic procedures, aid in the diagnosis and assessment of disease severity.

Early Detection of AKI

Serum creatinine lacks sensitivity in detecting AKI; thus, identifying novel biomarkers that are released within hours of injury with sensitivity and specificity would aid in early detection of AKI.[11] Nephrocheck® is the first commercially available point-of-care test for critically ill patients with cardiovascular or respiratory compromise that measures urine

Table 25–1

Staging System for AKI

Stage	Change in Serum Creatinine from Baseline		Urine Output	Need for Renal Replacement Therapy
1	0.3 mg/dL (27 μmol/L) or greater increase from baseline	150%–199% (1.5%–1.9-fold)	< 0.5 mL/kg per hour for 6–12 hours	No
2	—	200%–299% (2–2.9-fold)	< 0.5 mL/kg per hour for 12 hours or longer	No
3	Increase to 4 mg/dL (354 μmol/L) or greater	300% or greater (> 3-fold)	< 0.3 mL/kg per hour for 24 hours or anuria for ≥ 12 hours	Initiation of renal replacement therapy indicates stage 3 regardless of serum creatinine or urine output

Based on the KDIGO staging system for AKI. Only one of the three criteria needs to be met in order to qualify for the higher stage.

Clinical Presentation and Diagnosis of AKI

Symptoms of AKI

- Weight gain
- Nausea, vomiting, diarrhea, anorexia
- Fatigue
- Shortness of breath
- Pruritus
- Weight loss (prerenal AKI)
- Anuria alternating with polyuria (postrenal AKI)
- Colicky abdominal pain radiating from flank to groin (postrenal AKI)

Physical Examination Findings

- Increased blood pressure
- Peripheral edema
- Change in mental status
- Jugular venous distention (JVD)
- Pulmonary edema
- Crackles
- Asterixis
- Pericardial or pleural friction rub
- Hypotension or orthostatic hypotension (prerenal AKI)
- Rash (intrinsic AKI due to acute interstitial nephritis)
- Bladder distention (postrenal bladder outlet obstruction)
- Prostatic enlargement (postrenal AKI)

Laboratory Tests

- Elevated SCr (reference range ~0.6 to 1.2 mg/dL [53 to 106 µmol/L])
- Elevated BUN (reference range ~8 to 25 mg/dL [2.9 to 8.9 mmol/L])
- BUN-to-creatinine ratio greater than 20:1 for units of mg/dL (prerenal AKI); (urea to creatinine ratio cutoff of 100:1 when both urea and creatinine are expressed in molar units [eg, µmol/L])
- Hyperkalemia
- Metabolic acidosis

Urinalysis

- Sediment
  - Scant or bland (prerenal or postrenal AKI)
  - Brown, muddy granular casts (intrinsic ATN)
  - Proteinuria (glomerulonephritis or allergic interstitial nephritis)
  - Eosinophiluria (acute interstitial nephritis)
  - Hematuria or red blood cell casts (glomerular disease or bleeding in urinary tract)
  - WBCs or casts (acute interstitial nephritis or severe pyelonephritis)

Urinary Indices	Prerenal AKI	Intrinsic and Postrenal AKI
Urine osmolality (solute concentration in the urine in mOsm/kg or mmol/kg)	> 500	< 350
Urine sodium concentration (mEq/L or mmol/L)	< 20	> 40
Specific gravity	> 1.020	< 1.015
Urine-to-plasma creatinine ratio	> 40:1	< 20:1
Fractional excretion of sodium (FENa)	< 1%	> 1%–2%

Common Diagnostic Procedures

- Urinary catheterization is performed to rule out urethral obstruction; increased urine output may occur if postrenal obstruction is present.
- Renal ultrasound can assist in differentiating AKI [normal-sized kidneys] from CKD [small kidneys]. It can also show urinary tract obstruction and hydronephrosis, which indicates postrenal AKI.
- Computed tomography (CT) provides similar information as renal ultrasound but with greater spatial resolution. It assists in the diagnosis of masses, stones, and pyelonephritis.
- Magnetic resonance imaging (MRI) can be used as an alternative to CT scanning to avoid administering radiocontrast media.
- Renal angiography can be useful in identifying conditions such as renal artery stenosis and renal vein thrombosis.
- Retrograde pyelography is used to localize the site of urinary tract obstruction.
- Kidney biopsy may aid in the diagnosis of glomerular and interstitial diseases.

concentrations of IGF-binding protein 7 and tissue inhibitor of metalloproteinase-2. The test provides a positive risk score to indicate risk for moderate to severe kidney injury within 12 hours.[12] Although this test is not yet widely used, a positive score could trigger an early nephrology consult, avoidance of nephrotoxic medications, fluid resuscitation, and other therapies to prevent progression. Studies are underway to explore the utility of different biomarkers for early diagnosis/prognosis of AKI, to guide clinical decision-making, and to detect early drug-induced nephrotoxicity.[12]

The furosemide stress test is being investigated to predict the development of stage 3 AKI in early AKI. Initial studies have found that a urine volume of less than 200 mL at 2 hours following a one-time furosemide dose of 1.0 mg/kg in furosemide-naïve patients or 1.5 mg/kg in patients with prior furosemide exposure is predictive of severe AKI. Additional studies to validate the test, used alone and in combination with other biomarker tests, are needed to aid in the early detection of AKI.

TREATMENT

Desired Outcomes

LO 2

A primary goal in the care of patients with AKI is ameliorating identifiable underlying causes of AKI such as hypovolemia, nephrotoxic drugs, or ureter obstruction. Prerenal and postrenal AKI can be reversed if the underlying problem is promptly

identified and corrected, whereas treatment of intrinsic renal failure is primarily supportive until kidney function recovers. KEY CONCEPT There is no evidence that drug therapy hastens patient recovery, decreases length of hospitalization, or improves survival in intrinsic AKI.

Pharmacologic Therapy

▶ *Hydration*

To ensure adequate tissue perfusion in patients with prerenal AKI, isotonic crystalloid solutions such as 0.9% normal saline are used to expand intravascular volume and return volume status to neutral fluid balance (euvolemia).[14] Crystalloids (eg, normal saline, balanced solutions such as Lactated Ringer's or Plasma-Lyte A) are preferred over colloidal solutions (eg, albumin, hydroxyethyl starch) for fluid resuscitation.[14] Additionally, 0.9% normal saline is generally preferred over lower tonicity saline fluids such as 0.45% normal saline because a smaller fraction of hypotonic fluid remains in the intravascular space. Dextrose 5% in water is isotonic, but after the dextrose is absorbed by the body, only water is left in the intravascular space. Because plain water is hypotonic, it can have the same effect as 0.45% normal saline; therefore, it is not ideal for fluid resuscitation. Caution must be taken with hydration because overzealous fluid resuscitation can result in pulmonary edema, increased postoperative complications, and ultimately, increased mortality.[15] In addition, excess chloride from 0.9% normal saline can cause hyperchloremic metabolic acidosis.[16] Some evidence suggests that too much fluid can worsen AKI; thus, the goal of treatment is to return to a state of euvolemia or slightly negative fluid balance.[15] In instances of acute blood loss, blood transfusions may be indicated.

In addition to fluids, vasopressors (ie, norepinephrine, dopamine, vasopressin) may be needed in patients with shock to restore adequate organ perfusion. There are no definitive data to support one agent as superior over another; however, greater number of arrhythmic events have been reported with dopamine compared to norepinephrine.[17]

▶ *Loop Diuretics*

Most studies evaluating loop diuretics (ie, furosemide, bumetanide, torsemide, and ethacrynic acid) for prevention or treatment of AKI demonstrated improved urine output but no improvement in survival or need for dialysis. There are some reports that loop diuretics may worsen kidney function and may be harmful if given for prevention of AKI.[18] Thus, loop diuretics should be reserved for treating volume overload and should not be given to prevent AKI or hasten recovery of kidney function in euvolemic or hypovolemic individuals.[19]

Although bumetanide and torsemide are more potent than furosemide on a weight basis, all of the loop diuretics are equally effective in fluid removal when given in equipotent IV doses (40 mg furosemide = 1 mg of bumetanide = 10–20 mg torsemide). Therefore, selection is based on the side-effect profile, cost, and pharmacokinetic differences. **Ototoxicity** is a well-established side effect of ethacrynic acid and limits its use; this side effect occurs rarely with bumetanide and torsemide. The risk of ototoxicity with furosemide is significant when administered by the IV route at a rate exceeding 4 mg/min. Bioavailability is lower and more variable for furosemide compared to bumetanide and torsemide; therefore, the IV-to-oral ratio for furosemide is about 1:2. Furosemide, bumetanide, and torsemide all contain a sulfa moiety; however, a previous sulfonamide antimicrobial allergy does not prohibit loop diuretic administration. In the rare instance of a sulfonamide-like allergic reaction to one of the commonly used loop diuretics, ethacrynic acid could be given because it does not contain a sulfa moiety.

Loop diuretics exert their effect from the luminal (urinary) side of the tubule. Decreased tubular secretion of loop diuretics occurs in kidney disease and reduces drug concentration at the active site in the tubule lumen. Therefore, large doses of loop diuretics are often necessary in kidney disease to ensure that adequate drug reaches the nephron lumen. Loop diuretics also have a ceiling effect where maximal **natriuresis** occurs.[20] Thus, very large doses of furosemide (eg, 1 g) are not necessary and may unnecessarily increase the risk of ototoxicity.

Several adaptive mechanisms by the kidney limit effectiveness of loop diuretic therapy. As the concentration of diuretic in the loop of Henle decreases, postdiuretic sodium retention can occur. This effect can be minimized by decreasing the dosage interval (ie, dosing more frequently) or by administering a continuous infusion.[21]

Prolonged administration of loop diuretics can lead to a second type of diuretic resistance. Hypertrophy of distal convoluted tubule cells can occur secondary to enhanced delivery of sodium to the distal tubule.[20] Subsequently, increased sodium chloride absorption occurs in the distal tubule, which diminishes the effect of the loop diuretic on overall sodium excretion. Combining a distal convoluted tubule diuretic, such

Patient Encounter Part 1

A 65-year-old woman presents to the clinic with complaints of nausea and vomiting. She has a past medical history of stage 2 chronic kidney disease with proteinuria (baseline SCr 1.0 mg/dL [88 µmol/L]), gout, hypertension, and osteoarthritis. Her estimated GFR is 60 mL/min/1.73 m^2. She reports having nausea, vomiting, and a low-grade fever last week. Her fever resolved with ibuprofen, but she still feels weak and nauseated. She states that "her feet are swollen" even though she takes her "water pill." Her weight is usually about 150 pounds (68.2 kg), and today she weighs 155 lbs (70.5 kg). Upon preliminary examination, she was found to have bilateral 2 + pitting edema up to the knees, BP 170/94 mm Hg, and crackles on auscultation.

Meds:

Losartan/Hydrochlorothiazide 100/25 mg orally once daily

Simvastatin 40 mg orally daily in the evening

Metformin 500 mg orally twice daily

Glyburide 5 mg orally daily

Metoprolol 25 mg orally twice daily

Allopurinol 300 mg orally daily

Ibuprofen 400 mg orally four times as day as needed for arthritis and fever

What signs and symptoms suggest acute kidney injury (AKI)?

What risk factors does she have for developing AKI?

What additional laboratory information do you need to fully assess the patient?

What questions would you ask her regarding her pharmacotherapy?

as metolazone or hydrochlorothiazide, with a loop diuretic can result in a synergistic increase in urine output. There are no data demonstrating greater efficacy of one distal convoluted tubule diuretic over another. It is common practice to administer these diuretics 30 to 60 minutes prior to the loop diuretic to inhibit sodium reabsorption at the distal convoluted tubule before it is inundated with sodium from the loop of Henle. However, the effectiveness of this strategy has not been studied.

The usual starting dose of IV furosemide for treatment of AKI ranges from 40 to 80 mg (Figure 25–1). Reasonable starting doses for bumetanide and torsemide are 1 mg and 20 mg, respectively.[20] Efficacy of diuretic administration can be determined by assessing a patient's hourly fluid balance. Other methods to minimize volume overload, such as fluid restriction and concentration of IV medications, should be initiated as needed. If urine output does not increase to about 1 mL/kg/h, the diuretic dosage can be increased to a ceiling dose of 160 to 200 mg of furosemide or its equivalent (Figure 25–1).[22] Dosing frequency is based on the patient's response, the ability to restrict sodium intake, and the duration of action of the diuretic. Methods to improve diuresis can be initiated sequentially, such as (a) shortening the dosing interval, (b) adding hydrochlorothiazide or metolazone, and (c) switching to a continuous infusion loop diuretic. Continuous infusion loop diuretics may be easier to titrate than bolus dosing, require less nursing administration time, and may lead to fewer adverse reactions. The hemodynamic and fluid status of the patient should be monitored closely when loop diuretics are administered in high doses or with a continuous infusion, particularly in combination with distal convoluted tubule diuretics. Additionally, the electrolyte status of the patient should be monitored at least daily to prevent profound diuresis and electrolyte abnormalities, such as hypokalemia.

▶ *Other Agents*

Thiazide diuretics, when used as single agents, are generally not effective for fluid removal in patients with AKI. Mannitol is also not recommended for treating volume overload associated with AKI. In patients with renal dysfunction, mannitol excretion is decreased, resulting in expanded blood volume and hyperosmolality. Potassium-sparing diuretics, which inhibit sodium reabsorption in the distal nephron and collecting duct, are not sufficiently effective in removing fluid. In addition, they increase the risk of hyperkalemia in patients already at risk. KEY CONCEPT Thus, loop diuretics are the diuretics of choice for the managing volume overload in AKI.

Low-dose dopamine (LDD), in doses ranging from 0.5 to 3 mcg/kg/min, predominantly stimulates dopamine-1 receptors, leading to renal vasodilation and increased renal blood flow. Although this effect has been substantiated in healthy euvolemic individuals with normal kidney function, there is no conclusive efficacy data in patients with AKI. For this reason, LDD is not indicated for treatment of AKI.

Fenoldopam, a selective dopamine-1 receptor agonist approved for short-term management of severe hypertension, has also been studied for prevention and treatment of AKI. No results from adequately powered, multicenter trials conclusively support its use, and the risk of hypotension further limits routine administration. The current KDIGO Clinical Practice Guidelines do not recommend fenoldopam for prevention or treatment of AKI.[1]

Studies are underway to investigate the utility of atrial natriuretic peptide, a hormone secreted by the heart that generates sodium loss, in prevention or early treatment of AKI.

Nonpharmacologic Treatment

▶ *Renal Replacement Therapy*

RRT may be necessary in patients with established AKI to treat pulmonary edema and volume overload that is unresponsive to diuretics, to minimize accumulation of nitrogenous waste products, and to correct electrolyte and acid–base abnormalities, such as hyperkalemia and metabolic acidosis, while renal function recovers. There is wide variation in practice on indications for RRT, timing of initiation and discontinuation of RRT, intensity of treatment, and optimal type of RRT. Absolute indications for dialysis usually include:

- BUN greater than 100 mg/dL (35.7 mmol/L)
- Potassium greater than 6 mEq/L (mmol/L) with EKG abnormalities
- Magnesium greater than 8 mg/dL (3.29 mmol/L) with anuria and no deep tendon reflexes
- Metabolic acidosis with a pH less than 7.15
- Diuretic-resistant fluid overload.[23]

Approximately 10% to 30% of patients with AKI treated with RRT will not have recovery of kidney function and will need to remain on long-term dialysis.[24]

Two processes for solute removal occur during RRT: diffusion and convection. Diffusion is the movement of molecules from an area of high concentration in the blood to an area of low concentration in the dialysate across a semi-permeable dialysis membrane. Convection is removal of solutes secondarily to fluid removal from ultrafiltration, commonly known as "solute drag."

Two types of RRT modalities are used in AKI: intermittent hemodialysis (IHD) and continuous renal replacement therapy (CRRT). IHD is a higher efficiency form of dialysis that results in fluid removal by ultrafiltration and solute removal by diffusion that is provided for several hours a day at a variable frequency (usually daily or three to five times per week). CRRT is a form of dialysis that provides slow fluid and/or solute removal on a continuous (up to 24-hour) basis. The characteristics of the different types of CRRTs and their associated fluid and solute removal are described in Table 25–2.

The primary advantage of CRRT is hemodynamic stability and better volume control, particularly in patients who are unable to tolerate rapid fluid removal. The primary disadvantages associated with CRRT are continuous nursing requirements, continuous anticoagulation, frequent clotting of the dialyzer, patient immobility, and increased cost. There is no conclusive evidence that one type of dialysis is preferred over another in terms of mortality and recovery of renal function. Thus, selection of CRRT over IHD is often governed by the critical illness of the patient and by the comfort level of the institution with one particular type of dialysis. KDIGO Clinical Practice Guidelines suggest CRRT in hemodynamically unstable patients.[1] Mortality in critically ill patients receiving CRRT is 40% to 53%.[25]

▶ *Supportive Therapy*

Supportive therapy in AKI includes adequate nutrition, correction of electrolyte and acid–base abnormalities (particularly hyperkalemia and metabolic acidosis), fluid management, and correction of any hematologic abnormalities. Because AKI can be associated with multiorgan failure, treatment may include the medical management of infections, cardiovascular and GI conditions, and respiratory failure.

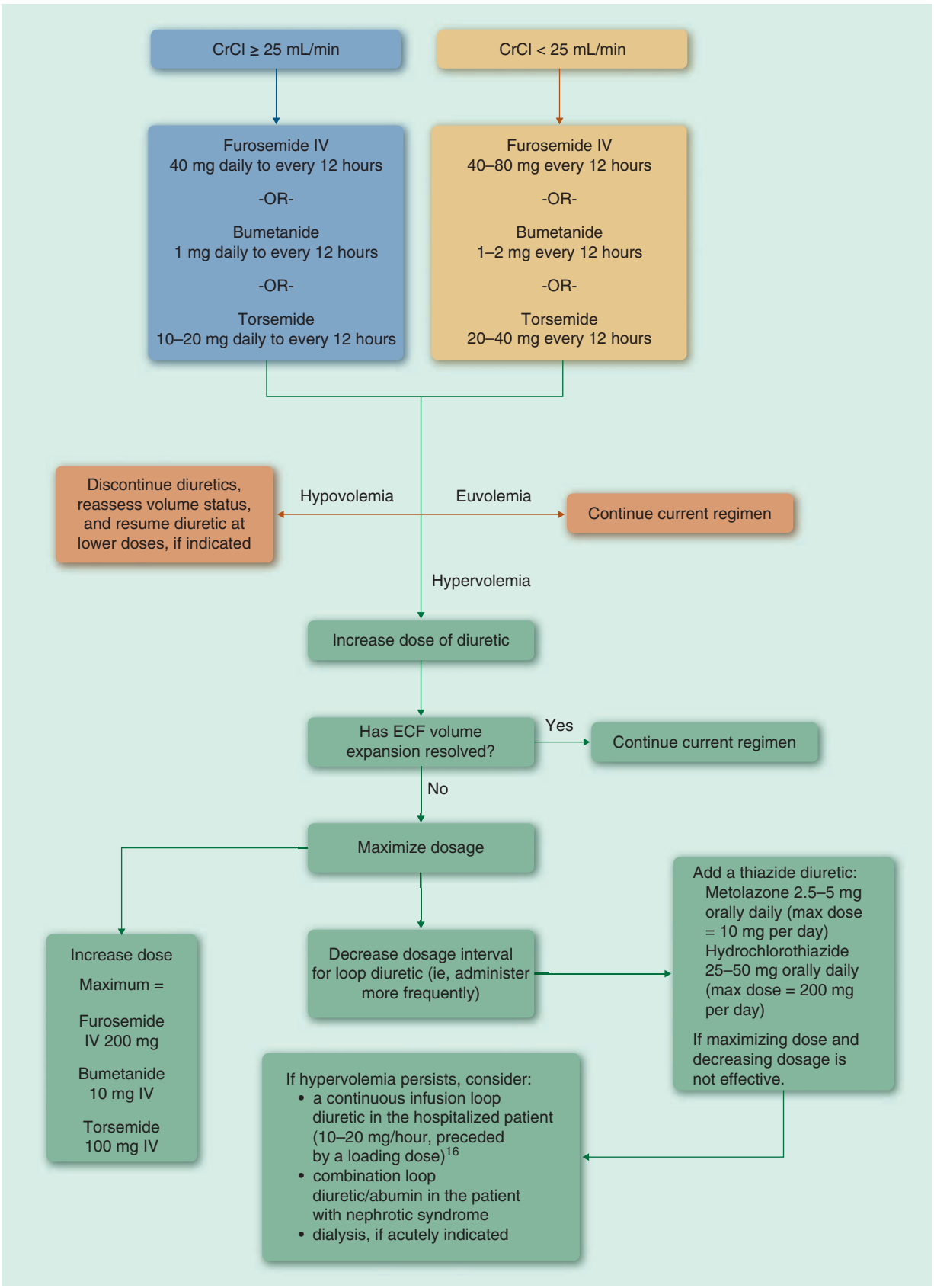

FIGURE 25–1. Algorithm for treatment of extracellular fluid expansion. (CrCl, creatinine clearance; ECF, extracellular fluid.)

Table 25–2

Modalities for Continuous Renal Replacement Therapy

		Technique		Process of Solute Removal		
Type of CRRT	Abbreviation	Filtration	Dialysis	Convection	Diffusion	Description
Slow **C**ontinuous **U**ltra**f**iltration	SCUF	√		√ (limited)		Low rate of fluid removal without significant solute removal
Continuous **V**eno**v**enous **H**emofiltration	CVVH	√		√		Higher rate of fluid removal and solute removal (small and large molecule)
Continuous **V**eno**v**enous **H**emo**d**ialysis	CVVHD		√		√	Diffusive removal of solutes (small molecule) with limited fluid removal
Continuous **V**eno**v**enous **H**emo**d**ia**f**iltration	CVVHDF	√	√	√	√	Fluid removal and removal of solutes (small and large molecule) via diffusion (dialysis)

Historically, patients were often placed on a protein-restricted diet to avoid the production of uremic toxins and minimize the rise in BUN. However, adequate protein intake should be administered to maintain metabolic balance. Protein intake of 0.8 to 1 g/kg/day is recommended in patients with AKI who are not undergoing dialysis, and higher protein intake in patients undergoing RRT or who are hypercatabolic.[1] Some studies have shown a beneficial effect of tight glycemic control on decreasing the incidence and severity of AKI, whereas others have shown a higher incidence of hypoglycemia. Thus, glycemic control in the range of 110 to 149 mg/dL (6.1–8.3 mmol/L) is recommended.[1]

PREVENTION OF ACUTE KIDNEY INJURY

KEY CONCEPT It is critically important to identify patients at high risk for developing AKI and to implement preventive methods to decrease its occurrence or severity.

Avoidance of Nephrotoxic Medications

The best preventive measure for AKI, especially in individuals at high risk, is to avoid medications known to precipitate AKI. Nephrotoxicity is a significant side effect of aminoglycosides, ACE inhibitors, ARBs, amphotericin B, NSAIDs, cyclosporine, tacrolimus, and radiographic contrast agents.[6] Unfortunately,

Patient Encounter Part 2: Medical History and Physical Examination

PMH: Type 2 diabetes mellitus for 10 years (labs from 3 months ago: A1C 7.4% [0.074; 57 mmol/mol hemoglobin], SCr 1.0 mg/dL [88 µmol/L])

Dyslipidemia for 10 years

Hypertension for 20 years

Gout

Osteoarthritis

FH: Father with history of type 2 diabetes and chronic kidney disease; mother with history of hypertension

SH: No smoking, no alcohol use

PE:

VS: BP 170/94 mm Hg, pulse 85 bpm, RR 22/min, temperature 37.6°C, Wt 70.5 kg (155 lb), Ht 5′4″ (163 cm)

Chest: Basilar crackles, inspiratory wheezes

CV: RRR, S_1 and S_2 normal

MS/Ext: bilateral 2 + pitting edema up to the knees

Urinalysis: Color, yellow; character, hazy; glucose (–); ketones (–); specific gravity 1.010; pH 5; (+) protein; no bacteria; nitrite (–); blood (–); osmolality 325 mOsm/kg (mmol/kg); urinary sodium 77 mEq/L (mmol/L); creatinine 25 mg/dL (2210 µmol/L)

Laboratory values: Sodium 136 mEq/L (mmol/L), potassium 5.0 mEq/L (mmol/L), chloride 105 mEq/L (mmol/L), bicarbonate 22 mEq/L (mmol/L), BUN 35 mg/dL (12.5 mmol/L), SCr 1.5 mg/dL (133 µmol/L), magnesium 1.6 mg/dL (0.66 mmol/L), glucose 120 mg/dL (6.7 mmol/L), WBC 8.0 × 10^3/mm^3 (8.0 × 10^9/L), hemoglobin 14.4 g/dL (144 g/L; 8.94 mmol/L), hematocrit 42% (0.42).

Interview information: Patient takes all of her medications as prescribed. She has been taking all of her medications for years, with the exception of ibuprofen. She started taking it for osteoarthritis last month, and then 3 to 4 doses over the past few days to treat her fever. She checks her fasting glucose each morning. It ranges from 110 to 125 mg/dL (6.1–6.9 mmol/L). She also checks it in the afternoons and it runs low 4 to 5 times per week (in the range of 60 to 70 mg/dL [3.3–3.9 mmol/L]).

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

an effective, nonnephrotoxic alternative may not always be appropriate for a given patient, and the risks and benefits of selecting a drug with nephrotoxic potential must be considered. For example, serious gram-negative infections may require double antibiotic coverage, and an aminoglycoside may be necessary based on culture and sensitivity reports. Monitoring of serum aminoglycoside concentrations is warranted in these situations.

▶ *Drug-Induced AKI*

Aminoglycosides Aminoglycosides (gentamicin, tobramycin, and amikacin) cause nonoliguric intrinsic AKI in about 10% to 25% of treated patients.[26] Injury is due to binding of aminoglycosides to proximal tubular cells in the renal cortex, with subsequent cellular uptake and cell death. In addition, aminoglycosides cause renal vasoconstriction and mesangial contraction.[27] In clinical practice, all aminoglycosides have comparable nephrotoxicity; thus, similar precautions should be used for all of the agents. Risk factors for aminoglycoside-induced AKI include high cumulative drug exposure, prolonged course of therapy (typically after 7 to 10 days of therapy), preexisting CKD, increased age, and concurrent administration of other nephrotoxic drugs. If feasible, alternative antibiotics should be selected in individuals at high risk for developing AKI.

Methods to minimize drug exposure with conventional dosing (multiple doses per day) include maintaining trough concentrations less than 2 mcg/mL (mg/L; 4.2 µmol/L) for gentamicin and tobramycin and less than 10 mcg/mL (mg/L; 17.1 µmol/L) for amikacin, minimizing length of therapy, and avoiding repeated courses of aminoglycosides. Concurrent exposure to other nephrotoxic medications and dehydration may also worsen AKI. There is conflicting evidence as to whether the combination of vancomycin and an aminoglycoside has a higher incidence of AKI than aminoglycoside therapy alone. Aminoglycoside-induced AKI is usually reversible upon drug discontinuation; however, dialysis may be needed in some individuals while kidney function improves.

Aminoglycosides demonstrate concentration-dependent killing and a prolonged postantibiotic effect.[28] Extended-interval (eg, once daily) aminoglycoside dosing reduces the incidence of nephrotoxicity by providing high transient concentrations of drug that saturate proximal tubule uptake sites. Once saturated, the remaining aminoglycoside molecules pass through the proximal tubule and are excreted in the urine.[28] Thus, less drug is available for cellular uptake during a 24-hour period. Extended-interval aminoglycoside dosing is as effective as conventional dosing and is not more nephrotoxic; some studies have shown it to be less nephrotoxic than conventional dosing. Extended-interval dosing is not recommended for patients with preexisting kidney disease, conditions where high concentrations are not needed (eg, urinary tract infections), hyperdynamic patients who may demonstrate increased drug clearance (eg, burn patients), and others where you would suspect altered pharmacokinetics or increased risk of ototoxicity.

Amphotericin B The reported incidence of amphotericin B-induced AKI varies widely in the literature, from about 30% to as high as 80% of patients treated with the conventional desoxycholate formulation.[28] Nephrotoxicity is due to renal arterial vasoconstriction and distal renal tubule cell damage. Risk factors for development of AKI include high daily dosage, large cumulative dose (> 2 to 3 g), preexisting kidney dysfunction, dehydration, and concomitant use of other nephrotoxic drugs. Tubular abnormalities manifesting as hypomagnesemia and hypokalemia often occur within the first 2 weeks of treatment, followed by the overt development of AKI.

Three lipid-based formulations of amphotericin B have been developed in an attempt to improve efficacy and limit toxicity, particularly nephrotoxicity: (1) amphotericin B lipid complex, (2) liposomal amphotericin B, and (3) amphotericin B cholesteryl sulfate (no longer available in the United States). The reported incidence of nephrotoxicity ranges from 15% to 25% with these formulations. The mechanism for decreased nephrotoxicity is thought to be due to preferential delivery of amphotericin B to the site of infection, with less affinity for the kidney.[30] Costs for lipid-based formulations are significantly higher than for the conventional formulation; thus, lipid-based formulations are typically recommended for individuals with risk factors for AKI. Administration of IV normal saline (1 L during the course of therapy) may also attenuate nephrotoxicity associated with amphotericin B.

It is unclear whether there are significant differences in nephrotoxicity among the lipid-based formulations. In a meta-analysis of eight studies evaluating the nephrotoxicity of liposomal amphotericin B compared with amphotericin B lipid complex, nephrotoxicity was similar.[31] However, large prospective studies are needed to definitively ascertain differences in nephrotoxicity among liposomal formulations.

Radiocontrast Agents Radiocontrast agents are administered during radiologic studies and are associated with a well-documented risk of contrast-induced AKI (CI-AKI). Although definitions vary, CI-AKI is frequently defined as a rise in SCr of at least 0.5 mg/dL (44 µmol/L) or a 25% increase in SCr within 48 hours of contrast administration. Patient-related risk factors for CI-AKI are CKD, diabetes, dehydration, older age, concomitant nephrotoxic drug administration, and high doses of contrast dye.[32]

Contrast agents are water-soluble, triiodinated, benzoic acid salts. Nephrotoxicity results from both ischemia and direct proximal tubule toxicity, with a resultant decrease in GFR and increase in SCr within 24 to 48 hours of the damage.[33] The incidence of nephrotoxicity with ionic and nonionic agents is similar in patients at low risk for developing AKI; however, in high-risk patients, nephrotoxicity is significantly greater when high ionic, high osmolar contrast agents are used. The cost of nonionic agents is approximately 10-fold higher, and their use is usually limited to high risk patients.

LO 4 Therapeutic measures to decrease the incidence of CI-AKI include extracellular volume expansion with isotonic solution, judicious use of contrast media, and use of nonionic contrast agents in high-risk patients.[34] Treatment with oral acetylcysteine has produced mixed results. Theophylline, fenoldopam, furosemide, mannitol, dopamine, statins, vitamins C and E, and calcium antagonists have been studied, but with no strong evidence that these agents prevent CI-AKI.[32, 35]

LO 4 KEY CONCEPT The most effective therapeutic maneuver to decrease the incidence of CI-AKI is extracellular volume expansion with an isotonic solution.[35] Hydration with normal saline or sodium bicarbonate is recommended.[36,37] Sodium bicarbonate may have the theoretical benefit of alkalinizing renal tubule fluid, which is thought to reduce the formation of oxygen free radicals. However, studies comparing sodium chloride to sodium bicarbonate have produced conflicting results.[1] The KDIGO Clinical Practice Guidelines workgroup recommends either agent until more definitive data is available.[1] The infusion should begin from 3 to 12 hours before the procedure and continue for 6 to 12 hours afterward to achieve a urine flow rate of at least 150 mL per hour.[1]

Fluid should be administered cautiously to patients with CHF, left ventricular dysfunction, and significant renal dysfunction.

Because production of reactive oxygen species has been implicated in the pathophysiology of contrast-induced AKI, prophylactic administration of the antioxidant acetylcysteine has been investigated, usually in combination with hydration. LO 4 Doses of acetylcysteine in clinical studies ranged from 600 to 1200 mg orally every 12 hours for 2 days, with the first one or two doses administered prior to the contrast procedure. A plethora of studies evaluating the efficacy of oral acetylcysteine have been conducted with mixed results.[38,39] The KDIGO Clinical Practice Guidelines suggest that oral acetylcysteine can be used in combination with IV fluids in patients at risk for CI-AKI due to its low risk of adverse effects and low cost.[1] It is not considered a replacement for adequate hydration, which remains the standard of care for prevention of CI-AKI.

Cyclosporine and Tacrolimus The calcineurin inhibitors cyclosporine and tacrolimus are administered as part of immunosuppressive regimens in kidney, liver, heart, lung, and bone marrow transplant recipients. They are also used in autoimmune disorders such as psoriasis and multiple sclerosis. The pathophysiologic mechanism for AKI is renal afferent arteriole vasoconstriction and ATN.[40,41] AKI often occurs within the first 6 to 12 months of treatment and can be reversible with dose reduction or drug discontinuation.[40] Risk factors include high dose, elevated trough blood concentrations, increased age, and concomitant therapy with other nephrotoxic drugs.[41] Cyclosporine and tacrolimus are extensively metabolized by the liver through the cytochrome P450 3A pathway; drugs that inhibit their metabolism (eg, erythromycin, clarithromycin, fluconazole, ketoconazole, verapamil, diltiazem, nicardipine) can increase blood concentrations of cyclosporine and tacrolimus and precipitate AKI. Pharmacogenetic variability in drug absorption and metabolism can also alter blood concentrations.

Careful monitoring of cyclosporine or tacrolimus trough concentrations and maintaining them in the target range can reduce the occurrence of AKI; however, AKI can still occur with therapeutic or even low blood concentrations. Calcium channel blockers may have a renoprotective effect through dilation of the afferent arterioles and are often used preferentially as antihypertensive agents in kidney transplant recipients.[42] However, the calcineurin inhibitor dose would need to be reduced to avoid high blood concentrations because of reduced metabolism.

It is often difficult to differentiate AKI from acute organ rejection in kidney transplant recipients because the conditions may present with similar symptoms and physical examination findings. However, fever and graft tenderness are more likely to occur with rejection, whereas neurotoxicity is more likely to occur with cyclosporine or tacrolimus toxicity. Kidney biopsy is often needed to confirm the diagnosis of rejection.

ACE Inhibitors and ARBs In instances of decreased renal blood flow (eg, kidney disease, renal artery stenosis, CHF, volume depletion), production of angiotensin II increases, causing efferent arteriole vasoconstriction and maintenance of glomerular capillary pressure and GFR. However, ACE inhibitors decrease angiotensin II synthesis, and ARBs block the action of angiotensin II at the receptor, which results in dilation of efferent arterioles, a reduction in glomerular capillary pressure, and a decrease in GFR.[29]

When initiating therapy with an ACE inhibitor or ARB for management of hypertension or prevention of CKD progression, a modest increase in SCr should be anticipated within the first week of starting therapy in predisposed individuals.[29] However, an increase of greater than 30% that does not plateau after several weeks of therapy suggests AKI, and the drug should be discontinued.[29] Risk factors for developing AKI are preexisting renal dysfunction, severe atherosclerotic renal artery stenosis, volume depletion, and severe CHF. Discontinuation of the drug usually results in return to baseline kidney function. Initiating therapy with low doses of a short-acting agent such as captopril is recommended for patients at risk of developing AKI. If tolerated, patients can later be converted to a longer-acting agent.

Nonsteroidal Anti-inflammatory Drugs Traditional non-selective NSAIDs (eg, ibuprofen, naproxen, sulindac) and the cyclooxygenase-2 (COX-2) selective inhibitor celecoxib can cause prerenal AKI through inhibition of prostaglandin-mediated renal vasodilation.[29] Risk factors are similar to those for ACE inhibitors and ARBs. Concurrent use of NSAIDs in patients on diuretics and ACE inhibitors or ARBs results in increased risk of AKI, particularly within the first 30 days of co-administration.[43]

The onset of AKI is often within days of initiating therapy, and patients typically present with oliguria, which is usually reversible with drug discontinuation. COX-2 selective inhibitors and traditional nonselective NSAIDs pose similar risk for AKI.

Patient Encounter Part 3: Follow-Up

The patient is admitted to the hospital for treatment of AKI.

Based on the information available, create a care plan for this patient's AKI and provide overall recommendations for her drug therapy. The plan should include (a) a statement of the drug-related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

OUTCOME EVALUATION

LO 5 Goals of therapy are to maintain a state of euvolemia with good urine output (at least 0.5 to 1 mL/kg/h), to return SCr to baseline, and to correct electrolyte and acid–base abnormalities. Additional goals include appropriate drug dosages based on kidney function and avoidance of nephrotoxic drugs. Assess vital signs, weight, fluid intake, urine output, BUN, creatinine, and electrolytes daily in unstable patients.

LO 5 In patients with volume overload, monitoring includes body weight changes, fluid input compared to urine output, signs of pulmonary and peripheral edema, and blood pressure.

DRUG DOSING CONSIDERATIONS IN AKI

Assessment of Kidney Function

Appropriate drug dosing in kidney disease requires an accurate assessment of kidney function. The best index of overall kidney function is GFR. Defined as the volume of plasma filtered across the glomerulus per unit time, GFR correlates with the excretory, endocrine, and metabolic functions of the kidney. Creatinine clearance (CrCl) is routinely used as a measure of kidney function for the purposes of drug dosing; however, equations to estimate CrCl (eg, Cockcroft–Gault equation) are not accurate or reliable in AKI, particularly in critically ill patients because they tend to overestimate CrCl.[44,45] Use of such equations should be limited to instances when SCr is at steady state, with no more than a 10% to 15% change in serum creatinine within 24 hours.

Measurement of 24-hour urinary creatinine clearance may be more accurate, and is calculated by the following formula:

$$\text{Measured CrCl (mL/min)} = \frac{[\text{Urine creatinine concentration (mg/dL)} \times \text{urine volume (mL)}]}{[\text{Plasma creatinine concentration (mg/dL)} \times \text{time (minutes)}]}$$

One study evaluated an abbreviated CrCl urinary measurement (eg, 4 hours) in critically ill patients which allowed early detection of AKI.[46] Equations and creatinine clearance measurements that rely on a single SCr will usually overestimate kidney function.

As part of kidney function test results, many laboratories report an estimated GFR (eGFR), typically calculated from the Modification of Diet in Renal Disease Study (MDRD) equation. This estimation is not accurate in AKI because nonsteady state conditions for serum creatinine are present, leading to inaccurate estimates.

Several equations (Jelliffe, Brater, Chiou) have been used to assess fluctuating or unstable kidney function. These equations estimate CrCl by considering the change in serum creatinine over a specified time period. These methods have not been validated, and drug dosage adjustments based on CrCl estimates from these formulas in patients with AKI have not been evaluated.

Factors Influencing Drug Dosing in AKI

Determining the optimal dose of drugs in AKI is challenging. A variety of factors influence drug dosing, such as (1) alterations in drug pharmacokinetics that occur during AKI, (2) difficulties in accurately quantifying kidney function in AKI, (3) the influence of intermittent or continuous RRT on drug clearance, and (4) challenges in interpreting information from the literature and applying it to a specific patient. See Table 25–3 for a more complete list of considerations when dosing medications in patients with AKI.

For drugs with a narrow therapeutic window, serum drug concentration monitoring may be available to guide drug dosing. If this is not available, dosing based on an estimated CrCl is recommended, with frequent reassessment of kidney function and evaluation of the patient's status to assess efficacy and adverse effects of therapy. Selection of a drug with hepatic elimination rather than renal excretion is a reasonable alternative, if possible.

In critically ill septic patients, interpatient variability in pharmacokinetics renders dosing of antibiotics difficult. Underdosing a critically ill patient may be a greater risk than potential adverse effects attributed to higher plasma concentrations, particularly with antibiotics such as beta lactams, quinolones, and carbepenems, for which therapeutic drug monitoring is not available.[47] Thus, the risk of undertreatment of the infection needs to be balanced with the risk of adverse effects from the antimicrobial agent.

DRUG DOSING CONSIDERATIONS IN DIALYSIS

Several characteristics of a drug influence its removal during dialysis: percentage of drug eliminated by the kidney, volume of distribution, and protein binding. Drug elimination is greater when renal clearance accounts for 30% or more of total body clearance of the drug, volume of distribution is less than 1 L/kg, and protein binding is less than 50%.[48] Other factors that affect drug clearance include type of RRT (ie, IHD, CVVH, CVVHD); permeability of the dialysis membrane; and blood, ultrafiltrate, and dialysate flow rates. Higher permeable filters result in greater drug elimination than lower permeable membranes, particularly for middle molecular weight drugs, such as vancomycin, that can pass through the pores of higher permeable filters.[49]

CRRT procedures that rely on convection for solute removal (eg, CVVH, CVVHDF) result in greater solute removal than procedures utilizing diffusion (eg, CVVHD, IHD). At low dialysate and/or ultrafiltration rates, drug clearance may be similar. However, at higher rates, drug removal with CVVH and CVVHDF is greater than with CVVHD.[49] Furthermore, creatinine clearance can be roughly approximated in CRRT by summing the dialysate and ultrafiltration rates, which may assist with initial drug dosing.[49] In the case of antibiotics, residual renal function, the seriousness of the infection, the minimum inhibitory concentration (MIC) of the organism, and the clinical status of the patient must also be considered to avoid underdosing the patient.

Table 25–3

Drug Dosing Considerations in AKI

Alteration in drug pharmacokinetics	• Increase in volume of distribution due to fluid retention may occur. • Reduction in excretion of both drugs and metabolites eliminated by the kidney. • Nonrenal clearance of some drugs may be reduced.
Difficulty in quantifying an accurate assessment of kidney function in AKI	• Cockcroft-Gault and MDRD equations are not meant for AKI population; equations are based on a single SCr. • SCr as a marker for kidney function is influenced by nonrenal factors (such as nutritional status and liver function). • Equations to estimate kidney function in cases of changing kidney function have not been well studied.
AKI patients undergoing dialysis	• Different types of dialysis modalities result in differences in drug removal (eg, IHD vs. CRRT). • Differences in intensity of dialysis dose may affect drug removal (eg, length of dialysis treatment, blood and dialysate flow rate). • Populations studied in the literature are likely to be different than the specific patient being treated (eg, different types of dialysis, length of treatment).
Textbook dosing and literature recommendations	• Studies in patients with AKI are sparse. • Many drug information resource recommendations on dosing are based on the manufacturer's original pharmacokinetics information, often in patients with chronic kidney disease. • Most drug dosing guidelines were developed prior to standardization of SCr measurements between labs; thus today's SCr measurements are 5% to 10% higher than those reported prior to 2010.[49] • There is growing support for incorporation of the MDRD equation in future pharmacokinetic studies and to guide drug dosing, although use of this equation is limited to chronic kidney disease.

MDRD, Modification of Diet in Renal Disease Study equation; SCr, serum creatinine.

Patient Care Process

Collect Information:

- Obtain a thorough and accurate drug history including the use of nonprescription drugs such as NSAIDs.
- Review the medical history, physical examination findings, and laboratory tests.

Assess the Information:

- Assess kidney function by evaluating a patient's signs and symptoms, laboratory test results (eg, SCr, BUN, electrolytes), and urinary indices; calculate creatinine clearance, if appropriate.
- Assess whether any current medications may be contributing to AKI. Consider not only drugs that can directly cause AKI (eg, aminoglycosides, amphotericin B, NSAIDs, cyclosporine, tacrolimus, ACE inhibitors, and ARBs) but also drugs that can predispose a patient to nephrotoxicity or prerenal AKI (ie, diuretics and antihypertensive agents).
- Based on physical examination and review of systems, determine whether the patient is experiencing hypervolemia or hypovolemia as a consequence of AKI.

Develop a Care Plan:

- Determine if any drugs need to be discontinued, or alternative drugs selected, to prevent worsening of kidney function based on the assessment of kidney function.
- Determine if any drugs undergo significant kidney elimination and require dosage reduction or specific monitoring during AKI.
- Determine if additional therapy is warranted. For example, determine if a patient should receive hydration (for volume depletion) or a loop diuretic (for volume overload).

Implement the Care Plan:

- Adjust drug dosages based on estimated kidney function or evidence of adverse drug reactions or interactions.
- Provide supportive therapy, including adequate nutrition, correction of electrolyte and acid–base abnormalities (particularly hyperkalemia and metabolic acidosis), fluid management, and correction of any hematologic abnormalities.
- Implement preventative strategies to decrease the risk of AKI, such as administration of saline with contrast media.
- Educate the patient and/or caregiver about changes in drug therapy, potential adverse effects related to new medications, and how to manage adverse effects that may occur.

Follow-up: Monitor and Evaluate:

- Monitor the patient's weight, urine output, electrolytes (such as potassium), and blood pressure to assess efficacy of the medication regimen.
- Monitor SCr to evaluate whether kidney function is worsening or improving.
- Review and encourage medication adherence.

Drug information references provide drug dosing recommendations in IHD and CRRT; however, they must be interpreted cautiously due to the variability in dialysis techniques used. Referring to more than one drug information resource is recommended due to variability in published recommendations.[49]

Abbreviations Introduced in This Chapter

ACE	Angiotensin-converting enzyme
AKI	Acute kidney injury
ARB	Angiotensin II receptor blocker
ARF	Acute renal failure
ATN	Acute tubular necrosis
BUN	Blood urea nitrogen
CHF	Congestive heart failure
CI-AKI	Contrast-induced acute kidney injury
CKD	Chronic kidney disease
CrCl	Creatinine clearance
CRRT	Continuous renal replacement therapy
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
FENa	Fractional excretion of sodium
GFR	Glomerular filtration rate
IHD	Intermittent hemodialysis
KDIGO	Kidney Disease: Improving Global Outcomes
JVD	Jugular venous distention
LDD	Low-dose dopamine
NSAIDs	Nonsteroidal anti-inflammatory drugs
RIFLE	Risk, Injury, Failure, Loss, and End-stage
RRT	Renal replacement therapy
SCr	Serum creatinine concentration

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1–138.
2. Lewington AJ, Cerda J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. Kidney Int. 2013;84:457–467.
3. Hoste EA, Bagshaw SM, Bellomo R, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41:1411–1423.
4. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. Clin J Am Soc Nephrol. 2014;9:1007–1014.
5. Mehta RL, Kellum JA, Shah SV, et al.; Acute Kidney Injury Network. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31.
6. Himmelfarb J, Joannidis M, Molitoris B, et al. Evaluation and initial management of acute kidney injury. Clin J Am Soc Nephrol. 2008;3:962–967.
7. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet 2005;365:417–430.
8. Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. Kidney Int. 2012;81:819–825.
9. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. Kidney Int. 2015;87:62–73.

10. Bellomo R, Kellum JA, Ronco C. Defining acute renal failure: physiologic principles. Intensive Care Med. 2004;30:33–37.
11. Alge JL, Arthur JM. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. Clin J Am Soc Nephrol. 2015;10:147–155.
12. Vijayan A, Faubel S, Askenazi DJ, et al.; American Society of Nephrology Acute Kidney Injury Advisory Group. Clinical use of the urine biomarker [TIMP-2] x [IGFBP7] for acute kidney injury risk assessment. Am J Kidney Dis. 2016;68:19–28.
13. Koyner AL, Davison DL, Brasha-Mitchell E, et al. Furosemide stress test and biomarkers for the prediction of AKI severity. J Am Soc Nephrol. 2015;26:2023–2031.
14. Godin M, Bouchard J, Mehta RL. Fluid balance in patients with acute kidney injury: emerging concepts. Nephron Clin Pract. 2013;123:238–245.
15. Besen BA, Gobatto AL, Meiro LM, Maciel AT, Park M. Fluid and electrolyte overload in critically ill patients: an overview. World J Crit Care Med. 2015;4:116–129.
16. Teixeira C, Garzotto F, Piccinni P, et al.; NEFROlogia e Cura INTensiva (NEFROINT) investigators. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care. 2013;17:R14.
17. De Backer D, Biston P, Devriendt J, et al.; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–789.
18. Ejaz AA, Mohandas R. Are diuretics harmful in the management of acute kidney injury? Curr Opin Nephrol Hyperten. 2014:23:155–160.
19. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380:756–766.
20. Brater DC. Update in diuretic therapy: clinical pharmacology. Semin Nephrol. 2011;31:483–494.
21. Asare K. Management of loop diuretic resistance in the intensive care unit. Am J Health Syst Pharm. 2009;66:1635–1640.
22. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line? Ann Pharmacother. 2009;43:1836–1847.
23. Gibney N, Hoste E, Burdmann EA, et al. Timing of initiation and discontinuation of renal replacement therapy in AKI: unanswered key questions. Clin J Am Soc Nephrol. 2008;3:876–880.
24. Cerdá J, Liu KD, Cruz DN, et al.; AKI Advisory Group of the American Society of Nephrology. Promoting kidney function recovery in patients with AKI requiring RRT. Clin J Am Soc Nephrol. 2015;10:1859–1867.
25. Allegretti AS, Steele DJ, David-Kasdan JA, Bajwa E, Niles JL, Bhan I. Continuous renal replacement therapy outcomes in acute kidney injury and end-stage renal disease: a cohort study. Crit Care. 2013;17:R109.
26. Pagkalis S, Mantadakis E, Mavros MN, Ammari C, Falagas ME. Pharmacological considerations for the proper clinical use of aminoglycosides. Drugs. 2011;71:2277–2294.
27. Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney Int. 2011;79:33–45.
28. Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. Crit Care Med. 2008;36:S216–S223.
29. Sadfar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B. Medicine (Baltimore). 2010;89:236–244.
30. Hamill RJ. Amphotericin B formulations: a comparative review of efficacy and toxicity. Drugs. 2013;73:919–934.
31. Moen MD, Lyseng-Williamson KA, Scott LJ. Liposomal amphotericin B: a review of its use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal infections. Drugs. 2009;69:361–392.
32. Ozkok S, Ozkok A. Contrast-induced acute kidney injury: a review of practical points. World J Nephrol. 2017;6:86–99.
33. McCullough PA, Choi JP, Feghali GA, et al. Contrast-induced acute kidney injury. J Am Coll Cardiol. 2016;68:1465–1473.
34. Au TH, Bruckner A, Mohiuddin SM, Hilleman DE. The prevention of contrast-induced nephropathy. Ann Pharmacother. 2014;48:1332–1342.
35. Vanmassenhove J, Vanholder R, Lameire N. Statins for the prevention of contrast-induced acute kidney injury. Curr Opin Nephrol Hypertens. 2016;25:508–517.
36. Solomon R, Gordon P, Manoukian SV, et al.; BOSS Trial Investigators. Randomized trial of bicarbonate or saline study for the prevention of contrast-induced nephropathy in patients with CKD. Clin J Am Soc Nephrol. 2015;10:1519–1524.
37. Maioli M, Toso A, Leoncini M, et al. Sodium bicarbonate versus saline for the prevention of contrast-induced nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. J Am Coll Cardiol. 2008;52:599–604.
38. Wu MY, Hsiang HF, Wong CS, et al. The effectiveness of N-Acetylcysteine in preventing contrast-induced nephropathy in patients undergoing contrast-enhanced computed tomography: a meta-analysis of randomized controlled trials. Int Urol Nephrol. 2013;45:1309–1318.
39. Li JX, Jin EZ, Yu LH, et al. Oral N-acetylcysteine for prophylaxis of contrast-induced nephropathy in patients following coronary angioplasty: a meta-analysis. Exp Ther Med. 2017;14:1568–1576.
40. Pallet N, Djamali A, Legendre C. Challenges in diagnosing acute calcineurin-inhibitor induced nephrotoxicity: from toxicogenomics to emerging biomarkers. Pharmacol Res. 2011;64:25–30.
41. de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. Am J Kidney Dis. 2000;35:333–346.
42. Rossi AP, Vella P. Hypertension, living kidney donors, and transplantation: where are we today? Adv Chronic Kidney Dis. 2015;22:154–164.
43. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ. 2013;346:e8525.
44. Bragadottir G, Redfors B, Ricksten SE. Assessing glomerular filtration rate (GFR) in critically ill patients with acute kidney injury—true GFR versus urinary creatinine clearance and estimating equations. Crit Care. 2013;17:R108.
45. Bouchard J, Macedo E, Soroko S, et al.; Program to Improve Care in Acute Renal Disease. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. Nephrol Dial Transplant. 2010;25:102–107.
46. Pickering JW, Frampton CM, Walker RJ, Shaw GM, Endre ZH. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. Crit Care. 2012;16:R107.
47. Blot S, Lipman J, Roberts DM, Roberts JA. The influence of acute kidney injury on antimicrobial dosing in critically ill patients: are dose reductions always necessary? Diagn Microbiol Infect Dis. 2014;79:77–84.
48. Susla GM. The impact of continuous renal replacement therapy on drug therapy. Clin Pharmacol Ther. 2009;86:562–565.
49. Churchwell MD, Mueller BA. Drug dosing during continuous renal replacement therapy. Semin Dialysis. 2009;22:185–188.

26 Chronic and End-Stage Renal Disease

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LEARNING OBJECTIVES

LO

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

1. List the risk factors that increase susceptibility for chronic kidney disease (CKD).
2. Explain the mechanisms associated with progression of CKD.
3. Outline the desired outcomes for treatment of CKD.
4. Develop a therapeutic approach to slow progression of CKD including lifestyle modifications and pharmacologic therapies.
5. Identify specific consequences associated with CKD.
6. Design an appropriate therapeutic approach for specific consequences associated with CKD.
7. Recommend an appropriate monitoring plan to assess the effectiveness of pharmacotherapy for CKD and specific consequences.
8. Educate patients with CKD about the disease state, the specific consequences, lifestyle modifications, and pharmacologic therapies used for treatment of CKD.

INTRODUCTION

The kidney is made up of approximately 2 million **nephrons** that are responsible for filtering, reabsorbing, and excreting solutes and water. The kidney has three primary functions: excretory (excrete fluid, electrolytes, and solutes); metabolic (metabolize vitamin D and some drugs, such as insulin and some beta-lactams); and endocrine (produce **erythropoietin** [EPO]). As the number of functioning nephrons declines, the primary functions of the kidney that are affected include:

- Production and secretion of EPO
- Activation of vitamin D
- Regulation of fluid and electrolyte balance
- Regulation of acid–base balance

Chronic kidney disease (CKD) is defined as abnormalities in the structure or function of the kidney, present for 3 months or more, with implications for health.[1] Markers of structural abnormalities include albuminuria (30 mg/24 hours or more or an albumin:**creatinine** ratio [ACR] of more than 30 mg/g [or 3.5 mg/mmol for female and 2.5 mg/mmol for male, but varies between different guidelines and location]); hematuria or casts in urine sediment; electrolyte and other abnormalities caused by renal tubular disorders; abnormalities detected by histology or imaging; or history of kidney transplantation. Functional abnormalities are indicated by a decline in **glomerular filtration rate** (GFR) less than 60 mL/min/1.73m^2 (0.58 mL/s/m^2). Generally, CKD is a progressive decline in kidney function (number of functioning nephrons) that occurs over several months to years. A rapid decline in kidney function over days to weeks is known as acute kidney injury (AKI), which is discussed in Chapter 25. Because the decline in kidney function in CKD is often irreversible, treatment of CKD is aimed at slowing the progression to end-stage kidney disease (ESKD).

EPIDEMIOLOGY AND ETIOLOGY

The United States Renal Data System (USRDS), using data from the National Health and Nutrition Examination Survey (NHANES), estimates the prevalence of CKD in the United States is 14.8%, corresponding to nearly 47 million people.[2] CKD is more common in people over age 60 years and African Americans. Diabetes increases the risk of developing CKD by more than threefold and hypertension increases the risk more than twice than those who do not have either disease.[2]

KEY CONCEPT The Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group developed a classification system for CKD.[1] The staging system defines the stages of CKD based on cause and GFR category (Table 26–1). The GFR is calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study equation[3]:

$$GFR = 175 \times (SCr)^{-1.154} \times (age)^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if African American})$$

Alternatively, GFR can be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)[1]:

$$GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if African American]}$$

where, κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{Cr}/κ or 1.

KEY CONCEPT CKD is a progressive disease that eventually leads to ESKD. The prevalence of ESKD has increased every year since 1980 to over 700,000 people in 2015 with over 124,000 new cases of ESKD diagnosed in 2015.[2] The prevalence of ESKD is related to ethnicity, affecting 9.5 times more American Indians/Alaska Natives, 3.7 times more African Americans, 1.5 times more Asians, and 1.4 more Hispanics as whites.[2]

Table 26–1

GFR Categories in CKD

GFR Category	GFR (mL/min/1.73 m²)	GFR (mL/s/m²)	Terms
G1[a]	≥ 90	≥ 0.87	Normal or high
G2[a]	60–89	0.58–0.86	Mildly decreased
G3a	45–59	0.43–0.57	Mildly to moderately decreased
G3b	30–44	0.29–0.42	Moderately to severely decreased
G4	15–29	0.14–0.28	Severely decreased
G5	< 15	< 0.14	Kidney failure

[a]Kidney damage must be present to meet criteria of CKD.

CKD, chronic kidney disease; GFR, glomerular filtration rate.

Data from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1–150.

Risk Factors for CKD

LO 1

Identifying risk factors for CKD is difficult because CKD progresses slowly and is often not diagnosed until late in the disease. Disease states and factors that can increase susceptibility to CKD are listed in Table 26–2. These factors can be used to identify targets for CKD screening programs. For example, older patients, those with low kidney mass or birth weight, or those with a family history of kidney disease should be routinely screened for CKD. Minority and low socioeconomic communities may be targets for more widespread CKD screening programs.

The three most common causes of CKD in the United States are diabetes mellitus (DM), hypertension, and glomerulonephritis, accounting for more than 82% of CKD cases.[2] These are discussed in further detail below. Other causes of CKD include polycystic kidney disease, Wegener granulomatosis, vascular diseases, human immunodeficiency virus (HIV) nephropathy, and AKI.

▶ *Diabetes*

DM is the most common cause of CKD, causing 37% of all CKD.[2] The risk of developing diabetic kidney disease (DKD) associated with DM is closely linked to hyperglycemia and is similar for both type 1 (DM1) and type 2 (DM2). Structural changes appear in the glomerulus as early as 2 years after diagnosis of DM1. Changes in GFR can occur as early as 5 to 7 years after diagnosis.[4] Similar changes occur in DM2, but the timing of onset of DM2 and presentation of kidney disease is more difficult to determine. Albuminuria develops in 40% of patients with DM2 and GFR is less than 30 mL/min/1.73 m² (0.29 mL/s/m²) within 15 years of diagnosis of DM2.[4]

Table 26–2

Risk Factors That Increase Susceptibility for CKD

- Diabetes mellitus
- Hypertension
- Autoimmune disease
- Polycystic kidney disease
- Human immunodeficiency virus (HIV)
- Drug toxicity
- Urinary tract abnormalities (infections, obstruction, stones)
- Advanced age
- Reduced kidney mass
- Low birth weight
- Racial/ethnic minority
- Family history of kidney disease
- Low income or education
- Systemic inflammation
- Dyslipidemia

▶ *Hypertension*

The second most common cause of CKD is hypertension, accounting for 29% of cases of ESKD.[2] It is more difficult to determine the true risk of developing CKD in patients with hypertension because the two are so closely linked, with CKD also being a cause of hypertension. The prevalence of hypertension is correlated with the degree of kidney dysfunction (decreased GFR) with 36% of patients with CKD G1, 48% of patients with CKD G2, and 85% of patients with CKD G3 presenting with hypertension.[5] The risk of developing ESKD increases with the degree of hypertension and is linked to both systolic and diastolic blood pressure.[5]

▶ *Glomerulonephritis*

The term *glomerulonephritis* includes many specific diseases that can affect glomerular function. These include such diseases as IgA nephropathy and glomerulonephritis associated with systemic lupus erythematosus and streptococcal disease, among many others. The etiologic and pathophysiologic features of glomerular diseases vary with the specific disease, making it difficult to extrapolate the risk for progression of CKD in patients affected by glomerular diseases. Certain glomerular diseases are known to rapidly progress to ESKD; others progress more slowly or may be reversible.

Risk Factors for Progression of CKD

Several factors increase the progression of CKD, or rate of decline in GFR. The most important risk factors for progression of CKD include proteinuria, elevated blood pressure, hyperglycemia, hyperlipidemia, and AKI. Smoking tobacco also plays a role in progression of CKD.

▶ *Proteinuria*

The presence of protein in the urine is a marker of glomerular dysfunction and some tubulointerstitial diseases. The degree of proteinuria correlates with the risk for progression of CKD.[6] The effects of proteinuria appear to be worse with milder stages of CKD. Compared with patients with no proteinuria, proteinuric patients with CKD G3 are 15 times more likely to double serum creatinine; patients with CKD G4 are 8 times more likely to double serum creatinine.[6] The mechanisms by which proteinuria potentiates CKD are discussed later.

▶ *Elevated Blood Pressure*

Systemic blood pressure correlates with glomerular pressure, and elevations in both independently contribute to glomerular damage. The rate of GFR decline is related to elevated systolic blood pressure and mean arterial pressure. The decline in GFR is estimated to be 14 mL/min per year (0.23 mL/s per year) in patients with diabetes with a sustained systolic blood pressure of 180 mm Hg. Conversely, the decline in GFR decreases to 2 mL/min per year (0.03 mL/s per year) with a systolic blood pressure of 135 mm Hg.[7]

▶ *Elevated Blood Glucose*

The reaction between glucose and protein in the blood produces advanced glycation end products (AGEs), which are metabolized in the proximal tubules. Hyperglycemia increases the synthesis of AGEs, which affects glomerular, tubular, and vascular function in the kidney. AGEs are known to affect podocyte activity, the epithelial cells responsible for filtering blood in the glomerulus, which contributes to proteinuria, and, in turn, damages tubules.[8]

▶ *Hyperlipidemia*

Dyslipidemia can promote kidney injury and subsequent progression of CKD.[9] The dyslipidemia in CKD is manifested primarily as elevated triglycerides and lipoprotein(a) levels, and decreased high-density lipoprotein cholesterol (HDL-C) levels. Total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels generally remain within normal limits, but LDL-C particles are smaller, denser, and more atherogenic. Furthermore, kidney disease alters lipid metabolism, allowing lipoproteins to remain in circulation longer.[9] In contrast, patients with nephrotic syndrome, characterized by urine protein rates that exceed 3 g/24 hours, often have elevated total cholesterol and LDL-C.[9]

▶ *Acute Kidney Injury*

Nephron damage that results from AKI increases the risk of developing CKD, even if renal function recovers.[10] The most predictive risk factor of whether patients will develop CKD is the severity of AKI. Severe AKI is associated with a 28-fold increased risk of developing CKD, but even mild AKI is associated with a twofold increased risk. Older age also increases the risk of developing CKD after AKI. The cause of AKI may also affect the risk of CKD.[10]

PATHOPHYSIOLOGY

A number of factors can cause initial damage to the kidney. The resulting sequelae, however, follow a common pathway that promotes progression of CKD and results in irreversible damage leading to ESKD (Figure 26–1).

LO 2

Regardless of the initial cause of kidney damage, the result is a decrease in the number of functioning nephrons. The remaining nephrons hypertrophy to increase glomerular filtration and tubular function, both reabsorption and secretion, in an attempt to compensate for the loss of kidney function. Initially, these adaptive changes preserve many of the clinical parameters of kidney function, including creatinine and electrolyte excretion. However, as time progresses, angiotensin II is required to maintain the hyperfiltration state of the functioning nephrons. Angiotensin II is a potent vasoconstrictor of both the afferent and efferent arterioles but has a preferential effect to constrict the efferent arteriole, thereby increasing the pressure in the glomerular capillaries. Increased glomerular capillary pressure expands the pores in the glomerular basement membrane, altering the size-selective barrier and allowing proteins to be filtered through the glomerulus.[11]

Proteinuria increases nephron loss through various complex mechanisms. Filtered proteins are reabsorbed in the renal tubules, which activate the tubular cells to produce inflammatory and

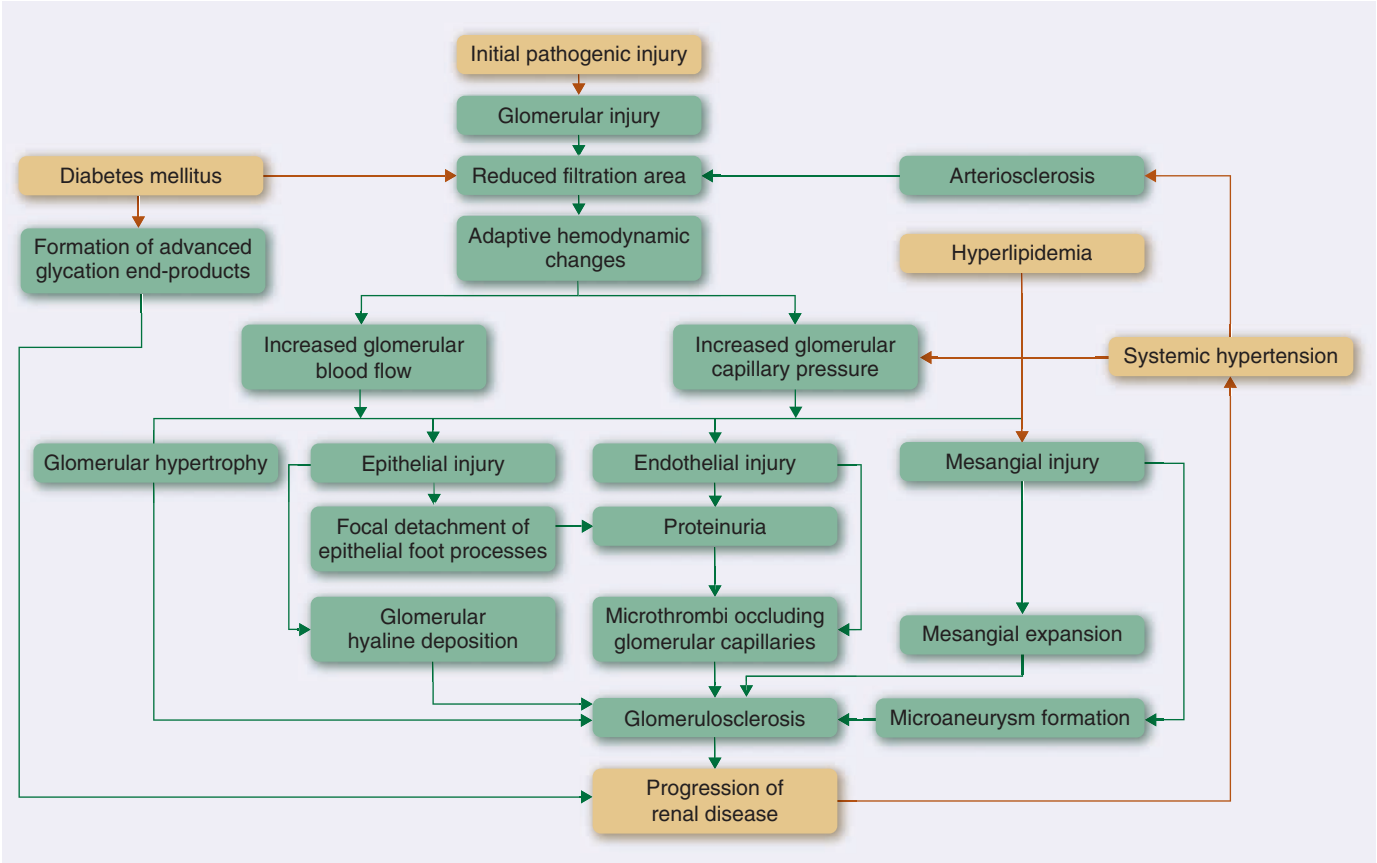

FIGURE 26–1. Proposed mechanisms for progression of kidney disease. (From Hudson JQ, Wazny LD. Chronic kidney disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill Education; 2017:612, with permission.)

vasoactive cytokines and trigger complement activation. These cytokines cause interstitial damage and scarring in the renal tubules, leading to damage and loss of more nephrons. Ultimately, the process leads to progressive loss of nephrons to the point where the number of remaining functioning nephrons is too small to maintain clinical stability, and kidney function declines.

ASSESSMENT

Because CKD often presents without symptoms, assessment for CKD relies on appropriate screening strategies in all patients with risk factors for developing CKD. Evaluation for CKD and the subsequent treatment strategies depend on the diagnosis, comorbid conditions, severity and complications of disease, and risk factors for the progression of CKD. KEY CONCEPT Early treatment of CKD and the associated complications of CKD are the most important factors to decrease morbidity and mortality associated with CKD. Screening for CKD should be performed in all people with an increased risk for developing CKD including patients with DM, hypertension, genitourinary abnormalities, autoimmune disease, increased age, a family history of kidney disease, or following AKI. Assessment for CKD includes measurement of SCr, measurement of creatinine clearance (ie, 24-hour urine collection) or estimation of GFR (ie, MDRD or CKD-EPI), urinalysis, blood pressure, serum electrolytes, and/or imaging studies. It is important to note that SCr should be stable when estimating GFR or measuring creatinine clearance in patients with CKD. In patients with known CKD, the presence and assessment of CKD-related complications, including anemia and secondary hyperparathyroidism (sHPT), involves measurement of blood counts, red blood cell (RBC) indices, iron stores, serum phosphorus, calcium, and parathyroid hormone (PTH) levels.

A key part of CKD assessment is analysis for proteinuria, which is the primary marker of structural kidney damage, even in patients with normal GFR. Protein excretion can be assessed by measuring urine albumin-to-creatinine ratio (ACR), urine protein-to-creatinine ratio, or urinalysis with a reagent strip test. A urinary protein excretion of 30 mg/day or more or an ACR or 30 mg/g (or 3.5 mg/mmol for female and 2.5 mg/mmol for male, but varies between different guidelines and locations) or more on a random untimed urine sample is considered to be significant in the context of CKD. Albuminuria should be assessed with GFR at least annually in people with CKD, and more frequently as GFR declines.[1]

Complications

KEY CONCEPT The decline in kidney function is associated with a number of complications, which are discussed later in the chapter, including:

- *Hypertension*
- *Fluid and electrolyte disorders*
- *Anemia*
- *Metabolic bone disease*

TREATMENT

Desired Outcomes

LO 3

The primary goal is to slow and prevent the progression of CKD to prevent a cardiovascular event, CKD complications, and the need for kidney replacement therapy. This requires early identification of patients at risk for CKD to initiate interventions early in the course of the disease.

Nonpharmacologic Therapy

▶ *Nutritional Management*

Protein intake should be lowered to 0.8 g/kg/day in adults with diabetes or people with a GFR less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2) who are not on **dialysis**. Protein intake should not exceed 1.3 mg/kg/day in any adult with CKD.[1] However, protein restriction must be balanced with the risk of malnutrition in patients with CKD. In particular, patients on dialysis are at risk for nutritional abnormalities, which can lead to increased rates of hospitalization and death.[12] Malnutrition is common in patients with ESKD for various reasons, including decreased appetite, protein catabolism due to protein losses in the urine, and nutrient losses through dialysis. For this reason, patients receiving dialysis should maintain protein intake of 1.2 g/kg/day and maintain a caloric intake of 30 to 35 kcal/kg (125–147 kJ/kg) of ideal body weight.[12]

Limiting salt intake to less than 2 g (90 mmol) of sodium per day (equivalent to 5 g sodium chloride) will help to control blood pressure and reduce water retention in CKD. Patients with CKD should be encouraged to increase physical activity, with a goal of at least 30 minutes 5 times per week, to achieve a healthy weight, with a goal BMI of 20 to 25 kg/m^2.[1]

Pharmacologic Therapy

▶ *CKD with Diabetes*

The target hemoglobin A1c (HbA1c) should be less than 7.0% (0.07; 53 mmol/mol Hgb) for patients with DM to decrease the incidence of albuminuria in patients with and without documented DKD.[1,13] This generally involves intensive insulin therapy for type 1 DM or insulin-dependent type 2 DM or optimizing doses of oral hypoglycemic agents in patients with noninsulin-dependent type 2 DM. However, glycemic control should be balanced with the risk of hypoglycemia, especially in patients with CKD and DM with comorbidities,[1,13] and higher A1c targets should be considered for patients with limited life expectancy with late stages of DM and CKD.

▶ *Optimal Blood Pressure Control*

Reductions in blood pressure are associated with a decrease in proteinuria, leading to a decrease in the rate of progression of kidney disease. The 2017 High Blood Pressure Clinical Practice Guideline recommends targeting a goal blood pressure of < 130/80 mm Hg for all patients with CKD.[14]

KEY CONCEPT Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) are the antihypertensive agents of choice in patients with CKD with an AER of 30 mg/day or more because of their greater effect on lowering proteinuria, compared with other antihypertensive agents. ACEIs and ARBs should be started at a low dose and the dose should be titrated upward slowly to minimize the risk of AKI (see Chapter 25). Ideally, the dose of ACEIs and ARBs should be increased to achieve a 30% to 50% reduction in urinary albumin excretion, but this may be limited by side effects, such as hyperkalemia, in patients with CKD.

In patients with CKD G5 who are receiving hemodialysis (HD), cardiovascular mortality is affected by blood pressure both before and after HD.[15] A systolic blood pressure greater than 160 mm Hg and diastolic blood pressure greater than 90 mm Hg after HD are independently associated with an increased risk of cardiovascular mortality (hazard ratio [HR]: 1.2 for each).[16] Similarly, a systolic blood pressure less than 120 mm Hg or diastolic blood pressure

Clinical Presentation and Diagnosis of CKD

General

The development of CKD is usually subtle in onset, often with no noticeable symptoms.

Symptoms

CKD G1 and G2 are generally asymptomatic.

CKD G3a–3b and G4 may be associated with minimal symptoms.

CKD G5 can be associated with pruritus, dysgeusia, nausea, vomiting, constipation, muscle pain, fatigue, and bleeding abnormalities.

Signs

Cardiovascular: Worsening hypertension, edema, dyslipidemia, left ventricular hypertrophy, electrocardiographic changes and chronic heart failure

Musculoskeletal: Cramping

Neuropsychiatric: Depression, anxiety, impaired mental cognition

GI: Gastroesophageal reflux disease, GI bleeding, and abdominal distention

Genitourinary: Changes in urine volume and consistency, "foaming" of urine (indicative of proteinuria), and sexual dysfunction

Laboratory Tests

CKD G1 and G2: Blood urea nitrogen (BUN) and serum creatinine (SCr) are generally within normal limits, despite mildly decreased GFR.

CKD G3a–G3b, G4, and G5: Increased BUN and SCr; decreased GFR.

Advanced stages: Increased potassium, phosphorus, and magnesium; decreased bicarbonate (metabolic acidosis); calcium levels are generally low in earlier stages of CKD and may be elevated in CKD G5, secondary to the use of calcium-containing phosphate binders (CCPBs).

Decreased albumin, if inadequate nutrition intake in advanced stages.

Decreased RBC count, hemoglobin (Hgb) and hematocrit (Hct); decreased iron stores (iron level, total iron binding capacity [TIBC], serum ferritin level, and transferrin saturation [TSat]). EPO levels are not routinely monitored and are generally normal to low. Urine positive for albumin or protein.

Increased PTH level; decreased vitamin D levels (CKD G4 or G5).

Stool may be Hemoccult-positive if GI bleeding occurs from uremia.

Other Diagnostic Tests

Structural abnormalities of kidney may be present on diagnostic examinations.

less than 60 mm Hg before HD is associated with a higher risk of cardiovascular mortality (HR: 1.1 and 1.3, respectively [$p < 0.05$ for each]); the same systolic or diastolic blood pressure at the end of HD is associated with a comparable risk (HR 1.1 and 1.2, respectively [$p < 0.05$ for each]).[16] However, there are no consensus guidelines on the optimal blood pressure goals before or after HD. Some evidence suggests that blood pressure on non-HD days may be a more appropriate measure, and correlates better with cardiovascular outcomes.[16] Cardiovascular outcomes may be impacted by the selection of antihypertensive agent in HD patients. One study found that ACEIs and ARBs increased cardiovascular events in patients on HD, compared to beta-blockers.[17]

Because hypertension and kidney dysfunction are linked, blood pressure control can be more difficult to attain in patients with CKD compared with patients with normal kidney function. All antihypertensive agents have similar effects on reducing blood pressure. However, two or more agents are generally required to achieve the blood pressure goal of less than 130/80 mm Hg in CKD patients.[14] Timing of blood pressure medications may also be important. One study suggests that administration of at least one antihypertensive medication at bedtime decreased cardiovascular risk by 14% in patients with CKD compared with taking all antihypertensive medications in the morning.[18]

▶ *Reduction in Proteinuria*

Albuminuria in CKD predicts long-term renal and cardiovascular prognosis.[19] The ability of antihypertensive agents to reduce protein excretion differs. ACEIs and ARBs decrease glomerular capillary pressure and volume because of their effects on angiotensin II. This, in turn, reduces the amount of protein filtered through the glomerulus, independent of the reduction in blood pressure,[19] which ultimately decreases the progression of CKD. The ability of ACEIs and ARBs to reduce proteinuria is greater than that of other antihypertensives, up to 35% to 40%,[19] making ACEIs and ARBs the antihypertensive agents of choice for all patients with CKD with an AER of 30 mg/day or more, unless contraindicated. While the combination of ACEIs and ARBs reduces proteinuria more than monotherapy, some trials have shown combining full doses of ACEIs and ARBs in patients with high vascular risk increases the risk of progression of CKD and nonfatal strokes.[20] The safety and efficacy of combining lower doses of ACEIs and ARBs continues to be investigated.[20]

The nondihydropyridine calcium channel blockers (CCBs) have been shown to also decrease protein excretion in patients with and without diabetes, but should not be used as first-line agents for proteinuria.[19] Dihydropyridine CCBs, however, do not have the same effects on protein excretion. In fact, dihydropyridine CCBs may worsen protein excretion, despite similar reductions in blood pressure as nondihydropyridine CCBs.[19] When blood pressure goals are not achieved, additional antihypertensive agents should be used to reach goals. Thiazide diuretics have complementary effects when added to ACEIs and ARBs.[19] Other drug classes should be considered when compelling indications warrant or if blood pressure goals are not achieved.

▶ *Hyperlipidemia Treatment*

Hyperlipidemia plays a role in the development of cardiovascular disease (CVD) in patients with CKD. Because

data do not support the use of LDL-C levels to guide treatment of hyperlipidemia, the KDIGO guidelines recommend starting statins for all patients with nondialysis-dependent CKD aged 50 years and older, regardless of GFR category.[21] Ezetimibe should be considered when GFR is less than 60 mL/min/1.73 m^2 (0.58 mL/s/m^2). Statins should also be used for patients aged 18 to 49 years who have known coronary artery disease, DM, prior ischemic stroke, or more than a 10% estimated 10-year incidence of coronary death or nonfatal myocardial infarction.[21] However, because of the lack of efficacy in reducing cardiovascular events and the risk of adverse effects associated with statins in patients with ESKD, statins should not be initiated in patients on dialysis, unless they were receiving statins prior to starting dialysis.[21]

Outcome Evaluation

The KDIGO guidelines recommend intervals for monitoring GFR and albuminuria in patients with CKD, based on the CKD stage and the degree of proteinuria.[1] In general, patients should be monitored more frequently as CKD stage increases and the severity of albuminuria increases.

Patients with CKD G3a should be monitored every 12 months until albuminuria is detected, then the frequency of monitoring should be increased to every 4 to 6 months, based on the severity of albuminuria. As CKD progresses, the frequency of monitoring should be increased to every 3 to 6 months.

Monitor SCr and potassium levels and blood pressure within 1 week after initiating ACEI or ARB therapy. Discontinue the medication and switch to another agent if a sudden increase in SCr greater than 30% occurs, hyperkalemia develops, or the patient becomes hypotensive. Titrate the dose of the ACEI or ARB every 1 to 3 months to effect using the maximum tolerable dose. If blood pressure is not reduced to goal, add another agent to the regimen. Refer the patient to a nephrologist to manage complications associated with CKD. As kidney function declines to CKD G4, begin discussion to prepare the patient for renal replacement therapy (RRT).

CONSEQUENCES OF CKD AND ESKD

Anemia of CKD

The progenitor cells of the kidney produce 90% of the hormone EPO, which stimulates red blood cell (RBC) production. KEY CONCEPT Reduction in the number of functioning nephrons decreases renal production of EPO, which is the primary cause of anemia in patients with CKD. The development of anemia of CKD results in decreased oxygen delivery and utilization, leading to increased cardiac output and left ventricular hypertrophy (LVH), which increase the cardiovascular risk and mortality in patients with CKD. Each 1 g/dL (10 g/L; 0.62 mmol/L) decrease in hemoglobin (Hgb) below 12 g/dL (120 g/L; 7.45 mmol/L) is associated with a 5% increase in the relative risk (RR) of mortality.[22]

▶ *Epidemiology and Etiology*

Current KDIGO guidelines define anemia as an Hgb level less than 13 g/dL (130 g/L or 8.07 mmol/L) in males and less than 12 g/dL (120 g/L or 7.45 mmol/L) in females.[23] A number of factors contribute to the development of anemia including deficiencies in vitamin B_{12} or folate, hemolysis, bleeding, or bone marrow resistance to EPO. Many of these can be detected by alterations in RBC indices, which should be included in the evaluation for anemia (see Chapter 66). A complete blood cell count is also helpful in evaluating anemia to determine overall bone marrow function. The prevalence of anemia correlates with the degree of kidney dysfunction. Only 8.4% of patients with CKD G1 have anemia, whereas the number increases to 53.4% with CKD G5.[24]

▶ *Pathophysiology*

The primary cause of anemia in patients with CKD is a decrease in EPO production. With normal kidney function, as Hgb, hematocrit (Hct), and tissue oxygenation decrease, the plasma concentration of EPO increases exponentially. As the number of functioning nephrons decreases, EPO production also decreases. Thus, as Hgb, Hct, and tissue oxygenation decrease in patients with CKD, plasma EPO levels remain constant within the normal

Patient Encounter 1

A 42-year-old African American man presents to the clinic for a routine checkup. He has no complaints today.

PMH: Hypertension, diagnosed 8 years ago

SH: He smokes 2 ppd; drinks alcohol occasionally (socially)

Meds: Amlodipine 10 mg orally daily; atenolol 50 mg orally daily; atorvastatin 20 mg orally daily

ROS: Unremarkable

PE:

VS: BP 166/98 mm Hg; P 82 beats/min; T 98.8°F (37.1°C); ht 5′11″ (180 cm); wt 252 lb (114.5 kg)

CV: RRR, normal S_1, S_2; no murmurs, rubs or gallops; lungs clear

Abd: No organomegaly, bruits or tenderness, (+) bowel sounds; heme (–) stool

Exts: 1+ pedal edema bilaterally; no lesions

Labs (Fasting): Sodium 143 mEq/L (mmol/L); potassium 4.1 mEq/L (mmol/L); chloride 101 mEq/L (mmol/L); carbon dioxide 24 mEq/L (mmol/L); blood urea nitrogen (BUN) 28 mg/dL (10 mmol/L); serum creatinine (SCr) 1.8 mg/dL (159 µmol/L); glucose 102 mg/dL (5.7 mmol/L); total cholesterol 260 mg/dL (6.72 mmol/L); low-density lipoprotein cholesterol (LDL-C) 176 mg/dL (4.55 mmol/L); high-density lipoprotein cholesterol (HDL-C) 24 mg/dL (0.62 mmol/L); triglycerides 300 mg/dL (3.39 mmol/L); urine albumin: creatinine 52 mg/g creatinine (5.9 mg/mmol creatinine)

What risk factors does the patient have for the development of CKD?

What signs and symptoms are consistent with CKD?

How would you classify his CKD?

What lifestyle modifications would you recommend for this patient with CKD?

What pharmacologic alternatives are available for this patient for treatment of CKD?

Clinical Presentation and Diagnosis of Anemia of CKD

General

Anemia of CKD generally presents with fatigue and decreased quality of life.

Symptoms

Anemia of CKD is associated with symptoms of cold intolerance, shortness of breath, and decreased exercise capacity.

Signs

Cardiovascular: Left ventricular hypertrophy, electrocardiogram (ECG) changes, congestive heart failure

Neurologic: Impaired mental cognition

Genitourinary: Sexual dysfunction

Laboratory Tests

Decreased RBC count, Hgb, and Hct

Decreased serum iron level, TSat and serum ferritin, and increased TIBC

range but low relative to the degree of hypoxia present. The result is a normochromic, normocytic anemia.

Several other factors contribute to the development of anemia in patients with CKD. **Uremia**, the accumulation of toxins that results from declining kidney function, decreases the lifespan of RBCs from a normal of 120 days to as low as 60 days in patients with CKD G5. Iron deficiency and blood loss from regular laboratory testing and HD also contribute to the development of anemia in patients with CKD.

▶ *Treatment*

Patients with CKD should be evaluated for anemia when the GFR falls below 60 mL/min (1.0 mL/s) or if the SCr rises above 2 mg/dL (177 µmol/L). An anemia workup should be performed if the Hgb is less than 13 g/dL (130 g/L or 8.07 mmol/L) in males or less than 12 g/dL (120 g/L or 7.45 mmol/L) in females. The workup for anemia should rule out other potential causes for anemia (see Chapter 66). Abnormalities found during the anemia workup should be corrected before initiating **erythropoiesis-stimulating agents** (ESAs), particularly iron deficiency, because iron is an essential component of RBC production. If Hgb is below 10 g/dL (100 g/L or 6.21 mmol/L) when all other causes of anemia have been corrected, EPO deficiency should be assumed. EPO levels are not routinely measured and have little clinical significance in monitoring progression and treatment of anemia in patients with CKD.

Nonpharmacologic Therapy Approximately 1 to 2 mg of iron is absorbed daily from the diet. This small amount is generally not adequate to preserve adequate iron stores to promote RBC production in patients with CKD-related anemia. RBC transfusions have been used in the past as the primary means to maintain Hgb and Hct levels in patients with anemia of CKD. This treatment is still utilized today in patients with severe anemia, when rapid Hgb correction is needed, especially for patients with CVD, or if patients have contraindications to ESAs.

Patient Encounter 2, Part 1

A 62-year-old Hispanic woman with a history of diabetes presents to your clinic for a routine checkup. She complains of getting fatigued easily at work. She works as a housekeeper for a hotel and notes that she is not able to keep up with her work. She notes that she feels winded when she walks even short distances.

Current meds: Lisinopril 40 mg orally daily; furosemide 20 mg orally daily; levothyroxine 125 mcg orally daily; insulin detemir 18 units SC daily

ROS: Skin pale in color; fatigue daily throughout the day with minimal exertion; otherwise unremarkable

PE:

VS: BP 127/82 mm Hg; P 88 bpm; T 97.5°F (36.4°C); ht 5′ (152 cm); wt 180 lb (81.8 kg)

CV: RRR, normal S_1, S_2

Abd: No organomegaly, bruits or tenderness; (+) bowel sounds; heme (–) stool

Ext: 1+ pedal edema bilaterally

Labs: Sodium 138 mEq/L (mmol/L); potassium 4.1 mEq/L (mmol/L); chloride 101 mEq/L (mmol/L); carbon dioxide 21 mEq/L (mmol/L); BUN 18 mg/dL (6.4 mmol/L); Scr 2.2 mg/dL (194 µmol/L); glucose 140 mg/dL (7.8 mmol/L); white blood cell (WBC) count 4.8×10^3 cells/mm^3 (4.8×10^9/L); red blood cell (RBC) count 2.8×10^6 cells/mm^3 (2.8×10^{12}/L); hemoglobin (Hgb) 9.4 g/dL (94 g/L; 5.83 mmol/L); hematocrit 28% (0.28); platelets 278×10^3 cells/mm^3 (278×10^9/L)

What signs and symptoms are consistent with anemia of CKD?

What additional information could you request to determine other causes of anemia in this patient?

Pharmacologic Therapy The first-line treatment for anemia of CKD involves replacement of iron stores with iron supplements. When iron supplementation alone is not sufficient to increase Hgb levels, ESAs are necessary to replace EPO. ESAs are synthetic formulations of EPO produced by recombinant human DNA technology. Use of ESAs increases the iron demand for RBC production and iron deficiency is common, requiring iron supplementation to correct and maintain adequate iron stores to promote RBC production. The approach to the management of anemia of CKD with iron supplementation and ESAs is illustrated in **Figure 26–2**.

Iron Supplementation. Use of ESAs can lead to iron deficiency if iron stores are not adequately maintained. According to the KDIGO guidelines, iron supplementation should be considered when:

- Serum ferritin levels less than 500 ng/mL (mcg/L; 1124 pmol/L)
- Transferrin saturation (TSat): less than 30% (0.30)[23]

Serum ferritin is an acute phase reactant that may become elevated with inflammation and infection. Thus when serum ferritin is normal or elevated in conjunction with TSat levels less than 30% (0.30), treatment should be based on the clinical picture of the patient. Iron supplementation may be indicated if Hgb levels are below the goal level, but avoided if the patient is infected.

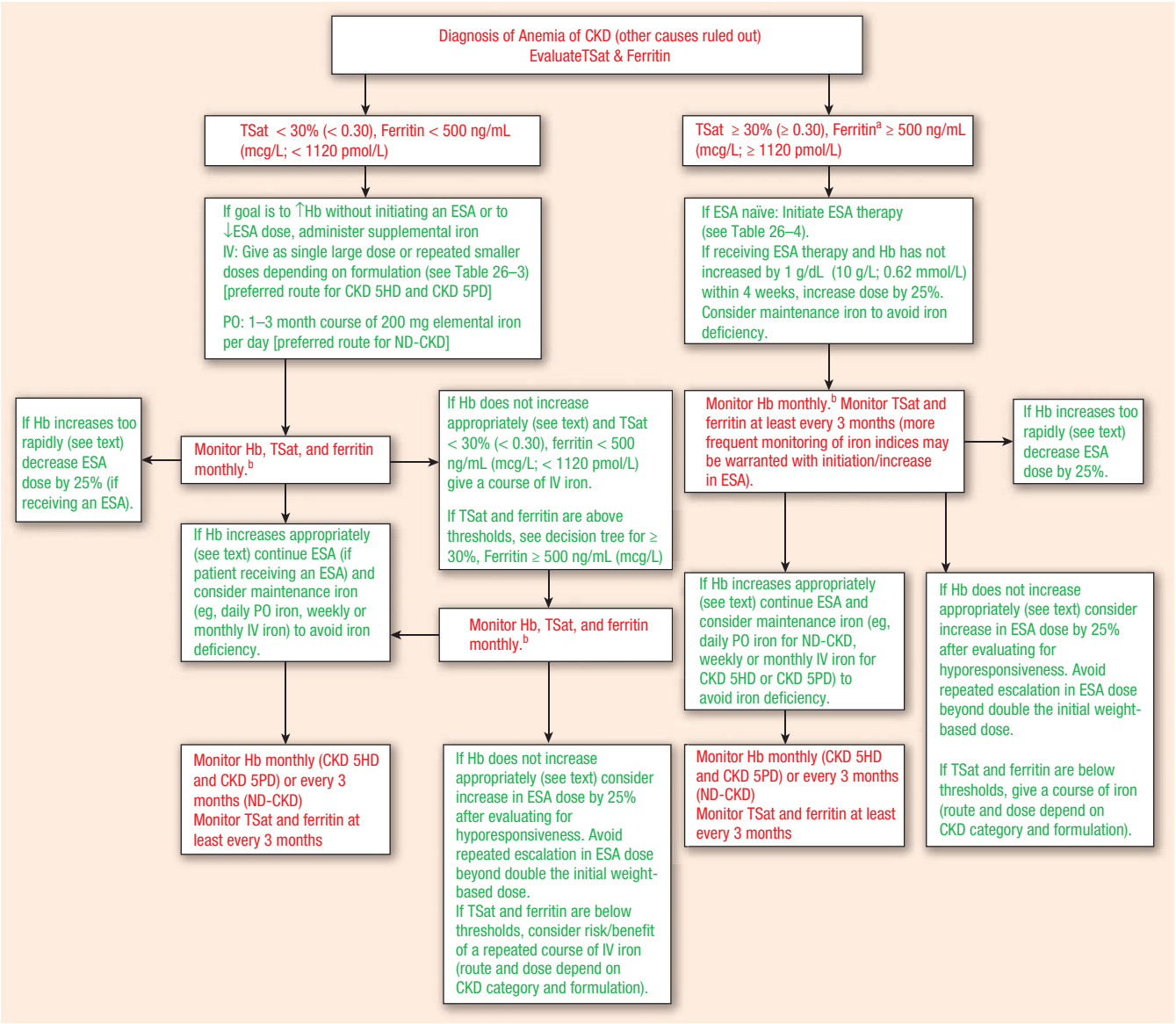

FIGURE 26–2. Algorithm for management of anemia of CKD. (CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; ND-CKD, nondialysis CKD patients; TSat, transferrin saturation.) [a]Clinical judgement should be used to determine if iron supplementation should be given when ferritin > 500 ng/mL (mcg/L; 1,124 pmol/L). [b]Weekly monitoring of Hb may be warranted. Wait at least 1 week after an IV dose of iron to measure TSat and ferritin. (From Hudson JQ, Wazny LD. Chronic kidney disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill Education; 2017:626, with permission.)

Oral iron supplements are generally less costly than IV supplements and are generally the first-line treatment for iron supplementation for patients with CKD not receiving HD. When administering iron by the oral route, 200 mg of elemental iron should be delivered daily in divided doses to increase iron stores.[23]

When oral iron is not effective to increase iron stores or for patients receiving HD, IV iron should be administered. Table 26–3 lists the Food and Drug Administration (FDA)-approved doses of the currently available IV iron products. Patients receiving HD have ongoing blood losses with each HD session, which can lead to iron losses of 1 to 2 g per year. For HD, IV iron may be administered episodically based on routine surveillance of iron stores as a total of 1 g of IV iron, administered in small sequential doses to replete iron stores. An alternative method to administer IV iron is to give smaller maintenance doses of iron weekly or with each dialysis session (eg, iron dextran or iron sucrose 20–100 mg/week; sodium ferric gluconate 62.5–125 mg/week). The latter approach of giving smaller maintenance doses may result in lower cumulative doses of iron and lower doses of ESAs.[23]

IV iron preparations are equally effective in increasing iron stores. Anaphylaxis may occur with all IV preparations, but most notably with iron dextran, which can also cause delayed reactions, such as arthralgias and myalgias. A test dose of 25 mg iron dextran should be administered 30 minutes before the full dose to monitor for potential anaphylactic reactions, although anaphylactic reactions can occur in patients who safely received

Table 26–3

IV Iron Products

Iron Formulation (Product)	FDA-Approved Indications	FDA-Approved Dosing	Warnings	Dose Ranges[a]	How Supplied
Iron dextran (INFeD®, Dexferrum®)	Patients with iron deficiency in whom oral iron is unsatisfactory	IV push: 100 mg over 2 minutes (25 mg test dose required)	Black box (risk of anaphylactic reactions)	25–1000 mg	2-mL vials containing 50 mg elemental iron per mL
Ferric gluconate (Ferrlecit®, Sodium ferric gluconate)	Adult and pediatric HD patients age 6 years and older receiving ESA therapy	IV push (adult): 125 mg over 10 minutes IV infusion (adult): 125 mg in 100 mL of 0.9% NaCl over 60 minutes IV infusion (pediatric): 1.5 mg/kg in 25 mL of 0.9% NaCl over 60 minutes; maximum dose 125 mg	General	6.25–500 mg	5-mL ampules containing 62.5 mg elemental iron (12.5 mg/mL)
Iron sucrose (Venofer®)	HD patients with CKD receiving ESA therapy	IV push: 100 mg over 2–5 minutes IV infusion: 100 mg in maximum of 100 mL of 0.9% NaCl over 15 minutes	General	25–500 mg	5-mL single-dose vials containing 100 mg elemental iron (20 mg/mL)
	Nondialysis-CKD patients receiving or not receiving ESA therapy	IV push: 200 mg over 2–5 minutes on five different occasions within 14-day period			
	PD patients receiving ESA therapy	IV infusion: 2 infusions 14 days apart, of 300 mg in maximum of 250 mL of 0.9% NaCl over 1.5 hour, followed by 1 infusion 14 days later, of 400 mg in maximum of 250 mL of 0.9% NaCl over 2.5 hours			
Ferumoxytol (Feraheme™)	Adults with iron-deficiency anemia associated with CKD	IV infusion: 510 mg (17 mL) in 50–200 mL 0.9% NaCl or 5% Dextrose over at least 15 minutes, followed by a second 510-mg infusion 3–8 days after the initial infusion	General	1020 mg (2 doses of 510 mg separated by 3–8 days)	17 mL vials containing 510 mg (0 mg/mL)
Ferric carboxymaltose (Injectafer®)	Adults with nondialysis-dependent CKD	IV push: 750 mg over 10 minutes IV infusion: 750 mg in 100–250 mL of 0.9% NaCl over at least 15 minutes	General	1500 mg (2 doses of 750 mg separated by at least 7 days)	15-mL vials containing 750 mg elemental iron

[a]Small dosing ranges (eg, 25 to 100 mg/week) generally used for maintenance regimens. Larger doses (eg, 1 g) should be administered in divided doses.

CKD, chronic kidney disease; ESA, erythropoietin-stimulating agent; HD, hemodialysis; PD, peritoneal dialysis.

prior doses of iron dextran. Ferumoxytol also carries a warning for serious allergic reactions and should be closely monitored. Sodium ferric gluconate, iron sucrose, and ferric carboxymaltose are associated with fewer severe reactions and a much lower risk of anaphylaxis and do not require a test dose, making them the preferred agents in CKD. The most common side effects seen with these preparations include hypotension, flushing, nausea, and injection site reactions.

After administering a 1-g course of IV iron, iron status should be monitored to determine the effectiveness of the treatment. Serum ferritin and TSat should be monitored no sooner than 1 week after the last dose of IV iron. If Hgb does not increase after a course of IV iron or serum ferritin is not greater than 500 ng/mL (mcg/L; 1124 pmol/L) and TSat greater than 30% (0.30), an additional 1 g of IV iron may be administered, based on the clinical situation.

Erythropoiesis-Stimulating Agents. ESAs may be considered if Hgb levels remain persistently low to improve symptoms of anemia. In patients not receiving dialysis, the decision to initiate ESAs should be based on the rate of Hgb decline, prior response to anemia treatment, risks associated with ESAs and the patient's symptoms. The KDIGO guidelines recommend considering initiating ESAs when Hgb is less than 10 g/dL

Table 26–4

Erythropoiesis Stimulating Agents in Chronic Kidney Disease

Drug	Brand Name	Starting Dose	Route of Administration	Half-Life (Hours)
Epoetin alfa	Epogen®, Procrit®	Adults: 50–100 units/kg three times per week Pediatrics: 50 units/kg three times per week	IV or SC	8.5 (IV) 24 (SC)
Darbepoetin alfa	Aranesp®	ND-CKD: 0.45 mcg/kg once every 4 weeks Dialysis: 0.45 mcg/kg once per week or 0.75 mcg/kg once every 2 weeks Pediatrics: 0.45 mcg/kg once weekly; may give 0.75 mcg/kg once every 2 weeks for nondialysis	IV or SC	25 (IV) 48 (SC)
Methoxy PEG-epoetin beta	Micera®	0.6 mcg/kg every 2 weeks; once Hgb stabilizes, double the dose and administer monthly (eg, if administering 0.6 mcg/kg every 2 weeks, give 1.2 mcg/kg every month)	IV or SC	134 (IV) 139 (SC)

CKD, chronic kidney disease; ND-CKD, nondialysis CKD; PEG, polyethylene glycol; SC, subcutaneous.

Adapted from Hudson JQ, Wazny LD. Chronic kidney disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill Education, 2017:624, with permission.

(100 g/L or 6.21 mmol/L).[23] However, the target for Hgb is unclear because use of ESAs to increase Hgb levels beyond 12 g/dL (120 g/L or 7.45 mmol/L) is associated with increased mortality.[23] The ESAs currently available in the United States are listed in Table 26–4. Epoetin α and epoetin β, which are available outside the United States, have the same biological activity as endogenous EPO. Darbepoetin alfa has two additional carbohydrate side chains that increase the half-life compared with epoetin alfa and endogenous EPO, allowing for less frequent dosing than that of epoetin alfa. Methoxy PEG-epoetin beta has the addition of an amide bond that produces a longer half-life than the other ESAs and is referred to as a continuous erythropoietin receptor activator (CERA). All ESAs are equivalent in their efficacy and have a similar adverse-effect profile.

The most common adverse effect seen with ESAs is increased blood pressure, which may require antihypertensive agents to control blood pressure. Caution should be used when initiating an ESA in patients with very high blood pressures (> 180/100 mm Hg). If blood pressures are refractory to antihypertensive agents, ESAs may need to be withheld. Seizures and pure red cell aplasia have also been reported in patients initiating ESA therapy, and have been reported more with the CERA product.

Subcutaneous (SC) administration of ESA is the preferred route of administration for all agents because it produces a more predictable and sustained response than IV administration, and lower doses of ESAs are generally needed. IV administration is often utilized in patients who have established IV access or are receiving HD. Starting doses of ESAs depend on the Hgb level, the target Hgb level, the rate of Hgb increase, and clinical circumstances. The initial increase in Hgb should be 1 to 2 g/dL (10–20 g/L or 0.62–1.24 mmol/L) per month.[23] The recommended starting doses of the ESAs are listed in Table 26–4.

When prescribing ESAs, clinicians should not attempt to target "normal" Hgb levels (ie, > 13 g/dL [130 g/L or 8.07 mmol/L] in males; > 12 g/dL [120 g/L or 7.45 mmol/L] in females). Several clinical trials have demonstrated that targeting Hgb levels greater than 13 g/dL (130 g/L or 8.07 mmol/L) resulted in more cardiovascular complications or death, compared with target Hgb levels less than 11 g/dL (110 g/L or 6.83 mmol/L).[23] Further studies are needed to evaluate the appropriate target level for Hgb. Nonetheless, based on these findings, the US FDA recommended addition of a black box warning to the product information for all ESAs indicating the maximum target Hgb should not exceed 11 g/dL (110 g/L or 6.83 mmol/L) and requires a medication guide be given to patients who are receiving ESAs. However, KDIGO suggests a maximum threshold of 11.5 g/dL (115 g/L or 7.14 mmol/L).[23]

▶ *Outcome Evaluation*

The outcomes to monitor for anemia of CKD include hemoglobin, iron status, and the need for blood transfusions. Hemoglobin should be monitored every 3 months in patients with CKD not on dialysis or receiving PD and monthly in patients receiving HD. Evaluate Hgb monthly when ESA therapy is initiated or the dose is adjusted to ensure Hgb does not exceed 11.5 g/dL (115 g/L or 7.14 mmol/L).[23] The ESA dose can increase monthly if Hgb is below goal. Once a stable Hgb is attained, evaluate Hgb every 3 months thereafter. While the patient is receiving

Patient Encounter 2, Part 2

The patient returns to your clinic in 1 week and states that her symptoms have not changed. She is asking about the results of her laboratory studies.

Labs: WBC 4.2×10^3 cells/mm^3 (4.2×10^9/L); RBC 2.7×10^6 cells/mm^3 (2.7×10^{12}/L); Hgb 9.2 g/dL (92 g/L; 5.71 mmol/L); hematocrit 27% (0.27); mean corpuscular volume (MCV) 86 fL; mean corpuscular hemoglobin concentration (MCHC) 31 g/dL (310 g/L); platelets 298×10^3 cells/mm^3 (298×10^9/L); iron 131 mcg/dL (23.4 µmol/L); total iron binding capacity (TIBC) 390 mcg/dL (69.8 µmol/L); ferritin 162 ng/mL (mcg/L; 364 pmol/L); transferrin saturation (TSat) 26% (0.26); stool guaiac negative × 3

What treatment would you recommend for this patient for treatment of anemia?

How would you evaluate the effectiveness of treatment of anemia?

ESA therapy, monitor iron stores at least every 3 months or more frequently when initiating or increasing the dose of ESAs, when monitoring response to a course of IV therapy, or when blood loss or other circumstances that may lead to depletion of iron stores occur.[23] When the goal Hgb is reached, monitor iron stores every 3 months. Serum ferritin and TSat should be monitored no sooner than 1 week after the last dose of IV iron is administered.

CKD-Mineral and Bone Disorder and Secondary Hyperparathyroidism

▶ *Epidemiology and Etiology*

Increases in parathyroid hormone (PTH) occur early as kidney function begins to decline. The actions of PTH on bone turnover lead to CKD-mineral and bone disorders (CKD-MBD). The majority of patients with CKD G3-G5 have CKD-MBD.[25]

▶ *Pathophysiology*

As kidney function declines in patients with CKD, decreased phosphorus excretion disrupts the balance of calcium and phosphorus homeostasis. Decreased vitamin D activation in the kidney also decreases calcium absorption from the gastrointestinal (GI) tract. Fibroblast growth factor 23 (FGF-23) is a hormone produced by osteocytes and osteoblasts that is stimulated by increased phosphate and calcitriol. In CKD, elevated phosphate concentrations increase expression of FGF-23, which promotes phosphorus excretion and downregulates vitamin D activation in the kidney.[26] Each of these stimulates the parathyroid glands.

KEY CONCEPT The parathyroid glands release PTH in response to decreased serum calcium and increased serum phosphorus levels. The actions of PTH include the following:

- Increasing calcium resorption from bone
- Increasing calcium reabsorption from the proximal tubules in the kidney
- Decreasing phosphorus reabsorption in the proximal tubules in the kidney
- Stimulating activation of vitamin D by 1-α-hydroxylase to calcitriol (1,25-dihydroxyvitmin D_3) to promote calcium absorption in the GI tract and increased calcium mobilization from bone

All of these actions are directed at increasing serum calcium levels and decreasing serum phosphorus levels, although the activity of calcitriol also increases phosphorus absorption in the GI tract and mobilization from the bone, which can worsen hyperphosphatemia. Calcitriol also decreases PTH levels through a negative feedback loop. These measures are sufficient to correct serum calcium levels in the earlier stages of CKD.

As kidney function continues to decline and the GFR falls less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2), phosphorus excretion continues to decrease and calcitriol production decreases,[26] causing PTH levels to begin to rise significantly, leading to sHPT. The excessive production of PTH leads to hyperplasia of the parathyroid glands, which decreases the sensitivity of the parathyroid glands to serum calcium levels and calcitriol feedback, further promoting sHPT. The most dramatic consequences of sHPT are vascular calcifications and alterations in bone turnover, which lead to renal osteodystrophy (ROD). The pathogenesis of sHPT and CKD-MBD is depicted in Figure 26–3.

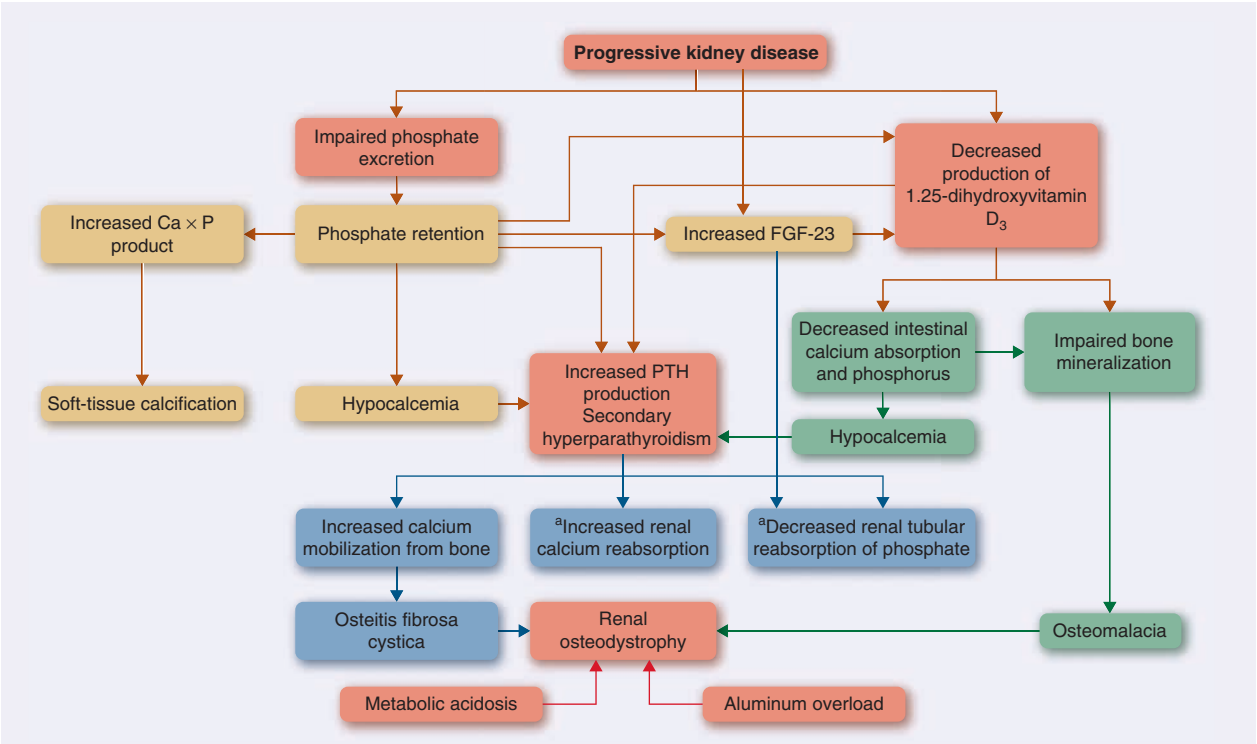

FIGURE 26–3. Pathogenesis of CKD-MBD. (Ca, calcium; FGF-23, fibroblast growth factor-23, PTH, parathyroid hormone.) [a]FGF-23 also increases in response to 1,25-dihydroxyvitamin D_3. [b]These adaptations are lost as kidney failure progresses. (From Hudson JQ, Wazny LD. Chronic kidney disease. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill Education; 2017:613, with permission.)

▶ *Treatment*

General Approach KEY CONCEPT Diagnosis and management of bone disease in CKD is based on corrected serum levels of calcium and phosphorus, and intact PTH levels (iPTH).[25,27] KDIGO guidelines recommend that hypercalcemia should be avoided in patients with CKD.[27] Phosphorus and PTH levels should be maintained as close to normal as possible.

Current recommendations suggest that treatment of CKD-MBD should take into consideration evaluations of calcium, phosphorus, and PTH level collectively and trends over time.[27] When phosphorus levels remain elevated, phosphorus-lowering treatment should be started. Management of sHPT often requires treatment with vitamin D analogs or cinacalcet in addition to phosphorus management.

Nonpharmacologic Therapy The first-line treatment for the management of hyperphosphatemia is dietary phosphorus restriction to 800 to 1000 mg/day in patients with CKD G3 or higher who have phosphorus levels at the upper limit of the normal range or elevated iPTH levels.[25,27] Many foods high in phosphorus are also high in protein, which can make it difficult to restrict phosphorus intake while maintaining adequate protein intake to avoid malnutrition. HD and peritoneal dialysis (PD) can remove up to 2 to 3 g of phosphorus per week. However, this is usually insufficient to control hyperphosphatemia, and pharmacologic therapy is necessary in addition to dialysis treatment.

Other nonpharmacologic strategies to manage sHPT and CKD-MBD include restriction of aluminum exposure and parathyroidectomy. Chronic ingestion of aluminum-containing antacids and other aluminum-containing products should be avoided in patients with CKD G4 and G5 (GFR less than 30 mL/min/1.73 m^2 [0.29 mL/s/m^2]) because of the risk of aluminum toxicity and potential uptake into the bone. Purification techniques for dialysate solutions also minimize the risk of exposure to aluminum.

Parathyroidectomy is a treatment of last resort for sHPT, but should be considered in patients with persistently elevated iPTH levels above 800 pg/mL (ng/L; 85.6 pmol/L) that is refractory to medical therapy to lower serum calcium and/or phosphorus levels.[25] A portion or all of the parathyroid tissue may be removed, and in some cases a portion of the parathyroid tissue may be transplanted into another site, usually the forearm for easy surgical access. After parathyroidectomy, serum calcium levels can decrease dramatically due to the low levels of PTH after the parathyroid tissue is removed, which decreases intestinal calcium absorption and bone resorption. Therefore, serum ionized calcium levels should be monitored frequently (every 4 to 6 hours for the first 48 to 72 hours) in patients receiving a parathyroidectomy. Calcium supplementation is usually necessary, administered IV initially, then orally (with vitamin D supplementation) once normal calcium levels are attained for several weeks to months after the procedure.

Clinical Presentation and Diagnosis of sHPT and ROD

General

Onset of sHPT and ROD is subtle and may not be associated with symptoms.

Symptoms

sHPT and ROD are usually asymptomatic in early disease. Calcification in the joints can be associated with decreased range of motion.

Conjunctival calcifications are associated with a gritty sensation in the eyes, redness, and inflammation.

Signs

Cardiovascular: Increased stroke index, heart rate, and diastolic and mean arterial pressures

Musculoskeletal: Bone pain, muscle weakness

Dermatologic: Pruritus

Laboratory Tests

Increased serum phosphorus levels

Low to normal serum calcium levels

Increased PTH levels

Decreased vitamin D levels

Diagnostic Tests

Radiographic studies show calcium–phosphate deposits in joints and/or cardiovascular system.

Bone biopsy of the iliac crest (not routinely performed)

Pharmacologic Therapy

Phosphate-Binding Agents. When serum phosphorus levels cannot be controlled by restriction of dietary intake, phosphate-binding agents are used to bind dietary phosphate in the GI tract to form an insoluble complex that is excreted in the feces. Phosphorus absorption is decreased, thereby decreasing serum phosphorus levels. The drugs used for binding dietary phosphate are listed in Table 26–5. The selection of the phosphate binding agent should be on sequential assessment of calcium and PTH levels in addition to the phosphorus level. These agents should be administered with each meal and can be tailored to the amount of phosphorus that is typically ingested during each meal. For example, patients can take a smaller dose with smaller meals or snacks, and a larger dose with larger meals. Although phosphate binders are not FDA approved for patients with CKD who are not receiving dialysis, they are used clinically when phosphorus levels are elevated, regardless of the GFR category.

Sevelamer and lanthanum phosphate binders do not contain calcium, iron, or aluminum. These agents are particularly useful in patients with hyperphosphatemia who have elevated serum calcium levels or who have vascular or soft tissue calcifications. Sevelamer is a cationic polymer that is not systemically absorbed and binds to phosphate in the GI tract, and it prevents absorption and promotes excretion of phosphate through the GI tract via the feces. Sevelamer has an added benefit of reducing LDL-C by up to 30% and increasing HDL-C levels.[25] The most common side effects of sevelamer are GI complaints including nausea, constipation, and diarrhea. However, some studies demonstrate that sevelamer may decrease mortality in patients receiving HD compared with CCPBs, primarily by decreasing the occurrence of calcifications in the coronary arteries.[25] Sevelamer carbonate may have added benefit to aid in the correction of metabolic acidosis.

Lanthanum is a naturally occurring trivalent rare earth element (atomic number 57). Lanthanum carbonate quickly dissociates in the acidic environment of the stomach, where the lanthanum ion binds to dietary phosphorus, forming an insoluble compound

Table 26–5

Phosphate-Binding Agents Used to Treat Hyperphosphatemia in CKD

Compound	Trade Name	Dosage Form	Compound Content (mg)	Elemental Compound Content (mg)	Starting Dose	Comments
Resin-based binders						
Sevelamer carbonate	Renvela®	Tablet, Powder for suspension	800		800 mg three times a day with meals	First-line agent; lowers LDL-C More expensive than calcium products; preferred in patients at risk for extraskeletal calcification May require large doses to control phosphorus levels
Elemental-based binders						
Lanthanum	Fosrenol®	Chewable tablet	500, 750, 1000	—	750–1500 mg three times a day with meals	Second-line agent; more expensive than calcium products; preferred in patients at risk for extraskeletal calcification Most patients require 1500–3000 mg/day to control phosphorus
Iron-based binders						
Sucroferric oxyhydroxide	Velphoro®	Chewable tablet	500	—	500 mg three times a day with meals	Do not use with levothyroxine; separate from doxycycline and alendronate by 1 hour
Ferric citrate	Auryxia®	Tablet	210	1 g ferric citrate	420 mg (2 tablets) three times a day with meals	Maximum dose is 12 tablets per day; iron is systemically absorbed
Calcium-containing binders						
Calcium carbonate (40% elemental calcium)	Tums®	Chewable tablet	500, 750, 1000; 1250	200, 300, 400, 500	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; dissolution characteristics and phosphorus-binding effect may vary from product to product; try to limit daily intake of elemental calcium to 1500 mg/day Approximately 39 mg phosphorus bound per 1 g calcium carbonate
	Oscal®-500	Tablet	1250	500		
	Caltrate® 600	Tablet	1500	600		
	Nephro-Calci™	Tablet	1500	600		
	LiquiCal™	Liquid gelcap	1200	480		
	Calci-Chew®	Chewable tablet	1250	500		
Calcium acetate (25% elemental calcium)	PhosLo®	Capsule, Tablet	667	167	0.5–1 g (elemental calcium) three times a day with meals	First-line agent; comparable efficacy to calcium carbonate with one-half the dose of elemental calcium; do not exceed 1500 mg elemental calcium intake per day Approximately 45 mg phosphorus bound per 1 g calcium acetate By prescription only
	Phoslyra®	Solution	667/5 mL			
Aluminum-based binders						
Aluminum hydroxide	AlternaGel® Amphojel®	Suspension	Various	—	300–600 mg three times a day with meals	Third-line agents; do not use concurrently with citrate-containing products Reserve for short-term use (4 weeks) in patients with hyperphosphatemia not responding to other binders

CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol.

that is excreted in the feces. Lanthanum has been shown to be as effective as other phosphate binders and may improve bone turnover, compared with calcium-containing products.[25] Side effects of lanthanum include nausea, peripheral edema, and myalgias.

Sucroferric oxyhydroxide and ferric citrate are iron-based phosphate binders that lower phosphate levels. Sucroferric oxyhydroxide is an insoluble form of iron that binds to phosphate in the GI tract and has been shown to be as effective as other phosphate binders with a lower pill burden.[28] Ferric citrate also lowers phosphate as effectively as other phosphate binders and can also increase serum ferritin and Tsat levels. The major side effects associated with both products are GI side effects, namely diarrhea. Sucroferric oxyhydroxide cannot be taken with levothyroxine and

must be taken 1 hour after doxycycline and alendronate.[28] This product was not studied in patients on PD, with significant liver or GI disease, or following major GI surgery.[28]

CCPBs, including calcium carbonate and calcium acetate, are effective in decreasing serum phosphate levels, as well as in increasing serum calcium levels. Calcium acetate binds more phosphorus than the carbonate salt, making it a more potent agent for binding dietary phosphate. Calcium carbonate can also aid in the correction of metabolic acidosis, another complication of kidney failure. Calcium citrate is usually not used as a phosphate-binding agent because the citrate salt can increase aluminum absorption. The dose of CCPBs should be limited because cardiovascular events and progression to dialysis are increased if calcium intake exceeds calcium losses.[27] In general, CCPBs should not be used if corrected serum calcium levels are near or above the upper end of the normal range or if arterial calcifications are present. Some evidence suggests that the use of CCPBs in CKD G3a-4 affects calcium balance, but does not decrease phosphorus balance.[29] Therefore, current guidelines recommend restricting the dose of CCPBs in all stages of CKD.[27] The most common adverse effects of CCPBs are constipation and hypercalcemia.

Aluminum-containing phosphate-binding agents are not recommended for chronic use in patients with CKD to avoid aluminum accumulation, leading to encephalopathy, bone disease, and anemia. These agents may be used for a short course of therapy (< 4 weeks) for significantly elevated phosphorus levels in AKI.

Vitamin D Therapy. Vitamin D regulates many processes in the body, including calcium and phosphorus absorption from the GI tract and kidney, PTH secretion, maintaining muscle, cardiovascular, immune and brain function, and glucose control. Vitamin D is activated in various tissues, with the liver and kidney being primary sites. In CKD, a decrease in renal metabolism of vitamin D decreases circulating concentrations of the activated form of vitamin D, calcitriol (1,25-dihydroxyvitamin D) and its precursor 25-hydroxyvitamin D. Vitamin D deficiency begins early in CKD and increases as kidney function declines.[30] PTH levels rise as early as CKD G3 as a result of low calcitriol concentrations.

Exogenous vitamin D compounds that mimic the activity of calcitriol act directly on the parathyroid gland to decrease PTH secretion by upregulation of the vitamin D receptor in the parathyroid gland, which decreases parathyroid gland hyperplasia and PTH synthesis and secretion. This is particularly useful when reduction of serum phosphorus levels does not sufficiently reduce PTH levels.

Vitamin D supplements (Table 26–6) can be used to lower serum PTH levels in patients with CKD. Ergocalciferol, cholecalciferol, and calcifediol have been shown to be effective in lowering PTH secretion in patients with CKD G3, and are useful in later stages of CKD to maintain adequate 25-hydroxyvitamin D levels for extrarenal functions.[27,30] In CKD G4 and G5, activated vitamin D analogs must be used to decrease PTH secretion in severe hyperparathyroidism.[27] Synthetic calcitriol has the same biologic activity as endogenous calcitriol. Doxercalciferol (1-α-hydroxyvitamin D_2) is another vitamin D analog that is hydroxylated in the liver to 1,25-dihydroxyvitamin D_2, which has the same biologic activity as calcitriol. Both calcitriol and doxercalciferol upregulate vitamin D receptors in the intestines, which increase calcium and phosphorus absorption, increasing the risk of hypercalcemia and hyperphosphatemia. It is important that serum calcium and phosphorus levels are within the normal range for the stage of CKD prior to starting either of these therapies. Paricalcitol (19-nor-1,25-dihydroxyvitamin D_2) is a vitamin D analog that has equal efficacy to calcitriol. Alfacalcidol (1-α-hydroxyvitamin D_3), falecalcitriol, and 22-oxacalcitriol (maxacalcitol) are only available outside the United States.

Calcimimetics. Cinacalcet and etelcalcetide are calcimimetics that increase the sensitivity of receptors on the parathyroid gland to serum calcium levels to reduce PTH secretion, but have no effect on intestinal absorption of calcium or phosphorus, and lower serum calcium levels.[25,31] Thus, calcimimetics are beneficial for patients with elevated PTH levels who have increased calcium or phosphorus levels or cannot use vitamin D therapy. Calcimimetics should also be used with caution in patients with seizure disorders because low serum calcium levels can lower the seizure threshold. Cinacalcet is an oral calcimimetic that is most widely used for sHPT. GI side effects, including nausea and vomiting, can decrease tolerability of cinacalcet for some patients. Etelcalcetide is an injectable agent that was recently developed to reduce GI side effects. It is administered as an IV three times a week after HD, which may improve adherence.[31]

Table 26–6

Available Treatments for Secondary Hyperparathyroidism

Generic Name	Trade Name	Dosage Range	Dosage Forms	Frequency of Administration
Vitamin D (prohormone)				
Ergocalciferol	Vitamin D_2	400–50,000 IU	PO	Daily (doses of 400–2000 IU) Weekly or monthly for higher doses (50,000 IU)
Cholecalciferol	Vitamin D_3			
Calcifediol	Rayaldee®	30–60 mcg	PO	Daily
Active vitamin D				
Calcitriol	Calcijex®	0.5–5 mcg	IV	Three times per week
	Rocaltrol®	0.25–5 mcg	PO	Daily, every other day, or three times per week
Vitamin D analogs				
Paricalcitol	Zemplar®	1–4 mcg	PO	Daily or three times per week
		2.5–15 mcg	IV	Three times per week
Doxercalciferol	Hectorol®	5–20 mcg	PO	Daily or three times per week
		2–8 mcg	IV	Three times per week
Calcimimetics				
Cinacalcet	Sensipar™	30–180 mg	PO	Daily
Etelcalcitide	Parsabiv™	2.5–15 mg	IV	Three times per week

Patient Encounter 3

A 58-year-old Caucasian man with a history of diabetes presents to your clinic for a routine follow-up. He has no complaints at this time.

PMH: Diabetes, diagnosed 5 years ago; hypertension, diagnosed 6 years ago; hyperlipidemia

Current meds: Aspirin 81 mg orally daily; atorvastatin 40 mg orally daily; carvedilol 12.5 mg orally twice daily; lisinopril 20 mg orally daily; glipizide 5mg orally twice daily; sitagliptin 25 mg orally daily

ROS: Unremarkable

PE:

VS: BP 136/84 mm Hg; P 70 beats/min; T 96.3°F (35.7°C); ht 6′1″ (185 cm); wt 277 lb (125.9 kg)

CV: RRR, normal S_1, S_2

Abd: No organomegaly, bruits, tenderness; (+) bowel sounds; heme (–) stool

Ext: 2+ edema bilaterally

Labs: Sodium 139 mEq/L (mmol/L); potassium 5.2 mEq/L (mmol/L); chloride 109 mEq/L (mmol/L); carbon dioxide 18 mEq/L (mmol/L); BUN 42 mg/dL (15 mmol/L urea); SCr 3.4 mg/dL (301 µmol/L); glucose 124 mg/dL (6.9 mmol/L); calcium 9.1 mg/dL (2.3 mmol/L); phosphate 7.2 mg/dL (2.33 mmol/L); intact parathyroid hormone (iPTH) 357 pg/mL (ng/L; 38.2 pmol/L); WBC 5.6×10^3 cells/mm^3 (5.6×10^9/L); RBC 3.9×10^6 cells/mm^3 (3.9×10^{12}/L); Hgb 9.8 g/dL (98 g/L; 6.08 mmol/L); Hct 29% (0.29); platelets 272×10^3 cells/mm^3 (272×10^9/L)

What signs are consistent with CKD mineral and bone disorder (MBD)?

What treatment would you recommend for CKD-MBD?

▶ *Outcome Evaluation*

KDIGO guidelines recommend monitoring serum calcium, phosphorus and PTH levels early in CKD, with increasing frequency as renal function declines. Calcium and phosphorus levels should be monitored every 6 to 12 months in CKD G3a-G3b; every 3 to 6 months in CKD G4, and every 1 to 3 months in CKD G5. PTH levels should be monitored every 6 to 12 months for CKD G3–G4 and every 3 to 6 months in CKD G5.[27]

Monitor serum calcium and phosphorus levels regularly in patients receiving phosphate-binding agents. When initiating therapy, monitor serum levels every 1 to 4 weeks, depending on the severity of hyperphosphatemia. Titrate doses of phosphate binders to maintain phosphorus levels near normal. Once target levels are achieved, monitor serum calcium and phosphorus levels every 1 to 3 months. Monitor intact PTH levels monthly while initiating vitamin D therapy, then every 3 months once stable iPTH levels are achieved. When starting or increasing the dose of cinacalcet, monitor serum calcium and phosphorus levels within 1 week; iPTH levels should be monitored within 1 to 4 weeks. Once target levels are achieved, decrease monitoring to every 3 months.

Impaired Electrolyte and Acid–Base Homeostasis

The kidney is responsible for regulating homeostasis for sodium, potassium, water, and acid–base. Reductions in the number of functioning nephrons decrease glomerular filtration regulation of electrolytes and acid secretion.

▶ *Pathophysiology*

As the number of functioning nephrons decreases, the remaining nephrons are able to increase excretion of sodium, water, potassium, and hydrogen ions. However, this is limited and as the number of functioning nephrons decreases as CKD progresses, total excretion of electrolytes and fluid eventually decreases.

Sodium and water balance is maintained by natriuretic peptides, namely atrial natriuretic peptide (ANP), which increases sodium excretion in the kidneys. The relative increase in sodium excretion by a smaller number of functioning nephrons results in an osmotic diuresis that promotes water excretion, but impairs the ability of the kidneys to concentrate and dilute urine. Thus, urine becomes fixed at an osmolality close to that of the plasma, approximately 300 mOsm/kg (mmol/kg), and presents as **nocturia**. Sodium and fluid retention increases intravascular volume and raises systemic blood pressure, which can present as early as CKD G3a-G3b.[32]

Potassium excretion occurs in both the distal tubules of the kidney and in the GI tract, which is mediated by aldosterone stimulation. Aldosterone increases in response to rising serum potassium, which then increases potassium excretion in both the functioning nephrons and GI tract. This maintains serum potassium concentrations within the normal range through CKD G1 to G4. Hyperkalemia begins to develop when GFR falls below 20% of normal, when the number of functioning nephrons and renal potassium secretion is so low that the capacity of the GI tract to excrete potassium has been exceeded.[33]

Medications can increase the risk of hyperkalemia in patients with CKD, including ACEI and ARBs, used for the treatment of proteinuria and hypertension. Potassium-sparing diuretics, used for the treatment of edema and chronic heart failure, can also exacerbate the development of hyperkalemia, and they should be used with caution in patients with CKD G3 or higher.

Hydrogen ions are excreted at the same rate of production by the kidney via buffers in the urine created by ammonia generation and phosphate excretion to maintain the pH of body fluids within a very narrow range. As kidney function declines, bicarbonate reabsorption is maintained, but hydrogen excretion is decreased because the ability of the kidney to generate ammonia is impaired. The positive hydrogen balance leads to metabolic acidosis, which is characterized by a serum bicarbonate level of 15 to 20 mEq/L (mmol/L), and an elevated anion gap greater than 17 mEq/L (mmol/L), resulting in a pH less than 7.35. Metabolic acidosis generally presents when the GFR declines below 25 mL/min/1.73 m^2 (0.24 mL/s/m^2).[34]

Metabolic acidosis contributes to various complications associated with CKD. Metabolic acidosis can directly cause bone disease, particularly in children, and contribute significantly to the bone disease induced by secondary hyperparathyroidism, as discussed previously. Metabolic acidosis also decreases hepatic albumin synthesis, which contributes to hypoalbuminemia and muscle wasting. Furthermore, metabolic acidosis can accelerate progression of CKD by causing tubular injury. Reversal of metabolic acidosis has been demonstrated to decrease progression of CKD, improve bone disease, and increase serum albumin concentrations.[34]

▶ *Treatment*

Nonpharmacologic treatment The kidney is unable to adjust to abrupt changes in sodium and potassium intake in patients

Clinical Presentation and Diagnosis of Electrolyte and Acid–Base Abnormalities

General

Alterations in sodium and water balance in CKD manifest as increased edema.

Hyperkalemia is generally asymptomatic in patients with CKD until serum potassium levels are greater than 5.5 mEq/L (mmol/L), when cardiac abnormalities present.

Metabolic acidosis is generally asymptomatic in patients with CKD.

Symptoms

Nocturia can present in CKD G3a-G3b.

Edema generally presents in CKD G4 or later.

Mild hyperkalemia and metabolic acidosis are generally not associated with overt symptoms.

Symptoms of hyperkalemia generally appear when GFR falls below 20 mL/min/1.73 m^2 (0.19 mL/s/m^2), such as muscle weakness, fatigue, nausea, and paresthesias.

Symptoms of chronic metabolic acidosis present as bone abnormalities and growth retardation in children.

Signs

Cardiovascular:

- Sodium: Worsening hypertension, edema
- Potassium: ECG changes (peaked T waves, widened QRS complex, loss of P wave)

Genitourinary: Sodium abnormalities result in change in urine volume and consistency.

Laboratory Tests

Sodium: Increased blood pressure; sodium levels remain within the normal range; urine osmolality is generally fixed at 300 mOsm/kg (mmol/kg)

Potassium: Increased serum potassium levels

Metabolic acidosis: Decreased serum bicarbonate levels (CO_2); decreased pH

with severe CKD. Electrolyte disorders resulting from an acute increase in intake can be more severe and prolonged.

Sodium and Water. Patients with CKD should be advised to refrain from adding salt to their diet but should not restrict sodium intake. Changes in sodium intake should occur slowly over a period of several days to allow adequate time for the kidney to adjust urinary sodium content. Sodium restriction produces a negative sodium balance, which causes fluid excretion to restore sodium balance. The resulting volume contraction can decrease perfusion of the kidney and hasten the decline in GFR. Saline-containing IV solutions should be used cautiously in patients with CKD because the salt load may precipitate volume overload.

Fluid restriction is generally unnecessary as long as sodium intake is controlled. The thirst mechanism remains intact in CKD to maintain total body water and plasma osmolality near normal levels. Fluid intake should be maintained at the rate of urine output to replace urine losses, usually fixed at approximately 2 L/day as urine concentrating ability is lost. Significant increases in free water intake orally or IV can precipitate volume overload and hyponatremia. Patients with CKD G5 require RRT to maintain normal volume status. Fluid intake is often limited in patients receiving HD to prevent fluid overload between dialysis sessions.

Diuretic therapy is often necessary to prevent volume overload in patients with CKD in those who still produce urine. When GFR falls below 30 ml/min/1.73 m^2 (0.29 mL/s/m^2), thiazide diuretics alone may not be effective in reducing fluid retention.[19] Loop diuretics are most frequently used to increase sodium and water excretion. As CKD progresses, higher doses, as much as 80 to 1000 mg/day of oral furosemide, or continuous infusion of loop diuretics may be needed, or combination therapy with loop and thiazide diuretics to increase sodium and water excretion.[19]

Potassium. Patients who develop hyperkalemia should restrict dietary intake of potassium to 50 to 80 mEq (mmol) per day. Potassium concentrations can also be altered in the dialysate for patients receiving HD and PD to manage hyperkalemia. Because GI excretion of potassium plays a large role in potassium homeostasis in patients with CKD G5, a good bowel regimen is essential to minimize constipation. Severe hyperkalemia is most effectively managed by HD.

Acute hyperkalemia can be managed medically until dialysis can be initiated. Diuretics, sodium polystyrene sulfonate, and fludrocortisone are useful in the management of hyperkalemia in patients with CKD. Acute hyperkalemia that results in cardiac abnormalities can be managed with calcium, insulin, and dextrose. The management of hyperkalemia is discussed in more detail in Chapter 27. Patiromer is a nonabsorbed potassium-binding polymer that is used for the treatment of hyperkalemia. Patiromer exerts its effect by exchanging calcium for potassium in the GI tract to enhance GI secretion of potassium. Serum potassium levels are significantly lowered within 7 hours of dosing.[35] Patiromer should be taken with food to enhance its effect and should be separated from all other oral medications by 3 hours.

Metabolic Acidosis. Pharmacologic therapy with sodium bicarbonate or citrate/citric acid preparations may be needed in patients with CKD G3 or higher to replenish body stores of bicarbonate. Calcium carbonate, used to bind phosphorus in sHPT, also aid in increasing serum bicarbonate levels, in conjunction with other agents. The management of acidosis is discussed in more detail in Chapter 28.

▶ *Outcome Evaluation*

Monitor serum electrolytes and bicarbonate levels regularly. Monitor edema after initiation of diuretic therapy. Monitor fluid intake to ensure obligatory losses are being met and avoid dehydration. If adequate diuresis is not attained with a single agent, consider combination therapy with another diuretic, such as a loop plus thiazide diuretic. In patients with cardiac abnormalities due to elevated potassium levels, monitor ECG continuously until serum potassium levels drop below 5 mEq/L (mmol/L) or cardiac abnormalities resolve. Evaluate serum potassium and glucose levels within 1 hour in patients who receive insulin and dextrose therapy. Evaluate serum potassium levels within 2 to 4 hours after treatment with patiromer, sodium polystyrene sulfonate (SPS), or diuretics. Repeat doses of diuretics or SPS if necessary until serum potassium levels fall below 5 mEq/L (mmol/L). Monitor blood pressure and serum potassium levels in 1 week after starting fludrocortisone. Correct metabolic acidosis slowly to prevent the development of metabolic alkalosis or other electrolyte abnormalities.

RENAL REPLACEMENT THERAPY

Patients who progress to ESKD require RRT. The modalities that are used for RRT are dialysis, including HD and PD, and kidney transplantation. The USRDS reported that the number of patients with ESKD was 703,243, with 124,114 new cases diagnosed in 2015.[2] The mortality rate of patients with ESKD was 13.6% in 2015, which is decreased from 20.4% in 1996.[2] The modality of RRT influences mortality considerably, with a 16.6% mortality rate with dialysis, compared to 3% mortality with transplant.[2] The improved survival makes kidney transplantation the preferred method of RRT; however, organ availability limits the number of patients who can receive a kidney transplant. Only 2.5% of patients with newly diagnosed ESKD receive kidney transplants each year.[2] Therefore, the most common form of RRT is dialysis, accounting for more than 97% of all patients with ESKD.[2] The principles and complications associated with dialysis are discussed later. Chapter 55 discusses the principles of kidney transplantation.

Indications for Dialysis

KEY CONCEPT Planning for dialysis should begin when GFR falls less than 30 mL/min/1.73 m^2 (0.29 mL/s/m^2) (CKD G4),[1] when progression to ESKD is inevitable, to allow time to educate the patient and family on the treatment modalities and establish the appropriate access for the modality of choice. Ideally, initiation of dialysis should be done at a point when the patient is ready to undergo treatment, rather than when the patient is in emergent need of dialysis.

Initiation of dialysis depends on the patient's clinical status and not based solely on laboratory values. Symptoms that may indicate the need for dialysis include persistent anorexia, nausea, vomiting, fatigue, and pruritus. Other criteria that indicate the need for dialysis include declining nutritional status, declining serum albumin levels, electrolyte abnormalities, particularly hyperkalemia, and volume overload, which may manifest as chronic heart failure and uncontrolled hypertension. **Blood urea nitrogen** (BUN) and SCr levels may be used as a guide for the initiation of dialysis, but they should not be the absolute indicator. Dialysis is initiated in most patients after the GFR falls below 15 mL/min/1.73 m^2 (0.14 mL/s/m^2).[1] Patients should determine which modality of dialysis to use based on their own preferences. Advantages and disadvantages of HD and PD are listed in Tables 26–7 and 26–8, respectively.

The goals of dialysis are to remove toxic metabolites to decrease uremic symptoms, correct electrolyte abnormalities, restore acid–base status, and maintain volume status to ultimately improve quality of life and decrease the morbidity and mortality associated with ESKD.

Hemodialysis

HD is the most common method of RRT, initiated in 88% of US patients with newly diagnosed ESKD each year, with a total of 428,588 patients receiving HD in 2014.[2] Home HD is becoming increasingly more popular, but most patients continue to receive HD from a dialysis center.

▶ *Principles of HD*

KEY CONCEPT HD involves the exposure of blood to a semipermeable membrane (dialyzer) against which a physiologic solution (dialysate) is flowing (Figure 26–4). The dialyzer is composed of thousands of capillary fibers made up of the semipermeable membrane, which are enclosed in the dialyzer, to increase the surface area of blood exposure to maximize the efficiency of removing substances. The dialysate is composed of purified water and electrolytes, and it is run through the dialyzer countercurrent to the blood on the other side of the semipermeable membrane. The process allows for the removal of several substances from the bloodstream, including water, urea, creatinine, electrolytes, uremic toxins, and some drugs. Sterilization is not required for dialysate because the membrane prevents bacteria from entering into the bloodstream. However, if the membrane ruptures during HD, infection becomes a major concern for the patient.

Three types of membranes used for dialysis are classified by the size of the pores and the ability to remove solutes from the bloodstream: low flux, high efficiency, and high flux. Low flux membranes have small pores, which limit solute removal to relatively small molecules, such as creatinine and urea. High-efficiency membranes also have small pores but have a higher surface area that increases removal of small molecules, such as water, urea, and creatinine from the blood. The most widely used dialyzers are high-flux membranes which larger pores allow for the removal of substances with higher molecular weight, including some drugs, such as vancomycin.

Three primary processes are utilized for the removal of substances from the blood:

- Diffusion is the movement of a solute across the dialyzer membrane from an area of higher concentration (usually the blood) to a lower concentration (usually the dialysate). This process removes small molecules from the bloodstream, such as electrolytes. At times, solutes can be added to the dialysate that are diffused into the bloodstream. Changing the composition of the dialysate allows for control of the amount of electrolytes that are being removed.
- Ultrafiltration is the movement of solvent (plasma water) across the dialyzer membrane by applying hydrostatic or osmotic pressure, and it is the primary means for removing

Table 26–7

Advantages and Disadvantages of Hemodialysis

Advantages

1. Higher solute clearance allows intermittent treatment.
2. Parameters of adequacy of dialysis are better defined and therefore underdialysis can be detected early.
3. The technique's failure rate is low.
4. Even though intermittent heparinization is required, hemostasis parameters are better corrected with hemodialysis than peritoneal dialysis.
5. In-center hemodialysis enables closer monitoring of the patient.

Disadvantages

1. Requires multiple visits each week to the hemodialysis center, which translates into loss of control by the patient.
2. Dysequilibrium, dialysis, hypotension, and muscle cramps are common. May require months before patient adjusts to hemodialysis.
3. Infections in hemodialysis patients may be related to the choice of membranes; the complement-activating membranes are more deleterious.
4. Vascular access is frequently associated with infection and thrombosis.
5. Decline of residual renal function is more rapid compared with peritoneal dialysis.

From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:640, with permission.

Table 26–8

Advantages and Disadvantages of Peritoneal Dialysis

Advantages

1. More hemodynamic stability (blood pressure) due to slow ultrafiltration rate
2. Increased clearance of larger solutes, which may explain good clinical status in spite of lower urea clearance
3. Better preservation of residual renal function
4. Convenient intraperitoneal route of administration of drugs such as antibiotics and insulin
5. Suitable for elderly and very young patients who may not tolerate hemodialysis well
6. Freedom from the "machine" gives the patient a sense of independence (for continuous ambulatory peritoneal dialysis)
7. Less blood loss and iron deficiency, resulting in easier management of anemia or reduced requirements for erythropoietin and parenteral iron
8. Systemic heparin not required
9. Subcutaneous versus IV erythropoietin or darbepoetin is usual, which may reduce overall doses and be more physiologic

Disadvantages

1. Protein and amino acid losses through the peritoneum and reduced appetite owing to continuous glucose load and sense of abdominal fullness predispose to malnutrition
2. Risk of peritonitis
3. Catheter malfunction, and exit site and tunnel infection
4. Inadequate ultrafiltration and solute dialysis in patients with a large body size, unless large volumes and frequent exchanges are employed
5. Patient burnout and high rate of technique failure
6. Risk of obesity with excessive glucose absorption
7. Mechanical problems such as hernias, dialysate leaks, hemorrhoids, or back pain may occur
8. Extensive abdominal surgery may preclude peritoneal dialysis
9. No convenient access for IV iron administration

From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:641, with permission.

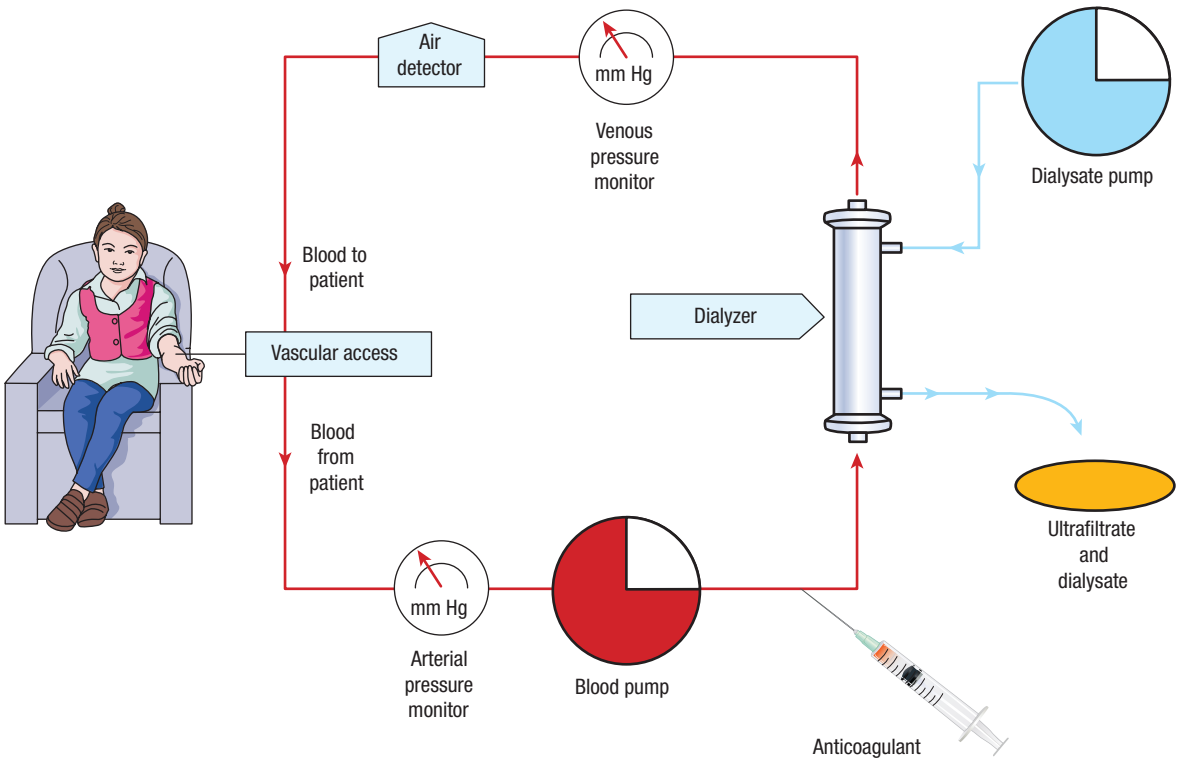

FIGURE 26–4. In hemodialysis, the patient's blood is pumped to the dialyzer at a rate of 300 to 600 mL/min. An anticoagulant (usually heparin) is administered to prevent clotting in the dialyzer. The dialysate is pumped at the rate of 500 to 1000 mL/min through the dialyzer countercurrent to the flow of blood. The rate of fluid removal from the patient is controlled by adjusting the pressure in the dialysate compartment. (From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2014:642, with permission.)

Patient Encounter 4, Part 1

A 35-year-old Caucasian man with a history of IgA nephropathy presents to the clinic with complaints that he "feels awful." He has not felt like eating for several weeks and has lost 15 lb (6.8 kg) in the last 3 months.

PMH: IgA nephropathy; depression; hypertension; hyperlipidemia

Current medications: Bupropion 150 mg orally daily; vitamin D_3 1000 IU orally daily; escitalapram 10 mg orally daily; hydralazine 50 mg orally three times daily; labetalol 200 mg orally twice daily; calcium acetate 1334 mg orally three times daily with meals; pravastatin 40 mg orally daily

ROS: Lethargic male in mild distress

PE:

VS: BP 178/108 mm Hg; P 86 beats/min; T 97.2°F (36.2°C); ht 5'10" (178 cm); wt 186 lb (84.5 kg)

CV: RRR, normal S_1, S_2, present

Lungs: Crackles at bases; mild inspiratory wheezes

Ext: 4+ bilateral lower extremity edema present to mid-thigh

Labs: Sodium 138 mEq/L (mmol/L); potassium 6.3 mEq/L (mmol/L); chloride 106 mEq/L (mmol/L); carbon dioxide 15 mEq/L (mmol/L); BUN 52 mg/dL (18.6 mmol/L); SCr 6.2 mg/dL (548 µmol/L); glucose 62 mg/dL (3.4 mmol/L); calcium 9.8 mg/dL (2.45 mmol/L); phosphate 5.6 mg/dL (1.81 mmol/L); iPTH 315 pg/mL (ng/L; 33.7 pmol/L); WBC 6.8 × 10^3 cells/mm^3 (6.8 × 10^9/L); RBC 4.0 × 10^6 cells/mm^3 (4.0 × 10^{12}/L); Hgb 10.4 g/dL (104 g/L; 6.46 mmol/L); Hct 30% (0.30); platelets 278 × 10^3 cells/mm^3 (278 × 10^9/L)

What indications does the patient have for dialysis?

What alternatives for renal replacement therapy exist for the patient?

What are the advantages and disadvantages of each modality for renal replacement?

water from the bloodstream. Changing the hydrostatic pressure applied to the dialyzer or the osmotic concentration of the dialysate allows for control of the amount of water being removed.

- Convection is the movement of dissolved solutes across the dialyzer membrane by "dragging" the solutes along a pressure gradient with a fluid transport and is the primary means for larger molecules to be removed from the bloodstream, such as urea. Changing the pore size of the dialyzer membrane alters the efficiency of convection and allows for control of the amount of water removed in relation to the amount of solute being removed.

▶ *Vascular Access*

Long-term permanent access to the bloodstream is a key component of HD. There are three primary techniques used to obtain permanent vascular access in patients receiving HD: arteriovenous fistulas (AVFs), arteriovenous grafts (AVGs), and central venous catheters. An AVF is the preferred access method because it has the longest survival rate and the fewest complications. An AVF is made by creating an **anastomosis** between an artery and a vein, usually in the forearm of the nondominant arm (**Figure 26–5**). An AVG results in a similar access site but uses a synthetic graft, usually made of polytetrafluoroethylene, to connect the artery and vein in the forearm (Figure 26–5). The advantage of the AVG is that it is able to be used within 2 to 3 weeks, compared with 2 to 3 months for an AVF. However, AVGs are complicated by stenosis, thrombosis, and infections, which lead to a shorter survival time of the graft. Double-lumen venous catheters, placed in the femoral, subclavian, or jugular vein, are often used as temporary access while waiting for the AVF or AVG to mature. The catheters are tunneled beneath the skin to an exit site to reduce the risk of infection. Venous catheters can also be used as permanent access in patients in whom arteriovenous access cannot be established. However, venous catheters carry the greatest risk of complications, namely thrombosis and infections.

▶ *Complications of HD*

Complications associated with HD include hypotension, muscle cramping, thrombosis, infection, and vitamin depletion. The physiology of these complications is described below and the management is listed in **Table 26–9**.

Hypotension Hypotension is the most common complication seen during HD. It has been reported to occur with approximately 20% to 30% of dialysis sessions.[36]

Pathophysiology. Hypotension associated with HD manifests as a symptomatic decrease in systolic blood pressure of more than 20 mm Hg or a decrease in mean arterial pressure of more than 10 mm Hg during the dialysis session. The primary cause is fluid removal from the bloodstream. Ultrafiltration removes fluid from the plasma, which promotes redistribution of fluids from extracellular spaces into the plasma. However, decreased serum albumin levels and removal of solutes from the bloodstream reduce the osmotic pressure of the plasma relative to the extracellular spaces, slowing redistribution during HD. The decreased plasma volume causes hypotension. Other factors that can contribute to hypotension include antihypertensive medications prior to HD, a target "dry weight" (the target weight after HD session is complete) that is too low, diastolic or autonomic dysfunction, low dialysate calcium or sodium, high dialysate temperature, or ingesting meals prior to or during HD. Elderly age, diabetes, autonomic neuropathy, uremia, and cardiac disease also increase the potential for hypotension.[36] The symptoms associated with hypotension during dialysis include dizziness, nausea, vomiting, abdominal pain, and muscle cramping.

Muscle Cramps Muscle cramps are reported in as many as 35% to 86% of patients receiving HD.[37] The cause is often related to excessive ultrafiltration, which causes hypoperfusion of the muscles. Other contributing factors to the development of muscle cramps include hypotension, hypoosmolality, and electrolyte and acid–base imbalances that occur during HD sessions.[37]

Thrombosis Thrombosis associated with HD most commonly occurs in patients with venous catheter access for dialysis and is a common cause of catheter failure. However, thrombosis can occur in synthetic grafts and less frequently in AVFs.

Infection Infections are an important cause of morbidity and mortality in patients receiving HD. The cause of infection is usually related to organisms found on the skin, namely *Staphylococcus epidermidis* and *S. aureus*, including methicillin-resistant

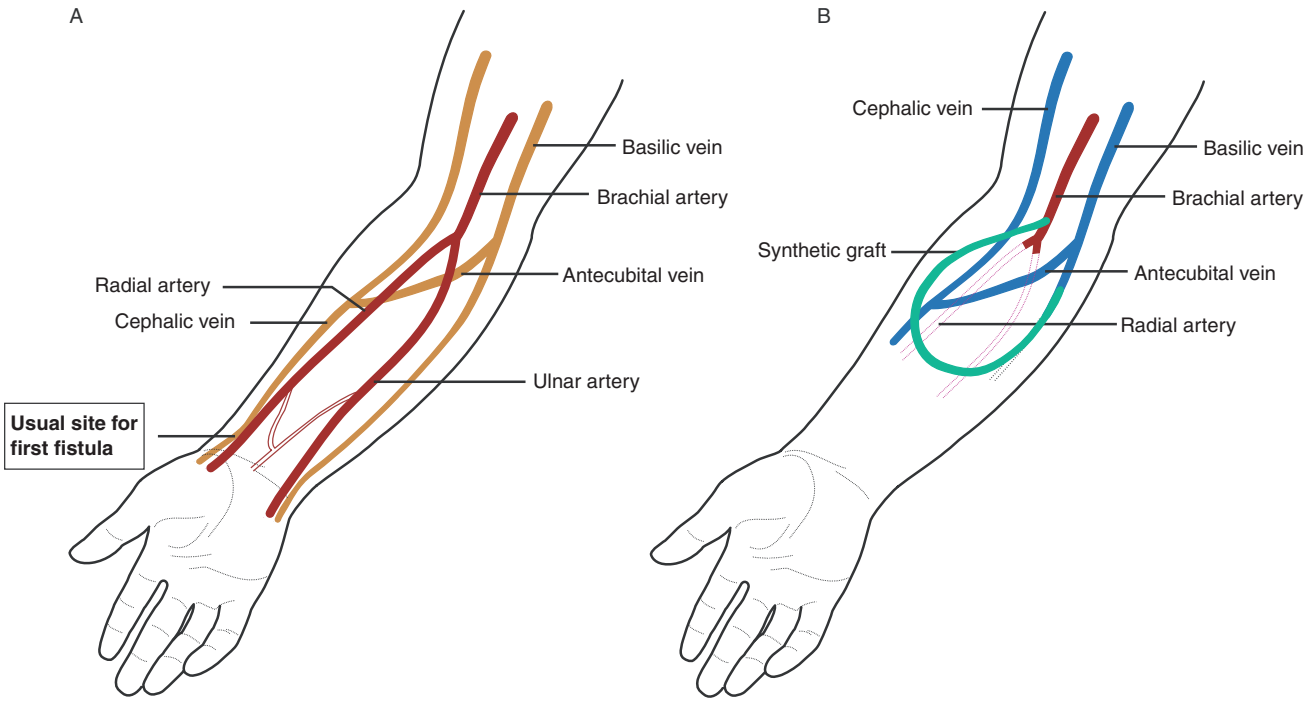

FIGURE 26–5. The predominant types of vascular access for chronic dialysis patients are (A) the arteriovenous fistula and (B) the synthetic arteriovenous forearm graft. The first primary arteriovenous fistula is usually created by the surgical anastomosis of the cephalic vein with the radial artery. The flow of blood from the higher-pressure arterial system results in hypertrophy of the vein. The most common AV graft (depicted in green) is between the brachial artery and the basilic or cephalic vein. The flow of blood may be diminished in the radial and ulnar arteries because it preferentially flows into the low pressure graft. (From Sowinski KM, Churchwell MD, Decker BS. Hemodialysis and peritoneal dialysis. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:642, with permission.)

S. aureus (MRSA). Gram-negative bacteria are more commonly associated with bacteremia. The greatest risk to patients receiving HD is the development of bacteremia, which is commonly associated with coagulase negative staphylococci and gram-negative bacteria. The risk of bacteremia is up to 10 times higher with venous catheters compared to AVF.[38]

Blood cultures should be obtained for any patient receiving HD who develops a fever. Nonpharmacologic management of

Table 26–9

Management of Complications Associated with Hemodialysis

Hypotension	Acute treatment	Place in Trendelenburg position (head lower than feet) Normal saline 100–200 mL Hypertonic saline (23.4%) 10–20 mL Mannitol 12.5 g
	Prevention	Accurate determination of "dry weight" Midodrine 2.5–10 mg 30 minutes prior to HD Other options with limited evidence: Levocarnitine 20 mg/kg IV after HD Sertraline 50–100 mg daily Fludrocortisone 0.1 mg before HD
Muscle cramps	Acute treatment	Normal saline 100–200 mL Hypertonic saline (23.4%) 10–20 mL Dextrose 50% 50 mL (for nondiabetic patients)
	Prevention	Decrease ultrafiltration rate Accurate determination of "dry weight" Stretching exercises, massage, flexing, compression devices Vitamin E 400 IU daily
Central venous catheter thrombosis	Acute treatment	Normal saline flush Alteplase 2 mg/2 mL per catheter lumen port Reteplase 0.4 units/0.4 mL per catheter lumen port
	Prevention	Heparin lock (1000–10,000 units/1 mL) Sodium citrate 4% lock
Vitamin depletion	Prevention	Multivitamin B complex with vitamin C supplement

infections involves preventive measures with sterile technique, proper disinfection, and minimizing the use and duration of venous catheters for HD access.

Pharmacologic management of infections should cover the gram-positive organisms that most frequently cause access-related infections. Patients who have positive blood cultures should receive treatment tailored to the organism isolated. Preventive measures for access-related infections include mupirocin at the exit site and povidone-iodine ointment. The recommendations of the National Kidney Foundation (NKF) for treatment of infections associated with HD are listed in Table 26–10.

Vitamin Depletion Water-soluble vitamins removed by HD contribute to malnutrition and vitamin deficiency syndromes. Patients receiving HD often require replacement of water-soluble vitamins to prevent adverse effects. The vitamins that may require replacement are ascorbic acid, thiamine, biotin, folic acid, riboflavin, and pyridoxine. Patients receiving HD should take a multivitamin B complex with vitamin C supplement, but they should not take supplements that include fat-soluble vitamins, such as vitamins A, E, or K, which can accumulate in patients with kidney failure.

Peritoneal Dialysis

PD is initiated in 9.6% of patients with newly diagnosed ESKD each year. In 2015, 49,205 patients were receiving PD.[2] PD is associated with improved survival compared with HD.[2] PD preserves residual renal function, which improves cardiovascular stability and may account for the improved survival. Thus, PD may be the preferred method of dialysis in patients with residual renal function.

Table 26–10

Management of Hemodialysis Access Infections[41]

AV Fistula	Treat as subacute bacterial endocarditis for 6 weeks Initial antibiotic choice should always cover gram-positive organisms (eg, vancomycin 20 mg/kg IV with serum concentration monitoring or cefazolin 20 mg/kg IV three times per week) Gram-negative coverage is indicated for patients with diabetes, HIV infection, prosthetic valves, or those receiving immunosuppressive agents (gentamicin 2 mg/kg IV with serum concentration monitoring)
Synthetic Grafts (AVG)	
Local infection	Empiric antibiotic coverage for gram-positive, gram-negative, and *Enterococcus* (eg, gentamicin plus vancomycin, then individualize after culture results become available); continue for 2–4 weeks
Extensive infection	Antibiotics as above plus total resection
Access less than 1-month old	Antibiotics as above plus removal of the graft
Tunneled Cuffed Catheters (Internal Jugular, Subclavian)	
Infection localized to catheter exit site	No drainage: topical antibiotics (eg, mupirocin ointment) Drainage present: Gram-positive coverage (eg, cefazolin 20 mg/kg IV three times a week)
Bacteremia with or without systemic signs or symptoms	Gram-positive coverage as above If stable and asymptomatic, change catheter and provide culture-specific antibiotic coverage for a minimum of 3 weeks

AV, arteriovenous.

Patient Encounter 4, Part 2

The patient returns to the dialysis center 1 month later for routine hemodialysis. Two hours after starting dialysis, he complains of dizziness.

PE:

VS: BP 95/68 mm Hg; P 108 beats/min; T 98.9° F (37.2° C); wt 184 lb (83.6 kg)

What is the most likely cause of his dizziness?

What treatment would you recommend?

► *Principles of PD*

PD utilizes similar principles as HD in that blood is exposed to a semipermeable membrane against which a physiologic solution is placed. In the case of PD, however, the semipermeable membrane is the peritoneal membrane, and a sterile dialysate is instilled into the peritoneal cavity. The peritoneal membrane is composed of a continuous single layer of mesothelial cells that covers the abdominal and pelvic walls on one side of the peritoneal cavity, and the visceral organs including the GI tract, liver, spleen, and diaphragm on the other side. The mesothelial cells are covered by microvilli that increase the surface area of the peritoneal membrane to approximate body surface area (1 to 2 m^2). Blood vessels that supply the abdominal organs, muscle, and mesentery serve as the blood component of the system.

The gaps between the mesothelial cells allow for large solutes to pass through into the bloodstream. Both the interstitium and endothelial cells of the blood vessels provide resistance to limit the solute size that is removed from the blood. Diffusion is the most important component of solute transport in PD, which is enhanced by the large surface area and volume of dialysate, as well as contact time with the peritoneal membrane. Ultrafiltration is achieved in PD by creating an osmotic pressure gradient between the dialysate and the blood. Traditionally, glucose has been used to create the osmotic gradient, but the solutions are not biocompatible with the peritoneal membrane, resulting in cytotoxicity of the cells. Polymeric glucose derivatives such as icodextrin may be used in place of glucose to create a colloid-driven osmosis that results in ultrafiltration and convection of solute removal, but are more expensive.

In PD, prewarmed dialysate is instilled into the peritoneal cavity where it "dwells" for a specified length of time (usually one to several hours, depending on the type of PD) to adequately clear metabolic waste products and excess fluids and electrolytes. At the end of the dwell time, the dialysate is drained and replaced with fresh dialysate. The continuous nature of PD provides for a more physiologic removal of waste products from the bloodstream, which mimics endogenous kidney function by limiting the fluctuations seen in serum concentrations of the waste products. Similarly, water is removed at a more constant rate, lessening the fluctuations in intravascular fluid balance and providing for more hemodynamic stability.

Several types of PD are used:

- Continuous ambulatory peritoneal dialysis (CAPD) is the most common. The patient exchanges 1 to 3 L of dialysate every 4 to 6 hours throughout the day with a longer dwell time overnight.

- Automated peritoneal dialysis (APD) procedures involve the use of a cycler machine that performs sequential exchanges overnight while the patient is sleeping.
- Continuous cycling PD (CCPD) performs three to five exchanges throughout the night. The final exchange remains in the peritoneal cavity to dwell for the duration of the day.
- Nightly intermittent PD (NIPD) performs six to eight exchanges throughout the night. The final exchange of dialysate is drained in the morning, and the peritoneal cavity remains empty throughout the day.
- Nocturnal tidal PD (NTPD) is similar to NIPD, with the exception that only a portion of the dialysate is exchanged throughout the night. The final exchange is drained in the morning, and the peritoneal cavity remains empty throughout the day.

▶ *Peritoneal Access*

Access to the peritoneal cavity requires placement of an indwelling catheter with the distal end of the catheter resting in the peritoneal cavity. The central portion of the catheter is generally tunneled under the abdominal wall and subcutaneous tissue where it is held in place by cuffs that provide stability and mechanical support to the catheter. The proximal portion of the catheter exits the abdomen near the umbilicus. Several types of indwelling catheters are available; the most common is the Tenckhoff catheter. Placement and handling of the catheter during PD exchanges requires a sterile environment to minimize the risk of infectious complications.

▶ *Complications of PD*

Complications associated with PD include mechanical problems related to the PD catheter, metabolic problems associated with the components of the dialysate fluid, damage to the peritoneal membrane, and infections (Table 26–11). Strategies to manage infectious complications of PD are discussed below.

Table 26–11

Common Complications during Peritoneal Dialysis

Mechanical Complications
Kinking in catheter
Catheter migration
Catheter adherence to peritoneal tissue
Excessive movement of catheter at exit site

Peritoneal Damage
Alterations in permeability of the peritoneal membrane
Sclerosis of the peritoneal membrane

Pain
Impingement of the catheter tip on visceral organs
Instillation pain
- Rapid inflow of dialysate
- Acidic pH of dialysate
- Chemical irritation from dialysate additives (eg, antibiotics)
- Low dialysate temperature

Infections
Peritonitis
Exit-site infections
Tunnel infections

Metabolic Complications
Exacerbation of diabetes mellitus from glucose load
Fluid overload
- Exacerbation of chronic heart failure
- Edema
- Pulmonary congestion

Electrolyte abnormalities

Malnutrition
- Albumin and amino acid loss
- Muscle wasting
- Increased adipose tissue
- Fibrin formation in dialysate

Weight gain

Peritonitis Peritonitis is a leading cause of morbidity in PD patients, which often leads to loss of the catheter and subsequent change to HD as the treatment modality. However, advances with connectors used during instillation and drainage of dialysate and delivery systems have dramatically decreased the incidence of peritonitis. Peritonitis can also be caused by chemical irritation or microorganisms.

Pathophysiology. Gram-positive organisms, namely *S. epidermidis*, are the most common cause of peritonitis. Other pathologic organisms include *S. aureus*, streptococcal species, enterococcus species, gram-negative organisms including *Escherichia coli* and *Pseudomonas* species, and fungal organisms. Peritonitis should be presumed if cloudy fluid is drained from the peritoneal cavity and the fluid should be evaluated by cultures. Antibiotic treatment should be initiated immediately, until cell counts and cultures prove otherwise.[39] Patients with peritonitis may also complain of abdominal pain, although pain may be absent in some cases.

Treatment. The International Society of Peritoneal Dialysis (ISPD) revised the recommendations for the treatment of PD-related infections in 2016.[39] Drug selection for empirical treatment of peritonitis should cover both gram-positive and gram-negative organisms specific to the dialysis center and be based on the protocols and sensitivity patterns of organisms known to cause peritonitis, as well as the history of infections in the patient. First-generation cephalosporins, such as cefazolin, or vancomycin are recommended for empirical coverage of gram-positive organisms. Appropriate coverage for gram-negative organisms includes third- or fourth-generation cephalosporins, such as ceftazidime or cefepime, or aminoglycosides. Alternatives for gram-negative coverage include oral fluoroquinolones and aztreonam. An example of an appropriate empiric treatment for peritonitis includes cefazolin in combination with ceftazidime, cefepime, or an aminoglycoside. If the patient has a β-lactam allergy, vancomycin in combination with an aminoglycoside or aztreonam is an alternative empirical treatment.[39] It should be noted that aminoglycosides can decrease residual renal function in patients receiving PD.

The preferred route of administration is intraperitoneal (IP) rather than IV to achieve maximum concentrations at the site of infection. Antibiotics can be administered IP intermittently as a single large dose in one exchange per day or continuously as multiple smaller doses with each exchange. Intermittent administration requires at least 6 hours of dwell time in the peritoneal cavity to allow for adequate systemic absorption and provides adequate levels to cover the 24-hour period. However, continuous administration is better suited for PD modalities that require more frequent exchanges (< 6-hour dwell time). See the ISPD guidelines for dosing recommendations for IP antibiotics in CAPD and automated PD patients.[39] The dose of the antibiotics should be increased by 25% for patients with residual kidney function who are able to produce more than 100 mL urine output per day.

Once the organism has been identified and sensitivities are known, drug selection should be adjusted to reflect the susceptibilities of the organism. Streptococcal, staphylococcal,

and enterococcal species sensitive to β-lactam antibiotics should be treated with continuous IP dosing to increase efficacy and minimize resistance.[39] Peritonitis caused by *S. aureus* or *P. aeruginosa* is often associated with catheter-related infections, which are difficult to treat and often require removal of the catheter. Two antibiotics are required for treatment of *P. aeruginosa* peritonitis.[39] If multiple organisms are cultured, treatment should cover all of the organisms, including anaerobic organisms, and the patient should be evaluated for other intra-abdominal pathologies.[39]

Peritonitis caused by fungal organisms is associated with mortality in 25% of patients,[39] which can be reduced by removing the catheter after fungal organisms are identified. If a fungal organism is identified, empirical treatment should include IP amphotericin B and flucytosine,[39] but alternative agents can be used based on susceptibilities. Although IP amphotericin administration is associated with chemical irritation and pain, penetration of amphotericin into the peritoneal cavity is poor with IV administration. Fluconazole, voriconazole, or caspofungin may be suitable alternatives, depending on culture results.

Catheter-Related Infections Catheter-related infections generally occur at the exit site or the portion of the catheter that is tunneled in the subcutaneous tissue. Previous infections increase the risk and incidence of catheter-related infections.

Pathophysiology. The major pathologic organisms responsible for causing catheter-related infections are *S. aureus* and *P. aeruginosa*. These organisms also cause the most serious catheter-related infections. *S. epidermidis* is found in less than 20% of catheter-related infections.[40]

Exit-site infections present with purulent drainage at the site. Erythema may or may not be present with an exit-site infection. Tunnel infections are generally extensions of exit-site infections and rarely occur alone. Symptoms of a tunnel infection may include tenderness, edema, and erythema over the tunnel pathway but are often asymptomatic. Ultrasound can be used to detect tunnel infections in asymptomatic patients. Exit-site infections caused by *S. aureus* and *P. aeruginosa* often spread to tunnel infections and are the most common causes of catheter-infection–related peritonitis.

Treatment. Exit-site infections may be treated immediately with empiric coverage, or treatment may be delayed until cultures return. Empiric treatment of catheter-related infections should cover *S. aureus* with a first-generation cephalosporin or penicillinase-resistant penicillin. Coverage for MRSA or *P. aeruginosa* should also be included if the patient has a history of infections with either organism. Vancomycin or clindamycin are used for empiric coverage of MRSA, while oral fluoroquinolones are used as first-line agents to treat *P. aeruginosa*.[40]

Cultures and sensitivity testing are particularly important in tailoring antibiotic therapy for catheter-related infections to ensure eradication of the organism and prevent recurrence or related peritonitis. Treatment of catheter-related infections should be continued until the exit site appears normal with no erythema or drainage. Generally, at least 2 weeks of therapy or longer are required to ensure complete eradication of the organism and prevent future recurrence, which is common with *S. aureus* and *P. aeruginosa*. Infections that do not resolve may require replacement of the PD catheter. Catheter-related

Patient Care Process: Chronic Kidney Disease

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review the medical history, laboratory tests, and physical assessment.
- Speak with the patient and review records to identify socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Identify risk factors that increase the risk for CKD (Table 26–2).
- Determine whether the patient has any concomitant diseases that may hasten the progression of CKD or increase the risk of CVD.
- Identify medications the patient is taking that may cause nephrotoxicity or require adjustment for renal dysfunction.
- Review relevant laboratory tests to determine if patient is experiencing complications of CKD.
- Calculate GFR to determine the staging of CKD (Table 26–1).
- Determine if the patient is experiencing signs and symptoms associated with CKD, or complications of CKD (Figures 26–2 and 26–3).

Develop a Care Plan:

- Determine if pharmacotherapy is indicated for proteinuria or other concomitant disease states.
- Select appropriate medical treatments to control complications of CKD, including anemia (Figure 26–2, Tables 26–4 and 26–5); mineral and bone diseases (Figure 26–3, Tables 26–7 and 26–8); and electrolyte imbalances.
- Select medications and doses that are appropriately adjusted for the level of kidney function.

Implement the Care Plan:

- Educate the patient about changes in drug therapy.
- Address patient's concerns about CKD and its management.
- Educate the patient on dietary and lifestyle changes to treat complications of CKD.
- Stress the importance of adherence with the treatments for CKD and associated complications including lifestyle modifications and medications.
- Recommend a therapeutic regimen that is easy for the patient to accomplish.

Follow-up: Monitor and Evaluate:

- Follow-up at regular intervals to assess effectiveness and safety of therapy.
- Review physical examination and lab tests to assess changes in clinical status.

infections that present in conjunction with or progress to peritonitis with the same organism require removal of the PD catheter until the peritonitis is resolved.[40]

Prophylaxis of Peritonitis and Catheter-Related Infections. Prevention of peritonitis and catheter-related infections starts when the catheter is placed. The exit site should be properly cared for until it is well healed before it can be used for PD. Patients should receive proper instructions for care of the catheter during this time period, which can last up to 2 weeks. Patients should also be instructed on the proper techniques to use for dialysate exchanges to minimize the risk of infections during exchanges, which is the most common cause of peritonitis.

Topical antibiotics, including mupirocin, gentamicin, or ciprofloxacin cream or ointment should be applied daily around the exit site to prevent catheter-related infections.[40] Intranasal *S. aureus* increases the risk of *S. aureus* exit-site infections, tunnel infections, peritonitis, and subsequent catheter loss.[40]

Outcome Evaluation. Clinical improvement should be seen within 48 hours of initiating treatment for peritonitis or catheter-related infections. Perform daily inspections of peritoneal fluid or the exit site to determine clinical improvement. Peritoneal fluid should become clear with improvement of peritonitis and erythema, and discharge should remit with improvement of catheter-related infections. If no improvement is seen within 48 hours, obtain additional cultures and cell counts to determine the appropriate alterations in therapy.

Abbreviations Introduced in This Chapter

ACEI	Angiotensin-converting enzyme inhibitor
AGE	Advanced glycation end-product
AKI	Acute kidney injury
APD	Automated peritoneal dialysis
ARB	Angiotensin receptor blocker
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BUN	Blood urea nitrogen
CAPD	Continuous ambulatory peritoneal dialysis
CCPB	Calcium-containing phosphate binder
CCPD	Continuous cycling peritoneal dialysis
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CKD-MBD	Chronic kidney disease mineral and bone disease
CVD	Cardiovascular disease
DKD	Diabetic kidney disease
DM	Diabetes mellitus
ECG	Electrocardiogram
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agent
GFR	Glomerular filtration rate
HbA1c	Hemoglobin A1c
Hct	Hematocrit
HD	Hemodialysis
HDL-C	High-density lipoprotein cholesterol
Hgb	Hemoglobin
IP	Intraperitoneal
iPTH	Intact parathyroid hormone
ISPD	International Society of Peritoneal Dialysis
KDIGO	Kidney Disease: Improving Global Outcomes
LDL-C	Low-density lipoprotein cholesterol
LVH	Left ventricular hypertrophy
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease (study)
MRSA	Methicillin-resistant *Staphylococcus aureus*
NIPD	Nightly intermittent peritoneal dialysis
NKF	National Kidney Foundation
NTPD	Nocturnal tidal peritoneal dialysis
PD	Peritoneal dialysis
PTH	Parathyroid hormone
RBC	Red blood cell
ROD	Renal osteodystrophy
RRT	Renal replacement therapy
SC	Subcutaneous
SCr	Serum creatinine
sHPT	Secondary hyperparathyroidism
SPS	Sodium polystyrene sulfonate
TIBC	Total iron binding capacity
TSat	Transferrin saturation
USRDS	United States Renal Data Service

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3:1–150.
2. U.S. Renal Data System (USRDS). USRDS 2017 annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, 2017.
3. Levey AS, Stevens LA, Schmid SH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612.
4. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12(12):2032–2045.
5. Telda FM, Brar A, Browne R, Brown C. Hypertension in chronic kidney disease: navigating the evidence. Int J Hypertens. 2011;2011:132405.
6. Hemmelgarn BR, Manns, BJ, Lloyd A. Relation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010;303(5):423–429.
7. Bakris GL. A practical approach to achieving recommended blood pressure goals in diabetic patients. Arch Int Med. 2001;161:2661–2667.
8. D'Agati V, Schmidt AM. RAGE and the pathogenesis of chronic kidney disease. Nat Rev Nephrol. 2010;6:352–360.
9. Mikolasevic I, Žutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: etiology ad management. Internat J Nephrol Renovasc Dis. 2017;10:35–45.
10. Heung M, Chawla LS. Predicting progression to chronic kidney disease after recovery from acute kidney injury. Curr Opin Nephrol Hypertens. 2012;21(6):628–634.
11. López-Novoa J, Martínez-Salgado C, Rodríguez-Peña AB, Hernández FJL. Common pathophysiological mechanisms of chronic kidney disease: therapeutic perspectives. Pharmacol Ther. 2010;128(1):61–81.
12. Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int. 2013;84(6):1096–1107.
13. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis. 2012;60(5):850–886.

14. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13. [Epub ahead of print.]
15. Robinson BM, Tong L, Zhang J, et al. Blood pressure levels and mortality risk among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2012;82(5):570–580.
16. Agarwal R. Blood pressure and mortality among hemodialysis patients. Hypertension. 2010;55:762–768.
17. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. Nephrol Dial Transplant. 2014:29(3):672–681.
18. Hermida RC, Ayala DE, Mojón A, Fernández JR. Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. J Am Soc Nephrol. 2011;22(12):2313–2321.
19. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012;2:337–414.
20. Gentile G, Remuzz G, Ruggenenti P. Dual renin-angiotensin system blockade for nephroprotection: still under scrutiny. Nephron. 2015;129:39–41.
21. Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO clinical practice guideline for lipid management in chronic kidney disease. Kidney Int Suppl. 2013;3:259–305.
22. Hörl WH. Anaemia management and mortality risk in chronic kidney disease. Nat Rev Nephrol. 2013;9:291–301.
23. Kidney Disease: Improving Global Outcomes. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2(4):279–335.
24. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS ONE. 2014;9(1):e84943.
25. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int. 2009;76 (suppl 113):S1–S130.
26. Portillo MR, Rodríguez-Ortiz ME. Secondary hyperparathyroidism: pathogenesis, diagnosis, preventative and therapeutic strategies. Rev Endocrin Metab Disord. 2017;18:79–95.
27. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017;7:1–59.
28. Nastou D, Fernández-Fernández B, Elewa U, et al. Next-generation phosphate binders: focus on iron-based binders. Drugs. 2014;74:863–877.
29. Hill KM, Martin BR, Wastney ME, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3–4 chronic kidney disease. Kidney Internat. 2013;83:959–966.
30. Friedl C, Zitt E. Vitamin D prohormone in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease. Internat J Nephrol Renovasc Dis. 2017;10:109–122.
31. Hamano N, Komaba H, Fukagawa M. Etelcalcetide for the treatment of secondary hyperparathyroidism. Epert Opin Pharmacother. 2017;18(5):529–534.
32. Berl T, Combs S. Water metabolism in chronic kidney disease. In: Kimmel PL, Rosenberg ME, eds. Chronic Renal Disease. San Diego: Elsevier, Inc; 2015:367–374.
33. Palmer BF. Potassium metabolism in chronic kidney disease. In: Kimmel PL, Rosenberg ME, eds. Chronic Renal Disease. San Diego: Elsevier, Inc; 2015:381–390.
34. Emmett M. Acid-base metabolism in chronic kidney disease. In: Kimmel PL, Rosenberg ME, eds. Chronic Renal Disease. San Diego: Elsevier, Inc; 2015:406–417.
35. Epstein M, Pitt B. Recent advances in pharmacological treatments of hyperkalemia: focus on patiromer. Expert Opin Pharmacother. 2016;17(10):1435–1448.
36. Chao CT, Huang JW, Yen CJ. Intradialytic hypotension and cardiac remodeling: a vicious cycle. Biomed Res Internat. 2015;2015:724147.
37. Ulu MS, Ahsen A. Muscle cramps during hemodialysis: what can we do? New approaches for treatment and preventing. Eur J Gen Med. 2015;12(3):277–281.
38. Böhlke M, Uliano G, Barcellos FC. Hemodialysis catheter-related infection: prophylaxis, diagnosis and treatment. J Vasc Access. 2015;16(5):347–355.
39. Li PKT, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. Periton Dial Internat. 2016;36:481–508.
40. Szeto CC, Li PKT, Johnson DW, et al. ISPD catheter-related infection recommendations: 2017 update. Periton Dial Internat. 2017;37:141–154.
41. KDIGO clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access. Am J Kidney Dis. 2006;48(suppl 1):S1–S322.

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27 Fluids and Electrolytes

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LEARNING OBJECTIVES

LO

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

1. Estimate the volumes of various body fluid compartments.
2. Calculate the daily maintenance fluid requirement for patients given their weight and gender.
3. Differentiate among currently available fluids for volume resuscitation.
4. Identify the electrolytes primarily found in the extracellular and intracellular fluid compartments.
5. Describe the unique relationship between serum sodium concentration and total body water (TBW).
6. Review the etiology, clinical presentation, and management for disorders of sodium, potassium, calcium, phosphorus, and magnesium.

BODY FLUID COMPARTMENTS

A thorough understanding of the fundamentals of fluid and electrolyte homeostasis is essential, given the frequency with which clinical disturbances are seen and the profound effects these disturbances can have on various aspects of patient care. However, the interplay of body fluids, serum electrolytes, and clinical monitoring is complex, and a thorough command of these issues is a challenging task even for advanced practitioners.[1] Practitioners must be familiar with the key concepts of body compartment volumes, calculation of daily fluid requirements, and the various types of fluid available for replacement. The management of disorders of sodium, potassium, calcium, phosphorus, and magnesium integrates these concepts with issues of dose recognition and patient safety.

The most fundamental concept to grasp is an assessment of total body water (TBW), which is directly related to body weight. KEY CONCEPT TBW constitutes approximately 50% of lean body weight in healthy females and 60% of lean body weight in males. For clinical purposes, most clinicians generalize that TBW accounts for 60% of lean body weight in adults, regardless of gender. The percentage of TBW decreases as body fat increases and/or with age (75%–85% of body weight is water for newborns). Unless the patient is obese (body weight > 120% of ideal body weight [IBW]), clinicians typically use a patient's actual body weight when calculating TBW.[2] In obese patients, it is customary to estimate TBW using lean body weight or IBW as calculated by the Devine–Devine method: males' lean body weight = 50 kg + (2.3 kg/in × [height in inches − 60]) and females' lean body weight = 45.5 kg + (2.3 kg/in × [height in inches − 60]).[3–5] Note that 1 kg is equivalent to 2.2 lb, 1 in is equivalent to 2.54 cm, and 1 L of water weighs 1 kg (2.2 lb).

LO 1

The intracellular fluid (ICF) represents the water contained within cells and is rich in electrolytes such as potassium, magnesium, phosphates, and proteins. KEY CONCEPT The ICF is approximately two-thirds of TBW regardless of gender. For a 70-kg person, this would mean that the TBW is 42 L and the ICF is approximately 28 L. Note that ICF represents approximately 40% of total body weight.

LO 1

The extracellular fluid (ECF) is the fluid outside the cell and is rich in sodium, chloride, and bicarbonate. KEY CONCEPT The ECF is approximately one-third of TBW (14 L in a 70-kg person) and is subdivided into two compartments: the interstitial fluid and the intravascular fluid. The interstitial fluid represents the fluid occupying the spaces between cells and is about 25% of TBW (10.5 L in a 70-kg person). The intravascular fluid (also known as plasma) represents the fluid within the blood vessels and is about 8% of TBW (3.4 L in a 70-kg person). Because the exact percentages are cumbersome to recall, many clinicians accept that the ECF represents roughly 20% of body weight (regardless of gender) with 15% in the interstitial space and 5% in the intravascular space.[6] Note that serum electrolytes are routinely measured from the ECF.

The transcellular fluid includes the viscous components of the peritoneum, pleural space, and pericardium, as well as the cerebrospinal fluid, joint space fluid, and the gastrointestinal (GI) digestive juices. Although the transcellular fluid normally accounts for about 1% of TBW, this amount can increase significantly during various illnesses favoring fluid collection in one of these spaces (eg, pleural effusions or ascites in the peritoneum). The accumulation of fluid in the transcellular space is often referred to as "third spacing." To review the calculations of the body fluid compartments in a representative patient, see Patient Encounter 1.

Fluid balance is assessed by several means each of which has its limitations. Blood pressure (BP) measurements estimate fluid status relative to the amount of blood volume pumped by the heart, but are affected by cardiac function and vascular pliability. Patients with significant volume deficiency may appear

Patient Encounter 1: Body Fluid Compartments

Calculate the TBW, ICF, and ECF in an 82-kg male.

hypotensive, but this is a late finding that may require greater than 20% of TBW to be lost. Patients with significant volume excess may appear edematous; however, third spacing may hide this finding until late in the course as well. The physical examination can indicate the presence of fluid deficits (dry mucous membranes) and fluid excess (peripheral edema, coarse breath sounds). Data suggest that dynamic assessments of volume status (pulse pressure variability, ultrasound-derived vena cava diameter variations, passive leg raising) are more accurate than either the bedside clinical examination or passive measurements of volume status (arterial catheter, central venous catheter, pulmonary artery catheter).

To maintain fluid balance, the total amount of fluid gained throughout the day (input, or "ins") must equal the total amount of fluid lost (output, or "outs"). Although most forms of the body's input and output can be measured, several cannot. For a normal adult on an average diet, ingested fluids are easily measured and average 1400 mL/day. Other fluid inputs, such as those from ingested foods and the water by-product of oxidation, are not directly measurable. Fluid outputs such as urinary and stool losses are also easily measured and referred to as sensible losses. Other sources of fluid loss, such as evaporation of fluid through the skin and/or lungs, are not readily measured and are called insensible losses. Table 27–1 shows the estimated ins and outs (I&Os) for a healthy 68-kg (150-lb) man.[6] The measurable I&Os are routinely measured in hospitalized patients and are used to estimate total fluid balance for each 24-hour period. It is important to realize that in hospitalized patients, multiple other forms of fluid loss must be considered. These include losses from enteric suctioning (most commonly, nasogastric [NG] tubes), from surgical drains (eg, chest tubes, nephrostomy tubes, and pancreatic drains), via fistulous tracts, and enhanced evaporative losses (burns and fever).

LO 2

LO 2

TBW depletion (often referred to as "dehydration") is typically a gradual, chronic problem. Because TBW depletion represents a loss of hypotonic fluid (proportionally more water is lost than sodium) from all body compartments, a primary disturbance of osmolality is usually seen. The signs and symptoms of TBW depletion include central nervous system (CNS) disturbances (mental status changes, seizures, and coma), excessive thirst, dry mucous membranes, decreased skin turgor, elevated serum sodium, increased plasma osmolality, concentrated urine, and acute weight loss. Common causes of TBW depletion include insufficient oral intake, excessive insensible losses, diabetes insipidus, excessive osmotic diuresis, and impaired renal concentrating mechanisms. Elderly long-term care residents are frequently admitted to the acute care hospital with TBW depletion secondary to lack of adequate oral intake, often with concurrent excessive insensible losses.

Table 27–1

Approximate I&Os for a Healthy 68-kg (150-lb) Man

Input	mL/day	Output	mL/day
Ingested fluid[a]	1400	Urine[a]	1500
Fluid in food	850	Skin losses	500
Water of oxidation	350	Respiratory tract losses	400
		Stool	200
Total	2600	Total	2600

[a]Readily quantifiable.

Table 27–2

Useful Calculations for the Estimation of Patient Maintenance Fluid Requirements

Neonate (1–10 kg) = 100 mL/kg
Child (10–20 kg) = 1000 mL + 50 mL for each kilogram > 10
Adult (> 20 kg) = 1500 mL + 20 mL for each kilogram > 20

LO 2

The volume of fluid required to correct TBW depletion equals the basal fluid requirement plus ongoing exceptional losses plus the fluid deficit. Basal daily fluid requirements are calculated using the formulas in Table 27–2. For an adult, this represents 1500 mL/day for the first 20 kg of body weight plus 20 mL/day for each additional kilogram. The volume of replacement fluids required for a given patient (the fluid deficit) can be estimated by the acute weight change in the patient (1 kg = 1 L of fluid). Because the precise weight change is not typically known, it is often calculated as follows: fluid deficit = normal TBW − present TBW. Normal TBW is estimated based on the patient's weight using the formulas in Table 27–2, and the present TBW is estimated based on the patient's current body weight. The choice of fluids used for replacement is guided by the presence of concurrent electrolyte abnormalities. The adequacy of replacement is guided by each patient's objective response to fluid replacement (improved skin turgor, adequate urine output, normalization of heart rate, BP, etc).

LO 2

Once TBW has been restored, the volume of "maintenance" fluid equals the basal fluid requirement plus ongoing exceptional losses. If the pathophysiologic process leading to TBW depletion has not been identified and corrected (or accounted for in the calculation of maintenance fluid requirements), TBW depletion will quickly recur. To review the concepts involved in the calculation of replacement fluids for a representative patient, see Patient Encounter 2.

Compared with TBW depletion, ECF depletion tends to occur acutely. In this setting, rapid and aggressive fluid replacement is required to maintain adequate organ perfusion. Because ECF depletion is generally due to the loss of isotonic fluid (proportional losses of sodium and water), major disturbances of plasma osmolality are not common. ECF depletion manifests clinically as signs and symptoms associated with decreased tissue perfusion: dizziness, orthostasis, tachycardia, decreased urine output, increased hematocrit, decreased central venous pressure, and/or hypovolemic shock. Common causes of ECF depletion include external fluid losses (burns, hemorrhage, diuresis, GI losses, and adrenal insufficiency) and third spacing of fluids (septic shock, anaphylactic shock, or abdominal ascites).

In clinical practice, the most commonly encountered problem is depletion of TBW and ECF. Accordingly, the fluid resuscitation strategy should address both of these compartments. As these compartments are repleted, serum electrolytes must be monitored closely as discussed in subsequent sections of this chapter.

Patient Encounter 2: Fluid Requirements

Calculate the daily fluid requirement for a 75-kg adult female.

THERAPEUTIC FLUIDS

Crystalloids

LO 3 KEY CONCEPT Therapeutic intravenous (IV) fluids include crystalloid solutions and colloidal solutions. Crystalloids are composed of water and electrolytes, all of which pass freely through semipermeable membranes and remain in the intravascular space for shorter periods of time. As such, these solutions are very useful for correcting electrolyte imbalances but result in smaller hemodynamic changes for a given unit of volume.

LO 3 Crystalloids can be classified further according to their tonicity. Isotonic solutions (ie, normal saline or 0.9% sodium chloride [NaCl]) have a tonicity equal to that of the ICF (approximately 310 mEq/L [mmol/L]) and do not shift the distribution of water between the ECF and the ICF. Because hypertonic solutions (ie, hypertonic saline or 3% NaCl) have greater tonicity than the ICF (> 376 mEq/L [mmol/L]), they draw water from the ICF into the ECF. In contrast, hypotonic solutions (ie, 0.45% NaCl) have less tonicity than the ICF (< 250 mEq/L [mmol/L]) leading to osmotic pressure gradient that favors shifts of water from the ECF into the ICF. The tonicity, electrolyte content, and glucose content of selected fluids are shown in Table 27–3.

The tonicity of crystalloid solutions is directly related to their sodium concentration. The most commonly used crystalloids include normal saline, dextrose/half-normal saline, hypertonic saline, and lactated Ringer's (LR) solution. Excessive administration of any fluid replacement therapy, regardless of tonicity, can lead to fluid overload, particularly in patients with cardiac or renal insufficiency. Glucose is often added to hypotonic crystalloids in amounts that result in isotonic fluids (D_5W, D5 ½ NS, and D5 ¼ NS). These solutions are often used as maintenance fluids to provide basal amounts of calories and water.

▶ *Normal Saline (0.9% NaCl or NS)*

LO 3 Normal saline is an isotonic fluid composed of water, sodium, and chloride. It provides primarily ECF replacement and can be used for virtually any cause of TBW depletion. Common uses of normal saline include perioperative fluid administration; volume resuscitation of shock, sepsis, hemorrhage, or burn patients; fluid challenges in hypotensive or oliguric patients; and hyponatremia. Normal saline can also be used to treat metabolic alkalosis (also known as contraction alkalosis). Large volumes of normal saline can cause a hyperchloremic metabolic acidosis.

▶ *Half-Normal Saline (0.45% NaCl or ½ NS)*

LO 3 Half-normal saline is a hypotonic fluid that provides free water in relative excess when compared with the sodium concentration. This crystalloid is typically used to treat patients who are hypertonic due to primary depletion of the ECF. Because half-normal saline is hypotonic, serum sodium must be closely monitored during administration.

▶ *5% Dextrose/Half-Normal Saline (D5 ½ NS)*

LO 3 D5 ½ NS is a hypotonic fluid that is commonly used as a maintenance fluid. This crystalloid is typically used once fluid deficits have been corrected with normal saline or LR solution. Because half-normal saline is hypotonic, serum sodium must be closely monitored during administration.

▶ *Hypertonic Saline (3% NaCl)*

LO 3 Hypertonic saline is obviously hypertonic and provides a significant sodium load to the intravascular space. This solution is used very infrequently given the potential to cause significant shifts in the water balance between the ECF and the ICF. It is typically used to treat patients with severe hyponatremia who have symptoms attributable to low serum sodium. Hypertonic

Table 27–3

Electrolyte and Dextrose Content of Selected Crystalloid Fluids

IV Solution	Osmolarity (mOsm or mmol)	Dextrose) (g/L) mmol/L	Sodium (mEq/L) mmol/L	Potassium (mEq/L) mmol/L	Calcium (mEq/L) mmol/L	Chloride (mEq/L) mmol/L	Lactate (mEq/L) mmol/L
D5%	250	50 / 2.78					
D10%	505	100 / 5.55					
0.9% NaCl	308		154			154	
0.45% NaCl	154		77			77	
3% NaCl	1025		512			512	
D5% and 0.45% NaCl	405	50 / 2.78	77			77	
D5% and 0.2% NaCl	329	50 / 2.78	34			34	
Ringer's injection	310		147	4	5 / 2.5	156	
Lactated Ringer's solution	274		130	4	3 / 1.5	109	28
Lactated Ringer's solution and D5%	525	50 / 2.78	130	4	3 / 1.5	109	28

D, dextrose; NaCl, sodium chloride.

saline in concentrations of 7.5% to 23.4% has been used to acutely lower intracranial pressure in the setting of traumatic brain injury and stroke. The literature is inconsistent for the optimal hypertonic concentration, dosing, timing of replacement, and goals for use in this population. Serum sodium and neurologic status must be very closely monitored whenever given.

▶ *Ringer's Lactate*

LO 3 This isotonic volume expander contains sodium, potassium, chloride, and lactate in concentrations that approximate the fluid and electrolyte composition of the blood. Ringer's lactate (also known as "Lactated Ringers") provides ECF replacement and is most often used in the perioperative setting and for patients with lower GI fluid losses, burns, or dehydration. The lactate component of LR works as a buffer to increase the pH. Accordingly, large volumes of LR may cause iatrogenic metabolic alkalosis. Because patients with significant liver disease are unable to metabolize lactate sufficiently, LR administration in this population may lead to accumulation of lactate with iatrogenic lactic acidosis.

▶ *5% Dextrose in Water (D_5W)*

LO 3 D_5W solution is a combination of free water and dextrose that provides a modest amount of calories but no electrolytes. Although it is technically isotonic, it acts as a hypotonic solution in the body. It is commonly used to treat severe hypernatremia. D_5W is also used in small volumes (100 mL) to dilute many IV medications or at a low infusion rate (10–15 mL/hour) to "keep the vein open" (KVO) for IV medications.

Colloids

LO 3 In contrast to crystalloids, colloids do not dissolve into a true solution and therefore do not pass readily across semipermeable membranes. As such, colloids effectively remain in the intravascular space and increase the oncotic pressure of the plasma. This effectively shifts fluid from the interstitial compartment to the intravascular compartment. In clinical practice, these theoretical benefits are generally short lived (given metabolism of colloidal proteins/sugars), and for most patients there is little therapeutic advantage of colloids over crystalloids or vice versa. Examples of colloids include 5% albumin, 25% albumin, the dextrans, hetastarch, and fresh-frozen plasma (FFP). Because each of these agents contains a substance (proteins and complex sugars) that will ultimately be metabolized, the oncotic agent will be ultimately lost and only the remaining hypotonic fluid delivery agent will remain. As such, use of large volumes of colloidal agents is more likely to induce fluid overload compared with crystalloids. Although smaller volumes of colloids have equal efficacy as larger volumes of crystalloids, they generally must be infused more slowly. Often the net result is that the time to clinical benefit is the same regardless of which class of fluid is utilized. For example, 500 mL of normal saline is required to increase the systolic BP to the same degree as seen with approximately 250 mL of 5% albumin; however, the normal saline can be administered twice as fast.

▶ *Albumin*

LO 3 Albumin is a protein derived from fractionating human plasma. Because albumin infusion is expensive and may be associated with adverse events, it should be used for acute volume expansion and *not* as a supplemental source of protein calories. Historically, albumin was used indiscriminately in the intensive care unit until anecdotal publications suggested that albumin might cause immunosuppression. However, the Saline Versus Albumin Fluid Evaluation (SAFE) trial found that the mortality for those who received albumin was the same as for those who received normal saline.[7] A subsequent post hoc analysis reported that patients with traumatic brain injury had higher mortality rates when given albumin for fluid resuscitation. These conflicting findings highlight the controversy and confusion surrounding the use of human albumin versus normal saline therapy for resuscitation of critically ill patients.[8,9] In 1818 patients with severe sepsis, albumin replacement with crystalloids as compared to crystalloids alone did not improve the rate of survival at 28 and 90 days.[10]

Based on limited availability, health systems and hospitals have had to define the appropriate albumin indications for their patients and ration albumin accordingly. Evidence-based indications for albumin include plasmapheresis/apheresis, large-volume paracentesis (> 4 L removed), hypotension in hemodialysis, and the need for aggressive diuresis in hypoalbuminemic hypotensive patients. Inappropriate uses of albumin include nutritional supplementation, impending hepatorenal syndrome, pancreatitis, alteration of drug pharmacokinetics, or acute normovolemic hemodilution in surgery. Practitioners can keep up with medication shortages by checking the American Society of Health-System Pharmacists (ASHP) website (www.ashp.org).

▶ *Hydroxyethyl Starch Solutions and Dextran*

While albumin is the most commonly used colloid, the other available products are not without their own risks and benefits.
LO 3 Hydroxyethyl starch (HES) solutions, including Hetastarch (various manufacturers) and Voluven, Hospira, contain 6% starch and 0.9% NaCl. Hextend, Hospira, is a comparable plasma expander that contains 6% hetastarch in lactated electrolyte solution. HES products have no oxygen-carrying capacity and are administered intravenously as plasma expanders. Limitations of these products include acquisition cost, hypersensitivity reactions, and bleeding. Dosing should be reduced in the presence of renal dysfunction. Clinical data linking HES solutions with an increased risk of mortality and renal injury requiring renal replacement therapy in critically ill patients prompted the US Food and Drug Administration (FDA) to issue a MedWatch safety communication in November 2013. FDA concluded these solutions should not be used in critically ill patients, including sepsis and those admitted to the intensive care unit, and a boxed warning to highlight the risk of mortality and severe renal injury is warranted. A list of recommendations for patients and healthcare providers to consider before use of HES solutions can be found on the FDA website (http://www.fda.gov/Safety/MedWatch/).

LO 3 Low molecular weight dextran (various manufacturers) and high molecular weight dextran (various manufacturers) are polysaccharide plasma expanders. Anaphylactic reactions and prolonged bleeding times have limited the use of these products. Potential mechanisms of colloid solution-induced bleeding include platelet inhibition or possible dilution of clotting factors via infusion of a large-volume colloid solution.

A Cochrane review regarding the use of colloids versus crystalloids for fluid resuscitation in critically ill patients found no evidence from randomized clinical trials that resuscitation with colloids reduces the risk of death in patients with trauma, burns, or following surgery. Additionally, the use of HES might be associated with mortality and given the lack of survival benefit and increased expense over crystalloids the continued use of colloids is limited.[11]

Fluid Management Strategies

LO 3

Classic indications for IV fluid include maintenance of BP, restoring the ICF volume, replacing ongoing renal or insensible losses when oral intake is inadequate, and the need for glucose as a fuel for the brain.[12] Although large volumes of fluid are given during the resuscitation of most trauma patients, a recent analysis reported uncertainty about the use of early large-volume fluid replacement in patients with active bleeding, calling into question our understanding of the need for fluids in various patient populations.[13]

When determining the appropriate fluid to be utilized, it is important to first determine the type of fluid problem (TBW vs ECF depletion), and start therapy accordingly. For patients demonstrating signs of impaired tissue perfusion, the immediate therapeutic goal is to increase the intravascular volume and restore tissue perfusion. The standard therapy is normal saline given at 150 to 500 mL/hour (for adult patients) until perfusion is optimized. Although LR is a therapeutic alternative, lactic acidosis may arise with massive or prolonged infusions. LR has less chloride content versus normal saline (109 mEq/L [mmol/L] vs 154 mEq/L [mmol/L]) and has the advantage of use when large volumes of normal saline produce acidosis during fluid resuscitation. In severe cases, a colloid or blood transfusion may be indicated to increase oncotic pressure within the vascular space. Once euvolemia is achieved, patients may be switched to a more hypotonic maintenance solution (D5 ½ NS or 0.45% NaCl) at a rate that delivers estimated daily needs.

The clinical scenario and the severity of the volume abnormality dictate monitoring parameters during fluid replacement therapy. These may include the subjective sense of thirst, mental status, skin turgor, orthostatic vital signs, pulse rate, weight changes, blood chemistries, fluid input and output, central venous pressure, pulmonary capillary wedge pressure, and cardiac output. Fluid replacement requires particular caution in patient populations at risk of fluid overload, such as those with renal failure, cardiac failure, hepatic failure, or the elderly. Other complications of parenteral fluid therapy include IV site infiltration, infection, phlebitis, thrombophlebitis, and extravasation.

In summary, common settings for fluid resuscitation include hypovolemic patients (eg, sepsis or pneumonia), hypervolemic patients (eg, congestive heart failure [CHF], cirrhosis, or renal failure), euvolemic patients who are unable to take oral fluids in proportion to insensible losses (eg, the perioperative period), and patients with electrolyte abnormalities (see next).

ELECTROLYTES

LO 4

Normally, the number of anions (negatively charged ions) and cations (positively charged ions) in each fluid compartment are equal. Cell membranes play the critical role of maintaining distinct ICF and ECF spaces, which are biochemically distinct. Serum electrolyte measurements reflect the stores of ECF electrolytes rather than that of ICF electrolytes. Table 27–4 lists the chief cations and anions along with their normal concentrations in the ECF and ICF. The principal cations are sodium, potassium, calcium, and magnesium; the key anions are chloride, bicarbonate, and phosphate. In the ECF, sodium is the most common cation and chloride is the most abundant anion; in the ICF, potassium is the primary cation and phosphate is the main anion. Normal serum electrolyte values are listed in Table 27–5.

Osmolality is a measure of the number of osmotically active particles per unit of solution, independent of the weight or nature of the particle. Equimolar concentrations of all substances in the undissociated state exert the same osmotic pressure. Although the normal serum osmolality is 280 to 300 mOsm/kg (mmol/kg), multiple scenarios exist where this value becomes markedly abnormal. KEY CONCEPT The calculated serum osmolality helps determine deviations in TBW content. As such, it is often useful to calculate the serum osmolality as follows:

$$\text{Serum osmolality (mOsm/kg)} = 2\,(\text{Na mEq/L}) + (\text{glucose [mg/dL]})/18 + (\text{BUN [mg/dL]})/2.8$$

$$\text{Serum osmolality using SI units (mmol/kg)} = 2\,(\text{Na mmol/L}) + (\text{glucose mmol/L}) + (\text{BUN mmol/L})$$

LO 5

Because the body regulates water to maintain osmolality, deviations in serum osmolality are used to estimate TBW stores. Water moves freely across all cell membranes, making serum osmolality an accurate reflection of the osmolality within all body compartments. An increase in osmolality is equated with a loss of water greater than the loss of solute (TBW depletion). A decrease in serum osmolality is seen when water is retained in excess of solute (CHF or hepatic cirrhosis).

Table 27–4

Normal Cation and Anion Concentrations in the ECF and ICF

	ECF		ICF	
Ion Species	Plasma (mEq/L [mmol/L])	Interstitial Fluid (mEq/L [mmol/L])	Ion Species	mEq/L [mmol/L]
Cations			**Cations**	
Na^+	142 [142]	144 [144]	K^+	135 [135]
K^+	4 [4]	4 [4]	Mg^{2+}	43 [21.5]
Ca^{2+}	5 [2.5]	2.5 [1.25]		
Mg^{2+}	3 [1.5]	1.5 [0.75]		
Total	154 [150]	152 [150]	Total	178 [156.5]
Anions			**Anions**	
Cl^-	103 [103]	114 [114]	PO_4^{2-}	90 [45]
HCO_3^-	27 [27]	30 [30]	Protein	70 [70]
PO_4^{2-}	2 [1]	2 [1]	SO_4^{2-}	18 [9]
SO_4^{2-}	1 [0.5]	1 [0.5]		
Organic acid	5 [5]	5 [5]		
Protein	16 [16]	0		
Total	154 [152.5]	152 [150.5]	Total	178 [124]

ECF, extracellular fluid; ICF, intracellular fluid.

Table 27–5

Normal Ranges for Serum Electrolyte Concentrations

Sodium	135–145 mEq/L (mmol/L)
Potassium	3.5–5.0 mEq/L (mmol/L)
Chloride	98–106 mEq/L (mmol/L)
Bicarbonate	21–30 mEq/L (mmol/L)
Magnesium	1.4–2.2 mEq/L or 0.7–1.1 mmol/L
Calcium	
Total	4.4–5.2 mEq/L (9–10.5 mg/dL) or 2.2–2.6 mmol/L
Ionized	2.2–2.8 mEq/L (4.5–5.6 mg/dL) or 1.1–1.4 mmol/L
Phosphorus	3–4.5 mg/dL (1.0–1.5 mmol/L)

Patient Encounter 3: Calculate the Plasma Osmolality

A 22-year-old college student was at a tailgate party prior to a football game. He tripped on uneven pavement while staggering to the ticket gate. When attended by EMT personnel, he was agitated and complaining of a broken arm. Upon transfer to your emergency department, rapid respiration, tachycardia, and a BP of 90/60 mm Hg were noted. The sodium is 138 mEq/L (mmol/L), potassium 3.2 mEq/L (mmol/L), chloride 105 mEq/L (mmol/L), bicarbonate 12 mEq/L (mmol/L), glucose 200 mg/dL (11.1 mmol/L), and BUN 28 mg/dL (10.0 mmol/L). The measured osmolality was 340 mOsm/kg (mmol/kg).

Calculate the osmolality.

Calculate the osmolar gap.

What is the likely cause of an increased gap in this patient?

The difference between the measured serum osmolality and the calculated serum osmolality, using the equation just stated, is referred to as the **osmolar gap**. Under normal circumstances the osmolar gap should be 10 mOsm/kg (mmol/kg) or less. An increased osmolar gap suggests the presence of a small osmotically active agent and is most commonly seen with the ingestion of alcohols (ethanol, methanol, ethylene glycol, or isopropyl alcohol) or medications such as mannitol or lorazepam. Patient Encounter 3 illustrates the utility of serum osmolality in a clinical setting.

Many of the electrolyte disturbances discussed in the remainder of this chapter represent medical emergencies that call for aggressive interventions including the use of concentrated electrolytes. It is very difficult to immediately reverse the effects of concentrated electrolytes when they are administered improperly, and these solutions are a frequent source of medical errors with significant potential for patient harm. KEY CONCEPT As such, The Joint Commission recommends that concentrated electrolyte solutions (KCl, potassium phosphate, and NaCl > 0.9%) be removed from patient care areas. Hospitals should keep concentrated electrolytes in patient care areas only when patient safety necessitates their immediate use and precautions are used to prevent inadvertent administration. Collaborative cooperation among pharmacists, nurses, and physicians is essential.[14]

Sodium

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The body's normal daily sodium requirement is 1.0 to 1.5 mEq/kg (mmol/kg) (80–130 mEq [mmol]) to maintain a normal serum sodium concentration of 135 to 145 mEq/L (mmol/L). Sodium is the predominant cation of the ECF and largely determines ECF volume. Sodium is also the primary factor in establishing the osmotic pressure relationship between the ICF and ECF. All body fluids are in osmotic equilibrium, and changes in serum sodium concentration are associated with shifts of water into and out of body fluid compartments. When sodium is added to the intravascular fluid compartment, fluid is pulled intravascularly from the interstitial fluid and the ICF until osmotic balance is restored. As such, a patient's measured sodium concentration should *not* be viewed as an index of sodium need because this parameter reflects the balance between total body sodium content and TBW. Disturbances in the sodium concentration most often represent disturbances of TBW. Sodium imbalances cannot be properly assessed without first assessing body fluid status.

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KEY CONCEPT Hyponatremia is the most common electrolyte disorder in hospitalized patients and is defined as a serum sodium concentration below 135 mEq/L (mmol/L). Clinical signs and symptoms appear at concentrations below 120 mEq/L (mmol/L) and typically consist of irritability, mental slowing, unstable gait/falls fatigue, headache, and nausea. With profound hyponatremia (< 110 mEq/L [mmol/L]), confusion, seizures, stupor/coma, and respiratory arrest may be seen. Clinical practice guidelines regarding the diagnosis and treatment of hyponatremia have recently been published. Hyponatremia can be classified based on serum sodium concentration, rate of development, symptom severity, serum osmolality, and volume status.[15] Because therapy is also influenced by volume status, hyponatremia is further defined as (a) hypertonic hyponatremia, (b) hypotonic hyponatremia with an increased ECF volume, (c) hypotonic hyponatremia with a normal ECF volume, and (d) hypotonic hyponatremia with a decreased ECF volume.[16]

Hypertonic hyponatremia is usually associated with significant hyperglycemia. Glucose is an osmotically active agent that leads to an increase in TBW with little change in total body sodium. For every 60 mg/dL (3.3 mmol/L) increase in serum glucose above 200 mg/dL (11.1 mmol/L), the sodium concentration is expected to decrease by approximately 1 mEq/L (mmol/L). Appropriate treatment of the hyperglycemia will return the serum sodium concentration to normal.[15]

Hypotonic hyponatremia with an increase in ECF (hypervolemic hyponatremia) is also known as dilutional hyponatremia. In this scenario, patients have an excess of total body sodium and TBW; however, the excess in TBW is greater than the excess in total body sodium. Common causes include CHF, hepatic cirrhosis, and nephrotic syndrome. Treatment includes sodium and fluid restriction in conjunction with treatment of the underlying disorder; for example, salt and water restrictions are used in the setting of CHF along with loop diuretics, angiotensin-converting enzyme inhibitors, and spironolactone.

In hypotonic hyponatremia with a normal ECF volume (euvolemic hyponatremia), patients have an excess of TBW with relatively normal sodium content. In essence, there is a presence of excess free water. This is most frequently seen in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Common causes of SIADH include carcinomas (eg, lung or pancreas), pulmonary disorders (eg, pneumonias or tuberculosis), CNS disorders (eg, meningitis, stroke, tumor, or trauma), and medications (eg, sulfonylureas, antineoplastic agents, barbiturates, morphine, antipsychotics, tricyclic antidepressants, nonsteroidal anti-inflammatory agents, selective serotonin reuptake inhibitors, dopamine agonists, and general anesthetics). These medications stimulate the release of antidiuretic hormone (ADH) from the pituitary gland resulting in water retention and dilution of the body's sodium stores.

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Short-term treatment of euvolemic hyponatremia includes fluid restriction, isotonic normal saline, hypertonic saline, or a vaptan. Initial treatment generally consists of fluid restriction alone. Hypertonic saline is used only when the sodium concentration is less than 110 mEq/L (mmol/L) and/or severe symptoms (eg, seizures) are present. Given the limitations associated with these treatment strategies (unpredictable therapeutic effects and side effects), the arginine vasopressin antagonist conivaptan (Vaprisol, Astellas Pharma) was developed for short-term treatment of

euvolemic hyponatremia. While conivaptan can also be used to manage hypervolemic hyponatremia in hospitalized patients, it should not be used for hypovolemic hyponatremia. Conivaptan is dosed 20 mg IV over 30 minutes, followed by a 20-mg continuous infusion over 24 hours for up to 4 days.

Long-term treatment options for euvolemic hyponatremia include fluid restriction, demeclocycline, loop diuretics, saline, lithium, urea, and tolvaptan. Demeclocycline (available as generic) is dosed at 600 to 1200 mg/day, takes days before clinical effect is realized, and can cause nephrotoxicity. Lithium (various generics) also has a slow onset of action and is limited by CNS side effects, GI disturbances, and cardiotoxicity. Furosemide (various generics) or other loop diuretics allow relaxation of fluid restriction but can cause significant volume depletion and electrolyte disturbances, and it has the potential for ototoxicity. No specific USP formulation exists for urea, and poor palatability and side effects limit its use. Tolvaptan (Samsca, Otsuka) is an oral alternative to IV conivaptan. This product is indicated for treatment of clinically significant hypervolemic and euvolemic hyponatremia (sodium < 125 mEq/L [mmol/L]) or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction. Patients with CHF, cirrhosis, and SIADH would be candidates for long-term use. Tolvaptan has a boxed warning for initiation of treatment in a hospital setting because of the need for close sodium monitoring. The initial dose is 15 mg orally daily and may be titrated up to a max of 60 mg. Concurrent use with potent CYP 3A4 inhibitors should be avoided: ketoconazole (available as generic), clarithromycin (available as generic), ritonavir (Norvir, Abbott), diltiazem (available as generic), verapamil (available as generic), fluconazole (available as generic), and grapefruit juice.

LO 5 In hypotonic hyponatremia with a decreased ECF volume (hypovolemic hyponatremia), patients usually have a deficit of both total body sodium and TBW, but the sodium deficit exceeds the TBW deficit. Common causes include diuretic use, profuse sweating, wound drainage, burns, GI losses (vomiting or diarrhea), hypoadrenalism (low cortisol and low aldosterone), and renal tubular acidosis. Treatment includes the administration

LO 6 of sodium to correct the sodium deficit and water to correct the TBW deficit. The sodium deficit can be calculated with the following equation[2]:

$$\text{Sodium deficit (mEq or mmol)} = (\text{TBW [in liters]})\,(\text{desired } Na^+ \text{ concentration [mEq/L or mmol/L]} - \text{current } Na^+ \text{ concentration})$$

Although both water and sodium are required in this instance, sodium needs to be provided in excess of water to fully correct this abnormality. As such, hypertonic saline (3% NaCl) is often used. One can estimate the change in serum sodium concentration after 1 L of 3% NaCl infusion using the following equation[16]:

$$\text{Change in serum } Na^+ \text{ (mEq/L or mmol/L)} = (\text{infusate } Na^+ - \text{serum } Na^+)/(\text{TBW} + 1)$$

In this formula, TBW is increased by 1 to account for the addition of the liter of 3% NaCl. Patient Encounters 4 and 5 illustrate the concepts of calculating and correcting the sodium deficit.

LO 4 Depending on the severity of the hyponatremia and acuity of onset, 0.9%, 3%, or 5% NaCl can be utilized. Most patients can be adequately managed with normal saline rehydration, which is generally the safest agent. Hypertonic saline (3% or 5% NaCl) is generally reserved for patients with severe hyponatremia (< 120 mEq/L [mmol/L]) accompanied by coma, seizures, or high urinary sodium losses. In general, a sodium replacement strategy should target a correction of 6 to 8 mEq/L (mmol/L) in serum per day. Overly aggressive correction of symptomatic hyponatremia (> 12 mEq/L [mmol/L] per day) can result in central pontine myelinolysis.[17] Given the potential for irreversible neurologic damage if untreated or if improperly treated, acute hyponatremia is an urgent condition that should be promptly treated with careful attention to monitoring serial sodium values and adjusting therapeutic infusions accordingly.[18]

Patient Encounter 4: Calculation of Serum Sodium Deficit

Calculate the sodium deficit for an 82-kg male with a serum sodium of 124 mEq/L (mmol/L).

Hypernatremia is a serum sodium concentration greater than 145 mEq/L (mmol/L) and can occur in the absence of a sodium deficit (pure water loss) or in its presence (hypotonic fluid loss).[19] The signs and symptoms of hypernatremia manifest with a serum sodium concentration greater than 160 mEq/L (mmol/L) and are usually the same as those found in TBW depletion: thirst, mental slowing, and dry mucous membranes. Signs and symptoms become more profound as hypernatremia worsens, with the patient eventually demonstrating confusion, hallucinations, acute weight loss, decreased skin turgor, intracranial bleeding, and/or coma. Many coexisting disorders and medications may complicate the diagnosis.

LO 5 The classic causes of hypernatremia are associated with TBW depletion. These include dehydration from loss of hypotonic fluid from the respiratory tract or skin, decreased water intake, osmotic diuresis (eg, mannitol, available as generic), and diabetes insipidus (eg, decreased ADH; phenytoin, available as generic; lithium, available as generic). Hypernatremia in hospitalized patients occurs secondary to inappropriate fluid management in patients at risk for increased free water losses and impaired

LO 6 thirst or restricted water intake.[20] Iatrogenic hypernatremia is occasionally caused by the administration of excessive hypertonic saline. Treatment of hypernatremia includes calculation of the TBW deficit followed by the administration of hypotonic fluids as previously described. The fluid volume should be replaced over 48 to 72 hours depending on the severity of symptoms and the degree of hypertonicity.[21] For asymptomatic patients, the rate of correction should not exceed 0.5 mEq/L/hour (mmol/L/hour). One rule of thumb is to reduce serum sodium by a maximum of 6 to 8 mEq (mmol) every 24 hours.[2,19] Excessively rapid correction of hypernatremia may lead to cerebral edema and death. Patient Encounters 6 and 7 reinforce the concepts of calculating TBW deficit and expected changes in serum sodium concentration with therapy.

Patient Encounter 5: Estimate the Anticipated Change in Serum Sodium

Estimate the anticipated change in serum sodium concentration after the infusion of 1 L of 3% NaCl in an 82-kg male with a serum sodium of 124 mEq/L (mmol/L).

Patient Encounter 6: Calculate Water Deficit

Calculate the water deficit in an 82-kg male with a serum sodium of 156 mEq/L (mmol/L).

Potassium

LO 4

The body's normal daily potassium requirement is 0.5 to 1 mEq/kg (mmol/kg) or 40 to 80 mEq (mmol) to maintain a serum potassium concentration of 3.5 to 5 mEq/L (mmol/L). Potassium is the most abundant cation in the ICF, balancing the sodium contained in the ECF and maintaining electroneutrality of bodily fluids. Because the majority of potassium is intracellular, serum potassium concentration is not a good measure of total body potassium; however, clinical manifestations of potassium disorders correlate well with serum potassium. The acid–base balance of the body affects serum potassium concentrations: hyperkalemia is routinely seen in patients with decreased pH (acidosis). Potassium regulation is primarily under the control of the kidneys with excess dietary potassium being excreted in the urine. Although mild abnormalities of serum potassium are considered a nuisance, severe hyperkalemia or hypokalemia can be life threatening.[22–24]

Hypokalemia (serum potassium < 3.5 mEq/L [mmol/L]) is a common clinical problem. While generally asymptomatic, signs and symptoms of hypokalemia include cramps, muscle weakness, polyuria, electrocardiogram (ECG) changes (flattened T waves and presence of U waves), and cardiac arrhythmias (bradycardia, heart block, atrial flutter, premature ventricular contractions, and ventricular fibrillation). Causes of hypokalemia include GI losses (vomiting, diarrhea, or NG tube suction), renal losses (high aldosterone and low magnesium), inadequate potassium intake (in IV fluids or oral), or alkalosis. Many medications can precipitate hypokalemia. β_2-Agonists (eg, albuterol, available as generic) and insulin (multiple product formulations) lower potassium via cellular redistribution. The use of loop diuretics (furosemide, Lasix, also available as generic), thiazide diuretics (hydrochlorothiazide, available as generic), high-dose antibiotics (penicillin, available as generic), and corticosteroids (prednisone, available as generic) causes renal potassium wasting. In addition, amphotericin B (available as generic), cisplatin (available as generic), and foscarnet (available as generic) can also produce hypokalemia secondary to depletion of magnesium. Hypomagnesemia diminishes intracellular potassium concentration and produces potassium wasting. Given the potential for significant morbidity and mortality, serum potassium concentrations should be monitored closely for patients with known (or suspected) hypokalemia.[2,24,25] Hypokalemia is a risk factor for digitalis toxicity.

Potassium repletion should be guided by close monitoring of serial serum concentrations instead of using empirically chosen amounts. Of the five potassium salts available, potassium acetate (10.2 mEq/K^+/g [mmol/K^+/g]) and KCl (13.4 mEq/K^+/g [mmol/K^+/g]) are the most commonly used forms. When hypokalemia occurs in the setting of alkalosis, KCl is the preferred agent; in acidosis, potassium should be provided in the form of acetate, citrate, bicarbonate, or gluconate salt. Table 27–6 outlines the potassium content of each potassium salt preparation, and Table 27–7 lists each of the oral potassium replacement products. Potassium acetate and chloride are available for IV infusions as premixed solutions. The usual dose of these agents is 10 to 20 mEq (mmol) diluted in 100 mL of normal saline.[2,25,26]

LO 6

Moderate hypokalemia is defined as a serum potassium of 2.5 to 3.5 mEq/L (mmol/L) without ECG changes. In this setting, potassium replacement can usually be given orally at a dose of 40 to 120 mEq/day (mmol/day). Anecdotally, oral potassium supplementation (see Table 27–7) is often more effective in repleting moderate hypokalemia. For patients with an ongoing source of potassium loss, chronic replacement therapy should be considered. The potassium deficit is a rough approximation of the amount of potassium needed to be replaced and can be estimated as follows:

$$\text{Potassium deficit (mEq or mmol/L)} = (4.0 - \text{current serum potassium}) \times 100$$

LO 6

Severe hypokalemia is defined as a serum potassium less than 2.5 mEq/L (mmol/L) or hypokalemia of any magnitude that is associated with ECG changes (eg, flattening of T wave or elevation of U wave) and cardiac arrhythmias. In these situations,

Table 27–6

Potassium Content in Various Potassium Salt Preparations

Potassium Salt	mEq/g (mmol/g)
Potassium gluconate[a]	4.3
Potassium citrate[a]	9.8
Potassium bicarbonate[a]	10.0
Potassium acetate[a]	10.2
Potassium chloride[b]	13.4

[a]Favored for hypokalemia and concurrent acidosis.

[b]Favored for hypokalemia and concurrent alkalosis.

Table 27–7

Oral Potassium Replacement Products

Product	Salt	Strength[a]
Extended/ controlled-release tablets	Chloride	10 mEq (750 mg) 20 mEq (1500 mg)
Effervescent tablets	Chloride and bicarbonate	10 mEq 20 mEq 25 mEq
Liquid	Chloride	20 mEq/15 mL (10%) 40 mEq/15 mL (20%)
Powder packets	Chloride	20 mEq 25 mEq

[a]For potassium, 1 mEq = 1 mmol.

Patient Encounter 7: Calculate the Anticipated Change in Serum Sodium

Calculate the anticipated change in serum sodium concentration after IV infusion of 1 L of 5% dextrose in an 82-kg male with a serum sodium of 156 mEq/L (mmol/L).

Table 27–8

Recommended Potassium Dosage/Infusion Rate

Clinical Scenario	Maximum Infusion Rate[a]	Maximum Concentration[a]	Maximum 24-Hour Dose[a]
K^+ > 2.5 mEq/L *and* No ECG changes of hypokalemia	10 mEq/hour	40 mEq/L	200 mEq
K^+ < 2.5 mEq/L *or* ECG changes of hypokalemia	40 mEq/hour	80 mEq/L	400 mEq

[a]For potassium, 1 mEq = 1 mmol.

IV replacement should be initiated urgently. KEY CONCEPT Potassium infusion at rates exceeding 10 mEq/hour (mmol/hour) requires cardiac monitoring given the potential for cardiac arrhythmias. Although the maximally concentrated solution for potassium replacement is 80 mEq/L (mmol/L), the maximum infusion rate is 40 mEq/hour (mmol/hour) and must be administered via a central line. Table 27–8 outlines current IV potassium replacement guidelines.

Caution must be exercised when repleting potassium with IV agents given possible vein irritation and/or thrombophlebitis. The risk of these complications is minimized by using less concentrated solutions and by giving infusions via central access if possible. Administration of potassium in vehicles containing glucose is discouraged because glucose facilitates the intracellular movement of potassium. Posttherapy improvements in serum potassium may be transient, and continuous monitoring is required. Patients with low serum magnesium will have exaggerated potassium losses from the kidneys and GI tract leading to refractory hypokalemia. In this situation, the magnesium deficit must be corrected in order to successfully treat the concurrent potassium deficiency. In the hypokalemic patient with concurrent acidosis, potassium is often given as the acetate salt, given that acetate is metabolized to bicarbonate. In the patient with depleted phosphorus and potassium, therapy with potassium phosphate is the natural choice.[22,27,28]

Hyperkalemia is defined as a serum potassium concentration greater than 5 mEq/L (mmol/L). Manifestations of hyperkalemia include muscle weakness, paresthesias, hypotension, ECG changes (eg, peaked T waves, shortened QT intervals, and wide QRS complexes), cardiac arrhythmias, and a decreased pH. Causes of hyperkalemia fall into three broad categories: (a) increased potassium intake, (b) decreased potassium excretion, and (c) potassium release from the intracellular space.

Increased potassium intake results from excessive dietary potassium (salt substitutes), excess potassium in IV fluids, and other select medications (potassium-sparing diuretics, cyclosporine [available as generic], angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory agents, pentamidine [available as generic], unfractionated heparin, and low molecular weight heparins). Decreased potassium excretion results from acute renal failure, chronic renal failure, or Addison disease. Excess potassium release from cells results from tissue breakdown (surgery, trauma, hemolysis, or rhabdomyolysis), blood transfusions, and metabolic acidosis.

In addition to discontinuing all potassium supplements, potassium-sparing medications, and potassium-rich salt substitutes, management of hyperkalemia addresses three concurrent strategies: (a) agents to antagonize the proarrhythmic effects of hyperkalemia, (b) agents to drive potassium into the intracellular space and acutely lower the serum potassium, and (c) agents that will definitively (but more gradually) lower the total body potassium content.[29] If the serum potassium concentration is greater than 7 mEq/L (mmol/L) and/or ECG changes are present, IV calcium is administered to stabilize the myocardium. Depending on the acuity of the situation, 1 g of calcium chloride (13.5 mEq or 6.75 mmol) is administered by direct injection or diluted in 50 mL of D_5W and delivered IV over 15 minutes. Clinical effects are seen within 1 to 2 minutes of infusion and persist for 10 to 30 minutes. Repeat doses may be administered as necessary. Because most patients with clinically significant hyperkalemia receive multiple boluses of calcium directed by ECG findings, iatrogenic hypercalcemia is a potential complication of hyperkalemia treatment. As such, total calcium concentration is commonly checked with each potassium concentration measurement. Ionized calcium measurements should be obtained in patients who have comorbid conditions that would lead to inconsistency between total serum calcium and free calcium (abnormal albumin, protein, or immunoglobulin concentrations).

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Dextrose and insulin (with or without sodium bicarbonate) are typically given at the time of calcium therapy in order to redistribute potassium into the intracellular space. Dextrose 50% (25 g in 50 mL) can be given by slow IV push over 5 minutes or dextrose 10% with 20 units of regular insulin can be given by continuous IV infusion over 1 to 2 hours. The onset of action for this combination is 30 minutes; the duration of clinical effects is 2 to 6 hours. High-dose inhaled β_2-agonists (eg, albuterol, available as generic) may also be used to acutely drive potassium into the intracellular space.

LO 6

It is critically important to recognize that the treatments of hyperkalemia discussed thus far are transient, temporizing measures. They are intended to provide time to institute definitive therapy aimed at removing excess potassium from the body. Agents that increase potassium excretion from the body include sodium polystyrene sulfonate (Kayexalate, available as generic), loop diuretics, and hemodialysis or hemofiltration (used only in patients with renal failure). Sodium polystyrene sulfonate can be given orally, via NG tube, or as a rectal retention enema and is dosed at 15 to 60 g in four divided doses per day. In September 2009, MedWatch issued a safety alert that cases of colonic necrosis and other serious GI-adverse events (bleeding, ischemic colitis, perforation) had been reported in association with sodium polystyrene sulfonate (Kayexalate) suspension. The majority of these cases reported the concurrent use of sorbitol. Concurrent administration of sorbitol is no longer recommended. Medication safety alerts are available at www.fda.gov/MedWatch. Patiromer (Veltassa, Relypsa), a nonabsorbed cation exchange polymer, increases fecal potassium excretion and is utilized to manage hyperkalemia in nonemergent situations, primarily in outpatients.

LO 6

Calcium

LO 4

More than 99% of total body calcium is found in bone; the remaining less than 1% is in the ECF and ICF. Calcium plays a critical role in the transmission of nerve impulses, skeletal muscle contraction, myocardial contractions, maintenance of normal cellular permeability, and the formation of bones and teeth. There is a reciprocal relationship between the serum calcium concentration (normally 8.6–10.2 mg/dL [2.15–2.55 mmol/L]) and the serum phosphate concentration that is regulated by a

complex interaction between parathyroid hormone, vitamin D, and calcitonin. About one-half of the serum calcium is bound to plasma proteins; the other half is free ionized calcium. Given that the serum calcium has significant protein binding, the serum calcium measurement must be corrected in patients who have low albumin concentrations (the major serum protein). The most commonly used formula adds 0.8 mg/dL (0.2 mmol/L) of calcium for each gram of albumin deficiency as follows:

Corrected [Ca mg/dL] = Measured [Ca mg/dL] + [0.8 × (4 – measured albumin g/dL)][30–32]

Corrected [Ca mmol/L] = Measured [Ca mmol/L] + [0.02 × (40 – measured albumin g/L)]

Clinical manifestations of hypocalcemia are seen with total serum concentrations less than 6.5 mg/dL (1.63 mmol/L) or an ionized calcium less than 1.12 mmol/L and include tetany, circumoral tingling, muscle spasms, hypoactive reflexes, anxiety, hallucinations, hypotension, myocardial infarction, seizures, lethargy, stupor, and **Trousseau sign** or **Chvostek sign**.[24,33] Ionized calcium concentrations are typically used to assess calcium status in the critically ill as these patients often have concurrent hypoalbuminemia.

Causes of hypocalcemia include hypoparathyroidism, hypomagnesemia, alcoholism, hyperphosphatemia, blood product infusion (due to chelation by the citrate buffers), chronic renal failure, vitamin D deficiency, acute pancreatitis, alkalosis, and hypoalbuminemia. In the setting of hypocalcemia, magnesium concentration should be checked and corrected if low. Given that hypocalcemia may be caused by hypomagnesemia, clinicians should be aware that the serum calcium concentrations may not normalize until serum magnesium is replaced. Medications that cause hypocalcemia include phosphate replacement products, loop diuretics, phenytoin (Dilantin, available as generic), phenobarbital (available as generic), corticosteroids, aminoglycoside antibiotics, and acetazolamide (available as generic).[34–36]

Oral calcium replacement products include calcium carbonate (Os-Cal, GlaxoSmithKline and various generics; Tums, GlaxoSmithKline and various generics) and calcium citrate (Citracal, Mission Bayer and various generics). IV calcium replacement products include calcium gluconate and calcium chloride (both products available as generic). KEY CONCEPT Calcium gluconate is preferred for peripheral use because it is less irritating to the veins; it may also be given intramuscularly. Each 10 mL of a 10% calcium gluconate solution provides 90 mg (4.5 mEq or 2.25 mmol) of elemental calcium. KEY CONCEPT Calcium chloride is associated with more venous irritation and extravasation and is generally reserved for administration via central line. Each 10 mL of a 10% calcium chloride solution contains 270 mg (13.5 mEq or 6.75 mmol) of elemental calcium. IV calcium products are given as a slow push or added to 500 to 1000 mL of 0.9% normal saline for slow infusion.[33,36] In addition to hypocalcemia, IV calcium may also be used for massive blood transfusions, calcium channel blocker overdose, and emergent hyperkalemia and hypermagnesemia.

For acute symptomatic hypocalcemia, 200 to 300 mg of elemental calcium is administered IV and repeated until symptoms are fully controlled. This is achieved by infusing 1 g of calcium chloride or 2 to 3 g of calcium gluconate at a rate no faster than 30 to 60 mg of elemental calcium per minute. More rapid administration is associated with hypotension, bradycardia, or cardiac asystole. Total calcium concentration is commonly monitored in critically ill patients. Under normal circumstances, about half of calcium is loosely bound to serum proteins while the other half is free. Total calcium concentration measures bound and free calcium. Ionized calcium measures free calcium only. Under usual circumstances, a normal calcium concentration implies a normal free ionized calcium concentration. Ionized calcium should be obtained in patients with comorbid conditions that would lead to inconsistency between total calcium and free serum calcium (abnormal albumin, protein, or immunoglobulin concentrations). For chronic asymptomatic hypocalcemia, oral calcium supplements are given at doses of 2 to 4 g/day of elemental calcium. Many patients with calcium deficiency have concurrent vitamin D deficiency that must also be corrected in order to restore calcium homeostasis.[2,33,37]

Hypercalcemia is defined as a calcium concentration greater than 10.2 mg/dL (2.55 mmol/L). It may be categorized as mild if total serum calcium is 10.3 to 12 mg/dL (2.58–3.00 mmol/L), moderate if total serum calcium is 12.1 to 13 mg/dL (3.03–3.25 mmol/L), or severe when serum concentration is greater than 13 mg/dL (3.25 mmol/L). Causes of hypercalcemia include hyperparathyroidism, malignancy, Paget's disease, Addison disease, granulomatous diseases (eg, tuberculosis, sarcoidosis, or histoplasmosis), hyperthyroidism, immobilization, multiple bony fractures, acidosis, and milk-alkali syndrome. Multiple medications cause hypercalcemia and include thiazide diuretics, estrogens, lithium (available as generic), tamoxifen (Nolvadex, available as generic), vitamin A, vitamin D, and calcium supplements.[2,33,36,37]

Because the severity of symptoms and the absolute serum concentration are poorly correlated in some patients, institution of therapy should be dictated by the clinical scenario. All patients with hypercalcemia should be treated with aggressive rehydration: normal saline at 200 to 300 mL/hour is a routine initial fluid prescription. For patients with mild hypercalcemia, hydration alone may provide adequate therapy. The moderate and severe forms of hypercalcemia are more likely to have significant manifestations and require prompt initiation of additional therapy. These patients may present with anorexia, confusion, and/or cardiac manifestations (bradycardia and arrhythmias with ECG changes). Total calcium concentrations greater than 13 mg/dL (3.25 mmol/L) are particularly worrisome because these concentrations can unexpectedly precipitate acute renal failure, ventricular arrhythmias, and sudden death.

Once fluid administration has repleted the ECF, forced diuresis (with associated calcium loss) can be initiated with a loop diuretic. For this approach to be successful, normal kidney function is required. In renal failure patients, the alternative therapy is emergent hemodialysis. Other treatment options include bisphosphonates (zoledronic acid [Zometa, Novartis], pamidronate [Aredia, available as generic]), hydrocortisone (available as generic), calcitonin, and gallium. Given their efficacy and favorable side-effect profile, bisphosphonates are typically the agents of choice. Table 27–9 outlines the treatment options for hypercalcemia including time to onset of effect, duration of effect, and efficacy.[2,33,34,37]

Phosphorus

Phosphorus is primarily found in the bone (80% to 85%) and ICF (15% to 20%): the remaining less than 1% is found in the ECF. Note that phosphorus is the major anion within the cells. Given this distribution, serum phosphate concentration does not accurately reflect total body phosphorus stores. Phosphorus

Table 27–9

Selected Treatment Options for the Management of Hypercalcemia

Therapy	Dose	Onset	Duration	Efficacy[a]
Normal saline	3–6 L/day	Hours	Hours	1–2 mg/dL (0.25–0.50 mmol/L)
Furosemide (Lasix, available as generic)	80–160 mg/day	Hours	Hours	1–2 mg/dL (0.25–0.50 mmol/L)
Hydrocortisone (available as generic)	200 mg/day	Hours	Days	Mild/unpredictable
Calcitonin (Miacalcin, Novartis)	4–8 units/kg	Hours	Hours	1–2 mg/dL (0.25–0.50 mmol/L)
Pamidronate (Aredia, available as generic)	30–90 mg/week	Days	1–4 weeks	1–5 mg/dL(0.25–1.25 mmol/L)
Zoledronic acid (Zometa, Novartis)	4–8 mg	Days	Weeks	1–5 mg/dL (0.25–1.25 mmol/L

[a]Expected decrease in serum Ca^{2+}.

is expressed in milligrams (mg) or millimoles (mmol), not as milliequivalents (mEq). Because phosphorus is the source of phosphate for adenosine triphosphate (ATP) and phospholipid synthesis, manifestations of phosphorus imbalance are variable.

LO 6 Dietary intake, parathyroid hormone levels, and renal function are the major determinants of the serum phosphorus concentration, which is normally 2.7 to 4.5 mg/dL (0.87– 1.45 mmol/L).[2,33,38,39] Hypophosphatemia is defined by a serum phosphorus concentration less than 2.5 mg/dL (0.81 mmol/L); severe hypophosphatemia occurs when the phosphorus concentration is less than 1 mg/dL (0.32 mmol/L). Hypophosphatemia can be caused by increased distribution to the ICF (hyperglycemia, insulin therapy, or malnourishment), decreased absorption (starvation, excessive use of phosphorus-binding antacids, vitamin D deficiency, diarrhea, or laxative abuse), or increased renal loss (diuretic use, diabetic ketoacidosis, alcohol abuse, hyperparathyroidism, or burns).[35,37] KEY CONCEPT Severe hypophosphatemia can result in impaired diaphragmatic contractility and acute respiratory failure. Medications that can cause hypophosphatemia include diuretics (acetazolamide [Diamox, available as generic], furosemide [Lasix, available as generic], hydrochlorothiazide [HydroDIURIL, available as generic]), sucralfate (Carafate, available as generic), corticosteroids, cisplatin (available as generic), antacids (aluminum carbonate, calcium carbonate, and magnesium oxide [antacids all available as generic]), foscarnet (available as generic), phenytoin (Dilantin, available as generic), phenobarbital (available as generic), and phosphate binders (sevelamer [Renvela, Genzyme Corp.] and calcium acetate [PhosLo, available as generic]).

LO 6 Signs and symptoms of hypophosphatemia include paresthesias, muscle weakness, myalgias, bone pain, anorexia, nausea, vomiting, red blood cell breakdown (hemolysis), acute respiratory failure, seizures, and coma.[37,40] For mild hypophosphatemia, patients should be encouraged to eat a high-phosphorus diet including eggs, nuts, whole grains, meat, fish, poultry, and milk products. For moderate hypophosphatemia (1–2.5 mg/dL, 0.32–0.81 mmol/L), oral supplementation of 1.5 to 2 g/day (30–60 mmol/day) is usually adequate. Diarrhea may be a dose-limiting side effect with oral phosphate replacement products.

LO 6 Injectable phosphate products are reserved for patients with severe hypophosphatemia or those in the intensive care unit.[41] The available agents are provided as sodium or potassium salts; however, unless concurrent hypokalemia is present, sodium phosphate is usually used. Empirically, for a mild serum phosphorus deficiency (2.3–3.0 mg/dL, 0.74–0.97 mmol/L), the corresponding IV phosphorus dose is 0.32 mmol/kg; for a moderate deficiency of serum phosphorus 1.6 to 2.2 mg/dL (0.52–0.71 mmol/L), the replacement dose is 0.64 mmol/kg; and the dose is 1 mmol/kg when the serum phosphorus is less than 1.5 mg/dL (0.48 mmol/L).[36] IV phosphorus preparations are usually infused over 4 to 12 hours. Table 27–10 compares the available phosphate replacement products.

LO 6 Hyperphosphatemia is defined by a serum phosphorus concentration greater than 4.5 mg/dL (1.45 mmol/L). The manifestations of hyperphosphatemia are similar to findings of hypocalcemia (see earlier), and include paresthesias, ECG changes (prolonged QT interval and prolonged ST segment), and metastatic calcifications. Causes of hyperphosphatemia include impaired phosphorus excretion (hypoparathyroidism or renal failure), redistribution of phosphorus to the ECF (acid–base imbalance, rhabdomyolysis, muscle necrosis, or tumor lysis during chemotherapy), and increased phosphorus intake (various medications).[37] Medications that can cause hyperphosphatemia include enemas containing phosphorus (eg, Fleet, Fleet), laxatives containing phosphate or phosphorus, parenteral or oral supplements (eg, K-Phos Neutral, Beach), vitamin D

Table 27–10

Phosphate Replacement Products

Product	Route	$mgPO_4^-$	$mmolPO_4^-$	mEq (mmol) Na^+	mEq (mmol) K^+
Potassium phosphate (KPO_4/mL), available as generic	IV	94	3	0	4.4
Sodium phosphate ($NaPO_4$/mL), available as generic	IV	94	3	4	0
Phos-NaK packets, Cypress	Oral	250	8	7.2	7
K-Phos Neutral tablets, Beach	Oral	250	8	13.1	1.4
K-Phos Original tablets, Beach	Oral	114	3.7	–	3.7

supplements, and the bisphosphonates (eg, pamidronate, various manufacturers).[42]

LO 6 Hyperphosphatemia is generally benign and rarely needs aggressive therapy. Dietary restriction of phosphate and protein is effective for most minor elevations. Phosphate binders such as aluminum-based antacids, calcium carbonate, calcium acetate (PhosLo, available as generic), sevelamer hydrochloride (Renagel, Genzyme), sevelamer carbonate (Renvela, Genzyme, Global), and lanthanum carbonate (Fosrenol, Shire) may be necessary for some patients (typically those with chronic renal failure).[43] Sucroferric oxyhydroxide (Velphoro, Fresenius Medical Care) is a noncalcium-based chewable phosphate binder administered with each meal. If patients exhibit findings of hypocalcemia (tetany), IV calcium should be administered empirically.

Magnesium

LO 4 The body's normal daily magnesium requirement is 300 to 350 mg/day to maintain a serum magnesium concentration of 1.5 to 2.4 mEq/L (0.75–1.20 mmol/L). Less than 1% of magnesium is found in the blood. Because magnesium is the second most abundant ICF cation, serum concentrations are a relatively poor measure of total body stores. Magnesium catalyzes and/or activates more than 300 enzymes, provides neuromuscular stability, and is involved in myocardial contraction. Magnesium is generally not part of standard chemistry panels and therefore must be ordered separately.[2,33,42,44,45]

LO 6 Hypomagnesemia is defined as a serum magnesium less than 1.5 mEq/L (0.75 mmol/L) and is most frequently seen in the intensive care and postoperative settings. Hypomagnesemia results from inadequate intake (alcoholism, dietary restriction, or inadequate magnesium in total parenteral nutrition [TPN]), inadequate absorption (steatorrhea, cancer, malabsorption syndromes, or excess calcium or phosphorus in the GI tract), excessive GI loss of magnesium (diarrhea, laxative abuse, NG tube suctioning, or acute pancreatitis), or excessive urinary loss of magnesium (primary hyperaldosteronism, certain medications, diabetic ketoacidosis, and renal disorders). Hypomagnesemia often occurs in the setting of hypokalemia and hypocalcemia. Clinicians should evaluate the magnesium concentration in these patients and correct if low. To evaluate magnesium status, both laboratory tests and clinical assessment are required. In order for calcium and potassium concentrations to normalize, magnesium supplementation is often required. Medications that potentially can cause hypomagnesemia include aminoglycoside antibiotics, amphotericin B (available as generic), cisplatin (available as generic), insulin, cyclosporine (available as generic), loop diuretics, and thiazide diuretics. There is also a strong correlation between hypokalemia and hypomagnesemia.[37,42,46,47] Clinicians should be alerted that the long-term use of proton pump inhibitors may be associated with unexplained hypomagnesemia, with subsequent hypokalemia or hypocalcemia.

LO 6 The findings of hypomagnesemia include muscle weakness, cramps, agitation, confusion, tremor, seizures, ECG changes (increased PR interval, prolonged QRS complex, peaked T waves, and increased QT interval), findings of hypocalcemia (see earlier), refractory hypokalemia (see earlier), metabolic alkalosis, and digoxin toxicity.[42,48,49]

LO 6 Asymptomatic mild magnesium deficiencies (1.0–1.5 mEq/L) (0.50–0.75 mmol/L) can be managed with increased oral intake of magnesium-containing foods or with oral supplementation. Magnesium oxide (Mag-Ox, Blaine Pharmaceuticals and various manufacturers) 400-mg tablets contain 241 mg (20 mEq or 10 mmol) of magnesium, and magnesium chloride hexahydrate tablets (Slow-Mag, Purdue) contain 64 mg of elemental magnesium. Diarrhea is often a dose-limiting side effect of oral supplementation. Severely deficient patients (< 1.0 mEq/L) (0.50 mmol/L) and all deficient critically ill patients should be managed with IV magnesium sulfate. Ten milliliters of a 10% magnesium sulfate solution contains 1 g of magnesium, which is equivalent to 98 mg (8.12 mEq or 4.06 mmol) of elemental magnesium. IV magnesium supplementation may also be used in the setting of status asthmaticus, premature labor, and torsade de pointes. In May 2013, the FDA released a drug safety communication recommending against the prolonged use of magnesium sulfate to stop preterm labor due to bone changes in exposed babies. Administration of magnesium sulfate injection to pregnant women longer than 5 to 7 days may lead to low calcium levels and bone fractures in the developing baby or fetus (http://www.fda.gov/Safety/MedWatch/). Magnesium concentrations need to be monitored closely in these patients. KEY CONCEPT Because magnesium concentration does not correlate well with total body magnesium stores, magnesium is often administered empirically to critically ill patients.[2,33]

The most common causes of hypermagnesemia are renal failure, often in conjunction with magnesium-containing medications (cathartics, antacids, or magnesium supplements), and lithium therapy (available as generic). Hypermagnesemia is defined as a serum magnesium concentration greater than 2.4 mEq/L (1.20 mmol/L). Mild hypermagnesemia is present if the serum magnesium concentration is between 2.5 and 4 mEq/L (1.25–2.00 mmol/L) and manifests as nausea, vomiting, cutaneous vasodilation, and bradycardia. Moderate hypermagnesemia is present if the serum magnesium concentration is between 4 and 12 mEq/L (2–6 mmol/L) and may manifest with hyporeflexia, weakness, somnolence, hypotension, and ECG changes (increased QRS interval). Severe hypermagnesemia is present if the serum magnesium concentration is greater than 13 mEq/L (6.5 mmol/L) and can manifest as muscle paralysis, complete heart block, asystole, respiratory failure, refractory hypotension, and death.[2,50]

LO 6 All patients with hypermagnesemia should have all magnesium supplements or magnesium-containing medications discontinued.[2,33] Iatrogenic hypermagnesemia has been observed after IV magnesium therapy for refractory asthma or preeclampsia. Mild hypermagnesemia and moderate hypermagnesemia without cardiac findings can be treated with normal saline infusion and furosemide therapy (assuming the patient has normal renal function). Moderate hypermagnesemia with cardiac irritability and severe hypermagnesemia require concurrent IV calcium gluconate to reverse the neuromuscular and cardiovascular effects. Calcium gluconate given at typical doses of 1 to 2 g IV will have transient effects and can be repeated as clinically indicated. Hemodialysis may be necessary for those with severely compromised renal function.

CONCLUSION

Because disturbances in fluid balance are routinely encountered in clinical medicine, it is essential to have a thorough understanding of body fluid compartments and the therapeutic use of fluids. Similarly, disturbances in serum sodium, potassium, calcium, phosphorus, and magnesium are ubiquitous and must be mastered by all clinicians. Dysregulation of fluid and/or electrolyte status has serious implications regarding the concepts of drug absorption, volumes of distribution, and toxicity. Similarly, many medications can disrupt fluid and/or electrolyte balance as an unintended consequence.

Patient Encounter 8: Putting It All Together

JW, a 67-year-old female nursing home resident, is admitted to the hospital with a 3-day history of altered mental status. The patient was unable to give a history or review of systems. On physical examination, the vital signs revealed a BP of 100/60 mm Hg, pulse 110 beats per minute, respirations 14 per minute, and a temperature of 38.3°C (101°F). Rales and dullness to percussion were noted at the posterior right base. The cardiac examination was significant for tachycardia. No edema was present. Laboratory studies included sodium 160 mEq/L (mmol/L), potassium 4.6 mEq/L (mmol/L), chloride 120 mEq/L (mmol/L), bicarbonate 30 mEq/L (mmol/L), glucose 104 mg/dL (5.8 mmol/L), BUN 34 mg/dL (12.1 mmol/L), and creatinine 2.2 mg/dL (194 µmol/L). The CBC was within normal limits. Chest x-ray indicated right lower lobe pneumonia. The patient is 5′7″ (170 cm) tall and currently weighs 65 kg (143 lb). Her normal weight is 70 kg (154 lb).

What are the likely causes for the increased sodium concentration in this patient?

Calculate the TBW, ICF, and ECF for this patient.

Calculate DM's fluid deficit if one is present.

In the next 24 hours, the medical team wants to replace 50% of the fluid deficit plus an extra 240 mL to account for increased insensible losses in addition to the patient's maintenance needs. Using the equation (1500 mL + 20 mL for each kilogram > 20 kg), calculate the rate of fluid administration for the total fluids needed in this 24-hour period and over the next 48 hours.

Calculate JW's daily maintenance fluids.

Calculate JW's fluid administration rate for the first 24 hours (hospital day 1).

Calculate JW's fluids for the subsequent 48 hours (hospital days 2 and 3) if the goal is to replete the remaining fluid deficit during that time.

What type of fluid should be used to treat JW's fluid disorder?

Abbreviations Introduced in This Chapter

ADH	Antidiuretic hormone
ASHP	American Society of Health-System Pharmacists
ATP	Adenosine triphosphate
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{+}	Calcium
CHF	Congestive heart failure
Cl	Chloride
D_5W	Dextrose 5% water
ECF	Extracellular fluid
ECG	Electrocardiogram
FFP	Fresh-frozen plasma
IBW	Ideal body weight
ICF	Intracellular fluid
I&Os	Ins and outs
IV	intravenous
K^{+}	Potassium
KPO_4	Potassium phosphate
KVO	Keep the vein open
LR	Lactated Ringer's (solution)
Mg^{++}	Magnesium
Na^{+}	Sodium
NaCl	Sodium chloride
$NaPO_4$	Sodium phosphate
NG	Nasogastric
NS	Normal saline
SI	Standardized international units
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
TBW	Total body water
TPN	Total parenteral nutrition

REFERENCES

1. Faber MD, Kupin WL, Heilig CW, Narins RG. Common fluid–electrolyte and acid–base problems in the intensive care unit: selected issues. Semin Nephrol. 1994;14:8–22.
2. Kraft MD, Btaiche IF, Sacks GS, Kudsk KA. Treatment of electrolyte disorders in adult patients in the intensive care unit. Am J Health Syst Pharm. 2005;62:1663–1682.
3. Faubel S, Topf J. The Fluid Electrolyte and Acid–Base Companion. San Diego, CA: Alert and Oriented Publishing, 1999.
4. Chenevey B. Overview of fluids and electrolytes. Nurs Clin North Am. 1987;22:749–759.
5. Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm. 1974;7:650–655.
6. Rose BD, Post TW. Clinical Physiology of Acid–Base and Electrolyte Disorders, 5th ed. New York, NY: McGraw Hill, 2001.
7. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–2256.
8. The Albumin Reviewers (Alderson P, Bunn F, Lefebvre C, Li Wan Po A, Li L, Roberts I, Schlerhout G. Human albumin solution for resuscitation and volume expansion in critically ill patients. Cochrane Database Syst Rev. 2004:CD001208.
9. Weil MH, Tang W. Albumin versus crystalloid solutions for the critically ill and injured. Crit Care Med. 2004;32: 2154–2155.
10. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or shock. N Engl J Med. 2014 Apr 10; 370(15):1412–1421.
11. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013 Feb 28;2:CD000567.
12. Shafiee MAS, Bohn D, Hoorn EJ, Halperin ML. How to select optimal maintenance intravenous therapy. QJ Med. 2003;96:601–610.
13. Kwan I, Bunn F, Roberts I, on behalf of the WHO Pre-Hospital Trauma Care Steering Committee. Timing and volume of fluid administration for patients with bleeding. Cochrane Database Syst Rev. 2003: CD002245.
14. Medication Storage—Concentrated Electrolytes—Storage in Patient Care Areas. The Joint Commission. Available from: https://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFAQId=1534. Accessed November 30, 2017.
15. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatremia. Intensive Care Med 2014;40:320–331.

16. Adrigoue H, Madias NE. Hyponatremia. N Engl J Med. 2000;342:1581–1589.
17. Sterns RH. The treatment of hyponatremia: first, do no harm. Am J Med. 1990;88:557–560.
18. Cluitmans FHM, Meinders AE. Management of severe hyponatremia: rapid or slow correction? Am J Med. 1990;88: 161–166.
19. Adrogue HJ, Madias NE. Hypernatremia. N Engl J Med. 2000;342:1493–1499.
20. Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalized patients. Ann Intern Med. 1996;124:197–203.
21. Kang SK, Kim W, Oh MS. Pathogenesis and treatment of hypernatremia. Nephron. 2002;92(suppl 1):14–17.
22. Mandal AK. Hypokalemia and hyperkalemia. Med Clin North Am. 1997;81:611–639.
23. Halperin ML. Potassium. Lancet. 1998;352:135–140.
24. Body JJ, Bouillon R. Emergencies of calcium homeostasis. Rev Endocr Metab Disord. 2003;4:167–175.
25. Gennari FJ. Hypokalemia. N Engl J Med. 1998;339:451–458.
26. Hamil RJ, Robinson LM, Wexler HR, Moote C. Efficacy and safety of potassium infusion therapy in hypokalemic critically ill patients. Crit Care Med. 1991;19:694–699.
27. Kruge JA, Carlson RW. Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. Arch Intern Med. 1990;150:613–617.
28. Cohn JN, Kowey PR, Whelton PK, Prisant M. New guidelines for potassium replacement in clinical practice. Arch Intern Med. 2000;160:2429–2436.
29. Williams ME. Hyperkalemia. Crit Care Clin. 1991;7:155–174.
30. Carroll MF, Schade DS. A practical approach to hypercalcemia. Am Fam Physician. 2003;67:1959–1966.
31. Bushinsky DA, Monk RD. Calcium. Lancet. 1998;352:305–311.
32. Zaloga GP. Hypocalcemia in critically ill patients. Crit Care Med. 1992;20:251–262.
33. Metheny NM. Fluid and Electrolyte Balance: Nursing Considerations, 4th ed. New York, NY: Lippincott, 2000.
34. Davidson TG. Conventional treatment of hypercalcemia of malignancy. Am J Health-Syst Pharm. 2001;58(suppl 3): S8–S15.
35. Weisinger JR, Bellorin-Font E. Magnesium and phosphorous. Lancet. 1998;352:391–396.
36. Brown KA, Dickerson RN, Morgan LM, Alexander KH, Minard G, Brown RO. A new graduated regimen for phosphorous replacement in patients receiving nutritional support. J Parenteral Enteral Nutr. 2006;30:209–214.
37. Series: Just the Facts. Fluids and Electrolytes. Philadelphia, PA: Lippincott Williams & Wilkins, 2005.
38. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med. 1977;137: 203–220.
39. Stoff JS. Phosphate homeostasis and hypophosphatemia. Am J Med. 1982;72:489–495.
40. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. N Engl J Med. 1985;313: 420–424.
41. Perreault MM, Ostron NI, Tiemey MG. Efficacy and safety of intravenous phosphate replacement in critically ill patients. Ann Pharmacother. 1997;31:683–688.
42. Kee JL, Paulanka BJ, Purnell LD. Fluids and Electrolytes with Clinical Applications: A Programmed Approach, 7th ed. Clifton Park, NY: Delmar Learning, 2000.
43. Schucker JJ, Ward KE. Hyperphosphatemia and phosphate buffers. Am J Health-Syst Pharm. 2005;62:2355–2361.
44. Oster JR, Epstein M. Management of magnesium depletion. Am J Nephrol. 1988;8:349–354.
45. Al-Ghamdi SMG, Cameron EC, Sutton AL. Magnesium deficiency: pathophysiologic and clinical overview. Am J Kidney Dis. 1994;24:737–752.
46. Bilezikian JP. Clinical review 51: management of hypercalcemia. J Clin Endocrinol Metab. 1993;77:1445–1449.
47. Salem M, Munoz R, Chernow B. Hypomagnesemia in critical illness: a common and clinically important problem. Crit Care Clin. 1991;7:225–252.
48. Zalman SA. Hypomagnesemia. J Am Soc Nephol. 1999:10: 1616–1622.
49. Dube L, Granry JC. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. Can J Anesth. 2003;50:732–746.
50. Van Hook JW. Hypermagnesemia. Crit Care Clin. 1991; 7:215–223.

28 Acid–Base Disturbances

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LEARNING OBJECTIVES

LO

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

1. Compare and contrast the four primary acid–base disturbances within the human body.
2. Apply simple formulas in a systematic manner to determine the etiology of simple acid–base disturbances and the adequacy of compensation.
3. Integrate the supplemental concepts of the anion gap and the excess gap to further assess for complex acid–base disturbances.
4. Discuss the most common clinical causes for each primary acid–base abnormality.
5. Describe the potential clinical complications of altered acid–base homeostasis.
6. Propose an appropriate treatment plan for patients with deranged acid–base physiology.

INTRODUCTION

Given its reputation for complexity and the need to memorize innumerable formulas, acid–base analysis intimidates many health care providers. In reality, acid–base disorders always obey well-defined biochemical and physiological principles. The pH determines a patient's acid–base status and an assessment of the bicarbonate (HCO_3^-) and arterial carbon dioxide ($PaCO_2$) values identifies the underlying process. Rigorous use of a systematic approach to arterial blood gases (ABGs) increases the likelihood that derangements in acid–base physiology are recognized and correctly interpreted. This chapter outlines a clinically useful approach to acid–base abnormalities and then applies this approach in a series of increasingly complex clinical scenarios.

Disturbances of acid–base equilibrium occur in a wide variety of illnesses and are among the most frequently encountered disorders in critical care medicine. The importance of a thorough command of this content cannot be overstated given that acid–base disorders are remarkably common and may result in significant morbidity and mortality. Although severe derangements may affect virtually any organ system, the most serious clinical effects are cardiovascular (arrhythmias, impaired contractility), neurologic (coma, seizures), pulmonary (dyspnea, impaired oxygen delivery, respiratory fatigue, respiratory failure), and/or renal (hypokalemia). Changes in acid–base status also affect multiple aspects of pharmacokinetics (clearance, protein binding) and pharmacodynamics.

PHYSIOLOGY OF ACID–BASE HOMEOSTASIS

Acid–base homeostasis is responsible for maintaining blood hydrogen ion concentration [H^+] near normal despite the daily acidic and/or alkaline loads derived from the intake and metabolism of foods. Acid–base status is traditionally represented in terms of pH, the negative logarithm of [H^+]. Because [H^+] is equal to 24 times the ratio of $PaCO_2$ to HCO_3^-, the pH can be altered by a change in either the bicarbonate concentration or the dissolved carbon dioxide (CO_2). A critically important concept is that [H^+] depends only on the *ratio* of $PaCO_2$ to HCO_3^- and not the absolute amount of either. As such, a normal $PaCO_2$ or HCO_3^- alone does not guarantee that the pH will be normal. Conversely, a normal pH does not imply that either the $PaCO_2$ or HCO_3^- will be normal.[1]

KEY CONCEPT Acid–base homeostasis is tightly regulated by the complex, but predictable, interactions of the kidneys, the lungs, and various buffer systems. The kidneys control serum HCO_3^- concentration through the excretion or reabsorption of filtered HCO_3^-, the excretion of metabolic acids, and synthesis of new HCO_3^-. The lungs control arterial CO_2 concentrations through changes in the depth and/or rate of respiration. The net result is tight regulation of the blood pH by these three distinct mechanisms working in harmony: extracellular HCO_3^- and intracellular protein buffering systems; pulmonary regulation of $PaCO_2$, effectively allowing carbonic acid to be eliminated by the lungs as CO_2; and renal reclamation or excretion of HCO_3^- and excretion of acids such as ammonium.

Because the kidneys excrete less than 1% of the estimated 13,000 mEq (mmol) of H^+ ions generated in an average day, renal failure can be present for prolonged periods before life-threatening imbalances occur. Conversely, cessation of breathing for minutes results in profound acid–base disturbances.[1]

The best way to assess a patient's acid–base status is to review the results of an ABG specimen. ABG analyzers directly measure the pH and $PaCO_2$, while the HCO_3^- value is calculated using the Henderson–Hasselbalch equation. A more direct measure of serum HCO_3^- is obtained by measuring the total venous carbon dioxide (tCO_2). Because dissolved CO_2 is almost exclusively in the form of HCO_3^-, tCO_2 is essentially equivalent to the measured serum HCO_3^- concentration. This value (HCO_3^-) is routinely reported on basic chemistry panels. In the remainder of this chapter, the pH and $PaCO_2$ values should be assumed to come from an ABG while HCO_3^- values should be considered to be the measured serum concentration.

BASIC PATHOPHYSIOLOGY

LO 1 Under normal circumstances, the arterial pH is tightly regulated between 7.35 and 7.45. Acidemia is an abnormally low arterial blood pH (< 7.35) while acidosis is a pathologic process that acidifies body fluids. Similarly, alkalemia is an abnormally high arterial blood pH (> 7.45) while alkalosis is a pathologic process that alkalinizes body fluids. As such, although a patient can simultaneously have acidosis *and* alkalosis, the end result will be acidemia *or* alkalemia.

LO 1 Changes in the arterial pH are driven by changes in the $PaCO_2$ and/or the serum HCO_3^-. CO_2 is a volatile acid regulated by the depth and rate of respiration. Because CO_2 can be either "blown off" or "retained" by the respiratory system, it is referred to as being under respiratory control. KEY CONCEPT Respiratory acidosis and alkalosis result from primary disturbances in the arterial CO_2 concentration. Metabolic compensation for respiratory disturbances is a slow process, often requiring days for the serum HCO_3^- to reach the steady state. KEY CONCEPT Respiratory acidosis is caused by respiratory insufficiency resulting in an increased arterial CO_2 concentration. The compensation for respiratory acidosis (if present for prolonged periods) is an increase in serum HCO_3^-. KEY CONCEPT Respiratory alkalosis is caused by hyperventilation resulting in a decreased arterial CO_2 concentration. The compensation for respiratory alkalosis (if present for prolonged periods) is a decrease in serum HCO_3^-.

LO 1 A respiratory acid–base disorder is a pH disturbance caused by pathologic alterations of the respiratory system or its central nervous system (CNS) control. Such an alteration may result in the accumulation of $PaCO_2$ beyond normal limits (> 45 mm Hg [6.0 kPa]), a situation termed *respiratory acidosis*, or it may result in the loss of $PaCO_2$ beyond normal limits (< 35 mm Hg or 4.7 kPa), a condition termed *respiratory alkalosis*. Variations in respiratory rate and/or depth allow the lungs to achieve changes in the $PaCO_2$ very quickly (within minutes).

HCO_3^- is a base regulated by renal metabolism via the enzyme carbonic anhydrase. As such, HCO_3^- is often referred to as being under metabolic control. KEY CONCEPT Metabolic acidosis and alkalosis result from primary disturbances in the serum HCO_3^- concentration. Respiratory compensation of metabolic disturbances begins within minutes and is complete within 12 hours. KEY CONCEPT Metabolic acidosis is characterized by a decrease in serum HCO_3^-. The anion gap is used to narrow the differential diagnosis because metabolic acidosis may be caused by the addition of acids (increased anion gap) or loss of HCO_3^- (normal anion gap). The compensation for metabolic acidosis is an increase in ventilation with a decrease in arterial CO_2. KEY CONCEPT Metabolic alkalosis is characterized by an increase in serum HCO_3^-. This disorder requires loss of fluid that is low in HCO_3^- from the body or addition of HCO_3^- to the body. The compensation for metabolic alkalosis is a decrease in ventilation with an increase in arterial CO_2.

LO 1 A metabolic acid–base disorder is a pH disturbance caused by derangement of the pathways responsible for maintaining a normal HCO_3^- concentration. This may result in a pathologic accumulation of HCO_3^- (> 26 mEq/L [mmol/L]), a condition termed *metabolic alkalosis*, or it may result in the loss of HCO_3^- beyond normal (< 22 mEq/L [mmol/L]), a condition termed *metabolic acidosis*. In contrast to the lungs' rapid effects on CO_2, the kidneys change the HCO_3^- very slowly (hours to days).

Respiratory and metabolic derangements can occur in isolation or in combination. If a patient has an isolated primary acid–base disorder that is not accompanied by another primary acid–base disorder, a simple (uncomplicated) disorder is present. The most common clinical disturbances are simple acid–base disorders. If two or three primary acid–base disorders are simultaneously present, the patient has a mixed (complicated) disorder. More complex clinical situations lead to mixed acid–base disturbances. Because CO_2 is a volatile acid, it can rapidly be changed by the respiratory system. If a respiratory acid–base disturbance is present for minutes to hours, it is considered an acute disorder, while if it is present for days or longer, it is considered a chronic disorder. By definition, the metabolic machinery that regulates HCO_3^- results in slow changes, and all metabolic disorders are chronic.

Changes that follow the primary disorder and attempt to restore the blood pH to normal are referred to as compensatory changes. It should be stressed that compensation never normalizes the pH. Because all metabolic acid–base disorders are chronic and the normal respiratory system can quickly alter the $PaCO_2$, essentially all metabolic disorders are accompanied by some degree of respiratory compensation.[2,3] Similarly, chronic respiratory acid–base disorders are typically accompanied by attempts at metabolic compensation.[4,5] However, with acute respiratory acid–base disorders there is insufficient time for the metabolic pathways to compensate significantly.[6] As such, acute respiratory derangements are essentially uncompensated.

The amount of compensation (metabolic or respiratory) can be reliably predicted based on the degree of derangement in the primary disorder. Table 28–1 outlines the simple acid–base disorders and provides formulas for calculating the expected compensatory responses.[7] Although it is not mandatory to memorize these formulas in order to interpret acid–base problems, they can be helpful tools. If the measured values differ markedly from the calculated values (the measured serum HCO_3^- is > 2 mEq/L [mmol/L] from the calculated value or the measured $PaCO_2$ is > 4 mm Hg [0.5 kPa] from the calculated value), a second acid–base disorder is present as outlined in Table 28–2.

Table 28–1

The Six Simple Acid–Base Disorders

Type of Disorder	pH	$PaCO_2$[a]	HCO_3^-
1. Metabolic acidosis	↓	Decreased[b] $PaCO_2 = (1.5 \times HCO_3^-) + 8$	Decreased[c]
2. Metabolic alkalosis	↑	Increased[b] $PaCO_2 = (0.9 \times HCO_3^-) + 15$	Increased[c]
3. Acute respiratory acidosis	↓	Increased[c]	Approximately normal $\Delta HCO_3^- = 0.1 \times \Delta PaCO_2$[a]
4. Chronic respiratory acidosis	↓	Increased[c]	Increased[d] $\Delta HCO_3^- = 0.35 \times \Delta PaCO_2$[a]
5. Acute respiratory alkalosis	↑	Decreased[c]	Approximately normal $\Delta HCO_3^- = 0.2 \times \Delta PaCO_2$[a]
6. Chronic respiratory alkalosis	↑	Decreased[c]	Decreased[d] $\Delta HCO_3 = 0.4 \times \Delta PaCO_2$[a]

[a] $PaCO_2$ in mm Hg and is calculated from kPa by dividing by 0.133.

[b] Respiratory compensation: If inappropriate, see Table 28–2.

[c] Primary disorder.

[d] Metabolic compensation: If inappropriate, see Table 28–2.

Table 28–2

Diagnosis of Concurrent Acid–Base Disturbances When Compensation Is Inappropriate

Primary Acid–Base Disturbance	Assessment of Compensation	Concurrent Acid–Base Disturbance
Metabolic acidosis	$PaCO_2$ too low[a]	Respiratory alkalosis
	$PaCO_2$ too high[a]	Respiratory acidosis
Metabolic alkalosis	$PaCO_2$ too low[a]	Respiratory alkalosis
	$PaCO_2$ too high[a]	Respiratory acidosis
Respiratory acidosis	HCO_3^- too low[b]	Metabolic acidosis
	HCO_3^- too high[b]	Metabolic alkalosis
Respiratory alkalosis	HCO_3^- too low[b]	Metabolic acidosis
	HCO_3^- too high[b]	Metabolic alkalosis

[a]Measured $PaCO_2$ more than 4 mm Hg (0.5 kPa) from the calculated value.

[b]Measured HCO_3^- more than 2 mEq/L (mmol/L) from the calculated value.

DIAGNOSIS

LO 2

When given an ABG for interpretation, it is essential to use an approach that is focused yet comprehensive.[8] An algorithm illustrating this concept is shown in Figure 28–1. Using this algorithm, step 1 is to identify all abnormalities in the pH, $PaCO_2$, and/or HCO_3^- and then decide which abnormal values are primary and which are compensatory. This is best done by initially looking at the pH. Whichever side of 7.40 the pH is on, the process that caused it to shift to that side is the primary abnormality. If the arterial pH is lower than 7.40 (acidemia), an elevated $PaCO_2$ (> 45 mm Hg [6.0 kPa], **respiratory acidosis**) or a lowered HCO_3^- (< 22 mEq/L [mmol/L], **metabolic acidosis**) would be the primary abnormality. If the arterial pH is higher than 7.40 (alkalemia), a decreased $PaCO_2$ (< 35 or 4.7 kPa, **respiratory alkalosis**) or an increased HCO_3^- (> 25 mEq/L [mmol/L], **metabolic alkalosis**) would be the primary abnormality. Once the primary disorder is established, step 2 is to apply the formulas from Table 28–1 to assess whether the observed compensation is appropriate for the primary disorder and to look for concurrent processes.[7]

An alternative to a diagnostic algorithm is use of a graphic nomogram.[9] Nomograms are plots of the pH, $PaCO_2$, and HCO_3^- that allow the user to rapidly determine whether ABG

Patient Encounter 1

An unconscious 27-year-old Afghanistan war veteran is brought to the emergency department by his wife who found him unconscious when she returned home from work. She reports that he is on disability and that the pain clinic has been making "lots of changes to all his pain pills" for the veteran's chronic low back pain. The initial ABG has a pH of 7.20 with a $PaCO_2$ of 65 mm Hg (8.6 kPa), and the serum HCO_3 is 27 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 2

The next patient is a 39-year-old man with advanced emphysema due to α_1 antitrypsin deficiency who is undergoing evaluation for lung transplantation. An ABG drawn as a routine part of the transplant workup shows a pH of 7.34, a $PaCO_2$ of 70 mm Hg (9.3 kPa), and an HCO_3^- of 35 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 3

A healthy 19-year-old undergraduate student is having an ABG drawn as part of a clinical trial she is participating in as a control. Her ABG shows a pH of 7.50, a $PaCO_2$ of 29 mm Hg (3.9 kPa), and an HCO_3^- of 22 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 4

An 87-year-old man has small vessel ischemic cardiomyopathy and chronic congestive heart failure as a complication of mantle field radiation he received for lymphoma in the early 1960s. He requires daily furosemide (Lasix) therapy to remain euvolemic. An ABG was drawn for increasing dyspnea and shows the following: pH of 7.50, a $PaCO_2$ of 47 mm Hg (6.3 kPa), and an HCO_3^- of 36 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 5

The final patient in this section is a 46-year-old woman with end-stage renal disease who was sent to the emergency room (ER) from the dialysis center for evaluation of hypotension. Upon arrival to dialysis she complained of several days of diarrhea and dizziness when standing. When her physical examination confirmed orthostatic changes in her blood pressure, she was sent to the ER without initiation of dialysis. Her ABG in the ER shows a pH of 7.20, a $PaCO_2$ of 20 mm Hg (2.7 kPa), and an HCO_3^- of 8 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

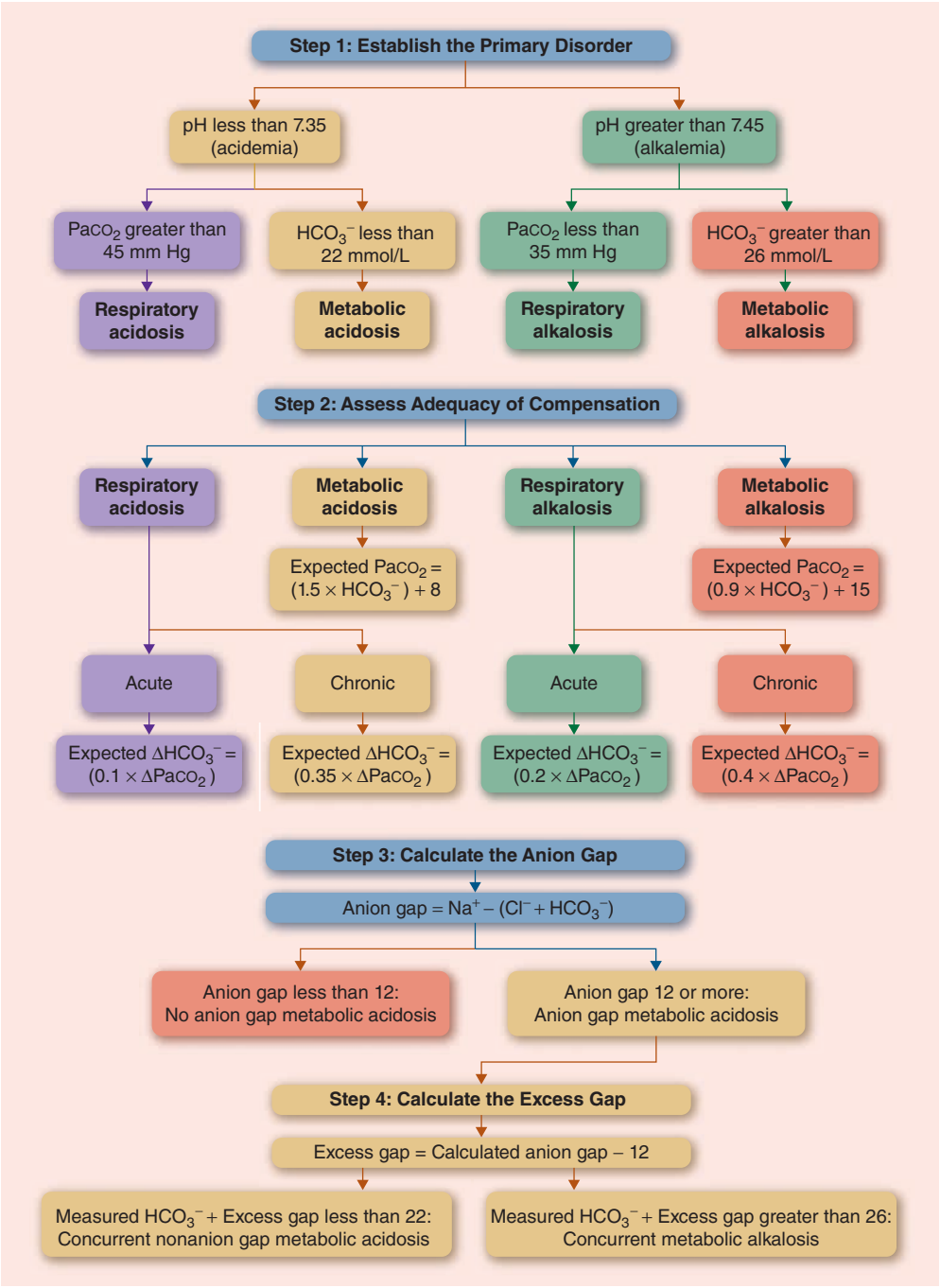

FIGURE 28–1. An algorithmic approach to acid–base disorders. Normal values: pH 7.35 to 7.45, $PaCO_2$ 35 to 45 mm Hg (4.7 to 6.0 kPa), HCO_3^- 22 to 26 mEq/L (mmol/L), anion gap less than 12 mEq/L (mmol/L). Note that $PaCO_2$ should be in units of mm Hg to use the equations in the figure. To convert $PaCO_2$ in units of kPa to mm Hg, divide by 0.133. (Cl^-, chloride ion; HCO_3^-, bicarbonate; Na^+, sodium ion; $PaCO_2$, partial pressure of arterial carbon dioxide.)

values are consistent with one of the six simple primary acid–base disturbances. Although nomograms are commonly used to identify acid–base disturbances in clinical practice, only individuals who fully comprehend the fundamental concepts of acid–base assessment should use these tools. Also, appreciate that nomograms have limited utility when dealing with complex acid–base derangements.

Acid–base disturbances are always manifestations of underlying clinical disorders. It is useful to specifically define the primary acid–base abnormality because each disorder is caused by a limited number of disease processes. Establishing the specific disease process responsible for the observed acid–base disorder is clinically important because treatment of a given disorder will only be accomplished by correcting the underlying disease process.

ADVANCED PATHOPHYSIOLOGY

LO 3

The concepts in this section are used to further expand on steps 3 and 4 of the diagnostic algorithm shown in Figure 28–1. Under normal circumstances, the serum is in the isoelectric state. This

means that the positively charged entities reported in a standard chemistry panel (cations: sodium [Na^+] and potassium [K^+]) should be exactly balanced by the negatively charged entities (anions: chloride [Cl^-] and bicarbonate [HCO_3^-]). However, this relationship is consistently incorrect because the measured cations are higher than the measured anions by 10 to 12 mEq/L (mmol/L). This discrepancy results from the presence of unmeasured anions (eg, circulating proteins, phosphates, and sulfates). This apparent difference in charges, the serum **anion gap**, is calculated as follows:

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

LO 3 Because the serum K^+ content is relatively small and is very tightly regulated, it is generally omitted from the calculation.[10]

It is important to realize that the serum HCO_3^- concentration may be affected by the presence of unmeasured endogenous acids (lactic acid or ketoacids). HCO_3^- will attempt to buffer these acids, resulting in a 1 mEq (mmol) loss of serum HCO_3^- for each 1 mEq (mmol) of acid titrated. Because the cation side of the equation is not affected by this transaction, the loss of serum HCO_3^- results in an increase in the calculated anion gap. Identification of an increased anion gap is very important because a limited number of clinical scenarios lead to this unique acid–base disorder. A mnemonic to recall the differential diagnosis for an anion gap acidosis is shown in Table 28–3. The concept of the increased anion gap is applied later in Patient Encounters 6 through 10.

Step 3 in Figure 28–1 suggests that any time an ABG is analyzed it is wise to concurrently inspect the serum chemistry values and to calculate the anion gap. The body does not generate an anion gap to compensate for a primary disorder. As such, if the calculated anion gap exceeds 12 mEq/L (mmol/L), there is a primary metabolic acidosis regardless of the pH or the serum HCO_3^- concentration. The anion gap may be artificially lowered by decreased serum albumin, multiple myeloma, lithium intoxication, or a profound increase in the serum potassium, calcium, or magnesium.[11]

LO 3 Step 4 in Figure 28–1 shows how calculation of the anion gap also facilitates determination of the **excess gap** or the degree to which the calculated anion gap exceeds the normal anion gap. The excess gap is calculated as follows:

$$\text{Excess gap} = \text{calculated anion gap} - \text{normal anion gap}$$
$$= [Na^+ - (Cl^- + HCO_3^-)] - 12$$

Table 28–3

Mnemonics for the Differential Diagnoses of Metabolic Acidosis

Elevated Anion Gap[a]	Normal Anion Gap[a]
M—Methanol, metformin	U—Ureteral diversion
U—Uremia	S—Saline infusion
D—Diabetic (or alcoholic) ketoacidosis	E—Exogenous acid
	D—Diarrhea
P—Paraldehyde, phenformin	C—Carbonic anhydrase inhibitors
I—Isoniazid, iron	A—Adrenal insufficiency
L—Lactic acidosis	R—Renal tubular acidosis
E—Ethylene glycol, ethanol	
S—Salicylates	

[a]Anion gap = serum sodium concentration – (serum chloride concentration + serum bicarbonate concentration). Under normal circumstances, the anion gap should be 10 mEq/L (mmol/L) or less.

LO 3 The excess gap represents the amount of HCO_3^- that has been lost due to buffering unmeasured cations. The excess gap can be added back to the measured HCO_3^- to determine what the patient's HCO_3^- would be if these endogenous acids were not present. This is a very valuable tool that can be used in narrowing the differential diagnosis of certain acid–base disorders as well as in uncovering occult or mixed acid–base disorders.

In summary, the approach to assessment of acid–base status involves four key steps as outlined in Figure 28–1: step 1 = initial inspection of the pH, $PaCO_2$, and HCO_3^-; step 2 = assessment of the adequacy of compensation; step 3 = calculation of the anion gap; and step 4 = calculation of the excess gap.

ETIOLOGY AND TREATMENT

KEY CONCEPT *ABGs*, serum electrolytes, physical examination findings, the clinical history, and the patient's recent medications must be reviewed in order to establish the etiology of a given acid–base disturbance. Tables 28–3 through 28–7 outline the most commonly encountered causes for each of the primary acid–base disorders. The therapeutic approach to each of these acid–base derangements should emphasize a search for the cause, as opposed to immediate attempts to normalize the pH.

KEY CONCEPT It is critical to treat the underlying causative process to effectively resolve most observed acid–base disorders. However, supportive treatment of the pH and electrolytes is often needed until the underlying disease state is improved.[12,13]

All patients with significant disturbances in their acid–base status require continuous cardiovascular and hemodynamic monitoring. Because frequent assessment of the patient's response to treatment is critical, an arterial line is often placed to minimize patient discomfort with serial ABG collections. If the anion gap was initially abnormal, serial chemistries should be followed to ensure that the anion gap resolves with treatment. Specific treatment decisions depend on the underlying pathophysiologic state (eg, dialysis for renal failure, insulin for diabetic ketoacidosis, or improving tissue perfusion and oxygenation for lactic acidosis).

Metabolic Acidosis

Metabolic acidosis is characterized by a reduced arterial pH, a primary decrease in the HCO_3^- concentration, and a compensatory reduction in the $PaCO_2$. The etiologies of metabolic acidosis are divided into those that lead to an increase in the anion gap and those associated with a normal anion gap and are listed in Table 28–4. Although there are numerous mnemonics to recall the differential diagnosis of the metabolic acidosis, two simple ones are shown in Table 28–3. High anion gap metabolic acidosis is most frequently caused by lactic acidosis, ketoacidosis, and/or renal failure. Although there is considerable variation, the largest anion gaps are caused by ketoacidosis, lactic acidosis, and methanol or ethylene glycol ingestion.[14]

LO 4

LO 5 Symptoms of metabolic acidosis are attributable to changes in cardiovascular, musculoskeletal, neurologic, or pulmonary functioning. Respiratory compensation requires marked increases in minute ventilation and may lead to dyspnea, respiratory fatigue, and respiratory failure. Acidemia predisposes to ventricular arrhythmias and reduces cardiac contractility, each of which can result in pulmonary edema and/or systemic hypotension.[15] Neurologic symptoms range from lethargy to coma and are usually proportional to the severity of the pH derangement. Chronic metabolic acidosis leads to a variety of musculoskeletal problems including impaired growth, rickets,

LO 5

Table 28–4

Common Causes of Metabolic Acidosis

Elevated Anion Gap[a]	Normal Anion Gap[a]
Intoxications	Bowel fistula
Methanol	Diarrhea
Ethylene glycol	Dilutional acidosis
Salicylates	Drugs
Paraldehyde	Acetazolamide[b]
Isoniazid	Ammonium chloride[b]
Ketoacidosis	Amphotericin B[b]
Diabetic	Arginine hydrochloride[c]
Ethanol	Cholestyramine[b]
Starvation	Hydrochloric acid[b]
Lactic acidosis	Lithium[b]
Carbon monoxide poisoning	Parenteral nutrition[b]
Drugs	Topiramate[b]
IV lorazepam (due to vehicle)[c]	Zonisamide[b]
Metformin[b]	Lead poisoning
Nitroprusside (due to cyanide accumulation)[b]	Renal tubular acidosis
	Surgical drains
Nucleoside reverse transcriptase inhibitors[b]	Ureteral diversion
	Villous adenomas (some)
Propofol[c]	
Seizures	
Severe hypoxemia	
Shock	
Renal failure	

[a]Anion gap = serum sodium concentration – (serum chloride concentration + serum bicarbonate concentration). Under normal circumstances, the anion gap should be 10 mEq/L (mmol/L) or less.

[b]May be observed with therapeutic doses or overdoses.

[c]Typically observed with overdoses or prolonged, high-dose infusions (the so-called propofol infusion syndrome).

osteomalacia, or osteopenia. These changes are believed to be caused by the release of calcium and phosphate during bone buffering of excess H^+ ions.

As previously discussed, in anion gap metabolic acidosis, the isoelectric state is maintained because unmeasured anions are present. With a *normal* anion gap metabolic acidosis, the isoelectric state is maintained by an increase in the measured chloride. Because of this, normal anion gap metabolic acidosis is often referred to as hyperchloremic acidosis.

Patient Encounter 6

A 19-year-old woman with Prader-Willi Syndrome and hyperphagia is admitted to the intensive care unit after ingesting an unknown quantity of aspirin tablets. Her presenting labs show a pH of 7.50, a $PaCO_2$ of 20 mm Hg (2.7 kPa), an HCO_3^- of 16 mEq/L (mmol/L), a sodium concentration of 140 mEq/L (mmol/L), and a chloride level of 103 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 7

A 56-year-old man is brought to the emergency room by his family. Because he has not felt well for the past week, he skipped his last three routine hemodialysis sessions. He had the onset of vomiting and confusion 2 days ago but consistently refused medical evaluation. When family members found him unresponsive today they called 911. Lab analyses show: pH of 7.40, $PaCO_2$ of 40 mm Hg (5.3 kPa), HCO_3^- of 24 mEq/L (mmol/L), sodium concentration of 145 mEq/L (mmol/L), and chloride level of 100 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 8

A boisterous, intoxicated 44-year-old woman is brought to the ER by rescue squad after police found her disrupting traffic by blocking multiple lanes of a very busy city street with her bicycle and personal belongings. Shortly after arrival in the ER she has multiple episodes of bloody emesis with an obvious aspiration event. She is transferred to the ICU where she becomes progressively hypoxic and requires intubation and mechanical ventilation during the ensuing hours. Her ABG immediately postintubation shows a pH of 7.50, a $PaCO_2$ of 20 mm Hg (2.7 kPa), an HCO_3^- of 15 mEq/L (mmol/L), a sodium concentration of 145 mEq/L (mmol/L), and a chloride level of 100 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

Patient Encounter 9

A frail, 69-year-old man is being evaluated for altered mental status. His wife says he has suffered from "stomach flu" for several days and has experienced frequent bouts of bilious emesis. He is a poorly controlled diabetic and his wife states that she stopped giving him his insulin since he has not been able to eat. He became more somnolent yesterday but she was unable to bring him to the ER because she was hosting a bridge party. She called an ambulance today when she noticed his breathing was very slow and shallow. The blood work drawn prior to urgent intubation shows a pH of 7.10, a $PaCO_2$ of 50 mm Hg (6.7 kPa), an HCO_3^- of 15 mEq/L (mmol/L), a sodium concentration of 145 mEq/L (mmol/L), and a chloride level of 100 mEq/L (mmol/L).

What is the primary acid–base disorder?

Is there a mixed disorder?

Given the clinical history, what is the most likely explanation for the ABG findings?

In patients with a normal anion gap metabolic acidosis, it is often helpful to calculate the urine anion gap (UAG).[16] The UAG is calculated as follows:

$$UAG = (Urine\ Na^+ + Urine\ K^+) - Urine\ Cl^-$$

The normal UAG ranges from 0 to 5 mEq/L (mmol/L) and represents the presence of unmeasured urinary anions. In metabolic acidosis, the excretion of NH_4^+ and concurrent Cl^- should increase markedly if renal acidification capacity is intact. This results in UAG values from −20 to −50 mEq/L (mmol/L). This occurs because the urinary Cl^- concentration now markedly exceeds the urinary Na^+ and K^+ concentrations. LO 4 Diagnoses consistent with an excessively negative UAG include proximal (type 2) renal tubular acidosis, diarrhea, or administration of acetazolamide or hydrochloric acid (HCl). Excessively positive values of the UAG suggest a distal (type 1) renal tubular acidosis.

In order to effectively treat metabolic acidosis, the *causative process* must be identified and treated.[17] The precise role of adjunctive therapy with sodium bicarbonate ($NaHCO_3$) is not universally agreed upon. However, most practitioners accept that LO 6 $NaHCO_3$ is indicated when renal dysfunction precludes adequate regeneration of HCO_3^- or when severe acidemia (pH < 7.15) is present. The metabolic acidosis seen with lactic acidosis and ketoacidosis generally resolves with therapy targeted at the underlying cause, and $NaHCO_3$ may be unnecessary regardless of the pH. The metabolic acidosis of renal failure, renal tubular acidosis, or intoxication with ethylene glycol, methanol, or salicylates is much more likely to require $NaHCO_3$ therapy.

If $NaHCO_3$ is used, the plasma HCO_3^- should not be corrected entirely. Instead, aim at increasing HCO_3^- above an absolute value of 10 mEq/L (mmol/L). The total HCO_3^- deficit can be calculated from the current bicarbonate concentration ($HCO_{3\ curr}^-$), the desired bicarbonate concentration ($HCO_{3\ post}^-$), and the body weight (in kilograms) as follows:

$$HCO_3^-\ deficit = [(2.4/HCO_{3\ curr}^-) + 0.4] \times weight \times (HCO_{3\ curr}^- - HCO_{3\ post}^-)$$

No more than half of the calculated HCO_3^- deficit should be given initially to avoid volume overload, hypernatremia, hyperosmolarity, overshoot alkalemia, hypocalcemia, and/or hypokalemia. The calculated HCO_3^- deficit reflects only the present situation and does not account for ongoing H^+ production and HCO_3^- loss. When giving HCO_3^- therapy, serial blood gases are needed to monitor therapy.

Historically, another option for patients with severe acidemia has been tromethamine (tris-hydroxymethyl aminomethane or THAM).[18] This inert amino alcohol buffers acids and CO_2 through its amine ($-NH_2$) moiety:

$$THAM - NH_2 + H^+ = THAM - NH_3^+$$
$$THAM - NH_2 + H_2O + CO_2 = THAM - NH_3^+ + HCO_3$$

Protonated THAM (with Cl^- or HCO_3^-) is excreted in the urine at a rate that is slightly higher than creatinine clearance. As such, THAM augments the buffering capacity of the blood without generating excess CO_2. THAM is less effective in patients with renal failure, and toxicities may include hyperkalemia, hypoglycemia, and possible respiratory depression. THAM is particularly useful in patients with volume overload because it does not contain sodium.

THAM is often administered as an empiric dose of 18 g (150 mEq [mmol]) in 500 mL water via slow intravenous (IV) infusion. Additional infusions are given as dictated by the severity and progression of acidosis. Unfortunately, the only US manufacturer of THAM discontinued its production in 2016 and no future production is anticipated.

LO 6 Chronic metabolic acidosis can successfully be managed using potassium citrate/citric acid (Polycitra-K, Cytra-K) or sodium citrate/citric acid (Bicitra, Oracit).

Metabolic Alkalosis

Metabolic alkalosis is characterized by an increased arterial pH, a primary increase in the HCO_3^- concentration, and a compensatory increase in the $PaCO_2$. Patients will always hypoventilate to compensate for metabolic alkalosis—even if it results in profound hypoxemia. For a metabolic alkalosis to persist there must concurrently be a process that elevates serum HCO_3^- concentration (gastric or renal loss of acids) and another that impairs renal HCO_3^- excretion (hypovolemia, hypokalemia, or mineralocorticoid excess). The etiologies of metabolic alkalosis are listed in Table 28–5.

LO 4 Patients with metabolic alkalosis rarely have symptoms attributable to alkalemia. Rather, complaints are usually related to volume depletion (muscle cramps, positional dizziness, weakness) or to hypokalemia (muscle weakness, polyuria, polydipsia).

LO 5 In order to effectively treat metabolic alkalosis, the *causative process* must be identified and treated. The major causes of metabolic alkalosis are often readily apparent after carefully reviewing the patient's history and medication list. In hospitalized patients, always look for administration of compounds such as citrate in blood products and acetate in parenteral nutrition that can raise the HCO_3^- concentration. If the etiology of the metabolic alkalosis is still unclear, measurement of the urinary chloride may be useful. Some processes leading to metabolic alkalosis (eg, vomiting, nasogastric suction losses, factitious diarrhea) will have low urinary Cl^- concentrations (< 25 mEq/L [mmol/L]) and are likely to respond to administration of saline. Other causes (eg, diuretics, hypokalemia, and mineralocorticoid excess) will have higher urinary Cl^- concentrations (> 40 mEq/L [mmol/L]) and are less likely to correct with saline infusion.

In general, contributing factors such as diuretics, nasogastric suction, and corticosteroids should be discontinued if possible. Any fluid deficits should be treated with IV normal saline. Again, patients with metabolic alkalosis and high urine Cl^- (while relatively

Table 28–5

Common Causes of Metabolic Alkalosis

Urine Cl^- < 10 mEq/L (mmol/L)	Urine Cl^- > 10 mEq/L (mmol/L)
Alkali administration	Drugs[a]
IV bicarbonate therapy	Corticosteroid therapy
Oral alkali therapy	Diuretics
Parenteral nutrition with acetate	Hypokalemia
"Contraction alkalosis" postdiuretic use	Mineralocorticoid excess
Decreased chloride intake	Hyperaldosteronism
Loss of gastric acid	Bartter syndrome
Vomiting	Cushing syndrome
Nasogastric suction	
Posthypercapnia	
Villous adenomas (some)	

[a]May be observed with therapeutic doses or overdoses.

uncommon) are generally resistant to saline loading. Potassium supplementation should always be given if it is also deficient.

LO 6 In patients with mild or moderate alkalosis who require ongoing diuresis but have rising HCO_3^- concentrations, the carbonic anhydrase inhibitor acetazolamide can be used to reduce the HCO_3^- concentration. Acetazolamide is typically dosed at 250 mg every 6 to 12 hours as needed to maintain the pH in a clinically acceptable range. This agent results in gradual changes in the serum HCO_3^- and is not used to acutely correct a patient's acid–base status. If alkalosis is profound and potentially life threatening (due to seizures or ventricular tachyarrhythmias), hemodialysis or transient HCl infusion can be considered. The hydrogen ion deficit (in mEq or mmol) can be estimated from the current bicarbonate concentration ($HCO_{3\ curr}^-$), the desired bicarbonate concentration ($HCO_{3\ post}^-$), and the body weight (in kg) as follows:

$$H^+ \text{ deficit} = 0.4 \times \text{weight} \times (HCO_{3\ curr}^- - HCO_{3\ post}^-)$$

After estimating the H^+ deficit, 0.1 to 0.2 N HCl is infused at 20 to 50 mEq/h (mmol/h) into a central vein. Arterial pH must be monitored at least hourly and the infusion stopped as soon as clinically feasible. Ammonium chloride and arginine hydrochloride, agents that result in the formation of HCl, are not commonly prescribed because they may lead to significant toxicity. Ammonium chloride may cause accumulation of ammonia leading to encephalopathy while arginine hydrochloride can induce life-threatening hyperkalemia through unclear mechanisms.

Respiratory Acidosis

Respiratory acidosis is characterized by a reduced arterial pH, a primary increase in the arterial $PaCO_2$ and, when present for sufficient time, a compensatory rise in the HCO_3^- concentration. Because increased CO_2 is a potent respiratory stimulus, respiratory acidosis represents ventilatory failure or impaired central control of ventilation as opposed to an increase in CO_2 production. As such, most patients will have hypoxemia in addition to hypercapnia. The most common etiologies of respiratory acidosis are listed in Table 28–6.

LO 5 Severe, acute respiratory acidosis produces a variety of neurologic abnormalities. Initially these include headache, blurred vision, restlessness, and anxiety. These may progress to tremors, asterixis, somnolence, and/or delirium. If untreated, terminal manifestations include peripheral vasodilation leading to hypotension and cardiac arrhythmias. Chronic respiratory acidosis is typically associated with cor pulmonale and peripheral edema.

LO 6 In order to effectively treat respiratory acidosis, the *causative process* must be identified and treated. If a cause is identified, specific therapy should be started. This may include naloxone for opiate-induced hypoventilation or bronchodilator therapy for acute bronchospasm. Because respiratory acidosis represents ventilatory failure, an increase in alveolar ventilation is required. This can often be achieved by controlling the underlying disease (eg, bronchodilators and corticosteroids in asthma) and/or physically augmenting ventilation.

LO 6 Although their precise role and mechanisms of action are unclear, agents such as medroxyprogesterone, theophylline, and doxapram stimulate respiration and have been used to treat mild to moderate respiratory acidosis. Of these, only doxapram is approved by the US Food and Drug Administration (FDA) for this indication. Doxapram is administered IV, typically 0.5 to 1 mg/kg repeated every 5 minutes to a maximum dose of 3 g per 24 hours. Patients given doxapram required monitoring of their blood pressure, pulse, and deep tendon reflexes as this drug can cause cardiac excitation and spasticity. Moderate or severe respiratory acidosis requires assisted ventilation. This can be provided to spontaneously breathing patients via bilevel positive airway pressure (BiPAP) delivered via a tight-fitting mask or by intubation followed by mechanical ventilation. In mechanically ventilated patients, respiratory acidosis is treated by increasing the minute ventilation. This is achieved by increasing the respiratory rate and/or tidal volume.

As with the treatment of metabolic acidosis, the role of $NaHCO_3$ therapy is not well defined for respiratory acidosis. Realize that administration of $NaHCO_3$ can paradoxically result in increased CO_2 generation ($HCO_3^- + H^+ \rightarrow H_2O + CO_2$) and worsened acidemia. Careful monitoring of the pH is required if $NaHCO_3$ therapy is started for this indication. The use of tromethamine in respiratory acidosis (see Metabolic Acidosis section earlier) has unproven safety and benefit.

LO 6 The goals of therapy in patients with chronic respiratory acidosis are to maintain oxygenation and to improve alveolar ventilation if possible. Because of the presence of metabolic compensation it is usually not necessary to treat the pH, even in patients with severe hypercapnia. Although the specific treatment varies with the underlying disease, excessive oxygen and sedatives should be avoided because they can worsen CO_2 retention.

Respiratory Alkalosis

Respiratory alkalosis is characterized by an increased arterial pH, a primary decrease in the arterial $PaCO_2$ and, when

Table 28–6

Common Causes of Respiratory Acidosis

- CNS disease
  - Brainstem lesions
  - Central sleep apnea
  - Infection
  - Intracranial hypertension
  - Trauma
  - Tumor
  - Vascular
- Drugs[a]
  - Aminoglycosides
  - Anesthetics
  - β-Blockers
  - Botulism toxin
  - Hypnotics
  - Narcotics
  - Neuromuscular blocking agents
  - Organophosphates
  - Sedatives
- Neuromuscular disease
  - Guillain-Barré syndrome
  - Muscular dystrophy
  - Myasthenia gravis
  - Polymyositis
- Pulmonary disease
  - Lower airway obstruction
  - Foreign body
  - Status asthmaticus
  - Chronic obstructive pulmonary disease
  - Pneumonia
  - Pneumonitis
  - Pulmonary edema
- Restrictive lung disease
  - Ascites
  - Chest wall disorder
  - Fibrothorax
  - Kyphoscoliosis
  - Obesity
  - Pleural effusion
  - Pneumoconiosis
  - Pneumothorax
  - Progressive systemic sclerosis
  - Pulmonary fibrosis
  - Spinal arthritis
- Smoke inhalation
- Upper airway obstruction
  - Foreign body
  - Laryngospasm
  - Obstructive sleep apnea
- Others
  - Abdominal distention
  - Altered metabolic rate
  - Congestive heart failure
  - Hypokalemia
  - Hypothyroidism
  - Inadequate mechanical ventilation

[a]May be observed with therapeutic doses or overdoses.

Table 28–7

Common Causes of Respiratory Alkalosis

CNS disease	Pulmonary disease
Infection	Early restrictive lung disease
Trauma	Infection
Tumor	Pneumothorax
Vascular	Pulmonary edema
Drug or toxin induced[a]	Pulmonary embolism
Catecholamines	Tissue hypoxia
Doxapram	Burn injury
Methylphenidate	Excessive mechanical ventilation
Methylxanthines	Fever
Nicotine	Hepatic failure
Progesterone	Hypoxemia
Salicylates	Pain
Psychiatric disease	Postmetabolic acidosis
Anxiety	Pregnancy
Hyperventilation	Severe anemia
Hysteria	Thyrotoxicosis
Panic disorder	

[a]May be observed with therapeutic doses or overdoses.

present for sufficient time, a compensatory fall in the HCO_3^- concentration. Respiratory alkalosis represents hyperventilation and is remarkably common. The most common etiologies of respiratory alkalosis are listed in Table 28–7 and range from benign (anxiety) to life threatening (pulmonary embolism). Some causes of hyperventilation and respiratory acidosis are remarkably common (hypoxemia or anemia).

LO 5

The symptoms produced by respiratory alkalosis result from increased irritability of the central and peripheral nervous systems. These include light-headedness, altered consciousness, distal extremity paresthesias, circumoral paresthesia, cramps, carpopedal spasms, and syncope. Various supraventricular and ventricular cardiac arrhythmias may occur in extreme cases, particularly in critically ill patients. An additional finding in many patients with severe respiratory alkalosis is hypophosphatemia, reflecting a shift of phosphate from the extracellular space into the cells. Chronic respiratory alkalosis is generally asymptomatic.

LO 6

It is imperative to identify serious causes of respiratory alkalosis and institute effective treatment. In spontaneously breathing patients, respiratory alkalosis is typically only mild or moderate in severity and no specific therapy is indicated. Severe alkalosis generally represents respiratory alkalosis imposed on metabolic alkalosis and may improve with sedation or rebreathing maneuvers (rebreathing mask, paper bag). Patients receiving mechanical ventilation are treated with reduced minute ventilation achieved by decreasing the respiratory rate and/or tidal volume. If the alkalosis persists in the ventilated patient, high-level sedation or paralysis is effective.

SUMMARY

Acid–base disturbances are common clinical problems that are not difficult to analyze if approached in a consistent manner. The pH, $PaCO_2$, and HCO_3^- should be inspected to identify all abnormal values. This should lead to an assessment of which deviations represent the primary abnormality and which represent compensatory changes. The serum electrolytes should always be used to calculate the anion gap. In cases in which the anion gap is increased, the excess anion gap should be added back to the measured HCO_3^-. The anion gap and the excess gap are useful tools that can identify hidden disorders. This rigorous assessment of the patient's acid–base status, incorporated with the available clinical data, increases the likelihood that the clinician will successfully determine the cause of each identified disorder. Although supportive therapy is often required for profound acid–base disturbances, definitive therapy must target the underlying process that has led to the observed derangements.

Patient Care Process

Collect Information:

- Every patient with a suspected acid–base disturbance should have an arterial blood gas and a serum chemistry panel drawn concurrently. The results of these tests should be reviewed using a systematic approach to ensure proper interpretation.

Assess the Information:

- What is the primary disorder? Has compensation occurred?
- Is the anion gap excessively large? If so, does calculation of the excess gap identify another acid–base disorder?

Develop a Care Plan and Implement the Care Plan:

- Continuous cardiovascular and hemodynamic monitoring should be used for significant pH disturbances because the most serious sequelae of acid–base disorders include electrolyte abnormalities, cardiac dysrhythmias, and hypotension.
- All acid–base abnormalities result from underlying disease processes. Definitive therapy for these disturbances requires treatment of the illness that has disrupted the pH equilibrium.
- Review each patient's history, physical examination, and current medication list for clues regarding potential causes of the observed acid–base disorder.

Follow-up: Monitor and Evaluate:

- Serial arterial blood gases and serum chemistries should be compared because every patient's acid–base status is continuously changing based on the underlying disease state and any therapy initiated.

Abbreviations Introduced in This Chapter

ABG	Arterial blood gas
BiPAP	Bilevel positive airway pressure
Cl^-	Chloride ion
CO_2	Carbon dioxide
Δ (delta)	Change
ER	Emergency room
IV	intravenous
H^+	Hydrogen ion
HCl	Hydrochloric acid
HCO_3^-	Bicarbonate
$HCO_{3\ curr}^-$	Current bicarbonate
$HCO_{3\ post}^-$	Posttherapy bicarbonate
Hg	Mercury
K^+	Potassium ion
Na^+	Sodium ion
$NaHCO_3$	Sodium bicarbonate
NH_2	Terminal amine group
NH_4^+	Ammonium

pH	Logarithm of the hydrogen ion concentration
$PaCO_2$	Partial pressure of arterial carbon dioxide
tCO_2	Total venous carbon dioxide
THAM	Tromethamine
UAG	Urine anion gap

REFERENCES

1. Rose BD, Post TW. Clinical Physiology of Acid–Base and Electrolyte Disorders, 5th ed. New York, NY: McGraw-Hill, 2001:299.
2. Schlichtig R, Grogono A, Severinghaus J. Human $PaCO_2$ and standard base excess for compensation of acid–base imbalances. Crit Care Med. 1998;26:1173–1179.
3. Pierce NF, Fedson DS, Brigham KL, Mitra RC, Sack RB, Mondal A. The ventilatory response to acute base deficit in humans. Time course during development and correction of metabolic acidosis. Ann Intern Med. 1970;72:633–640.
4. Javaheri S, Kazemi H. Metabolic alkalosis and hypoventilation in humans. Am Rev Respir Dis. 1987;136:1011–1016.
5. Polak A, Haynie GD, Hays RM, Schwartz WB. Effects of chronic hypercapnia on electrolyte and acid–base equilibrium. J Clin Invest. 1961;40:1223–1237.
6. Gennari FJ, Goldstein MB, Schwartz WB. The nature of the renal adaptation to chronic hypocapnia. J Clin Invest. 1972;51:1722–1730.
7. van Yperselle de Striho C, Brasseur L, de Coninck JD. The "carbon dioxide response curve" for chronic hypercapnia in man. N Engl J Med. 1966;275:117–122.
8. Haber RJ. A practical approach to acid–base disorders. West J Med. 1991;155:146–151.
9. Arbus GS. An *in-vivo* acid–base nomogram for clinical use. Can Med Assoc J. 1973;109:291–293.
10. Narins R. Clinical Disorders of Fluid and Electrolyte Metabolism, 5th ed. New York, NY: McGraw-Hill, 1994:778.
11. Goodkin DA, Gollapudi GK, Narins RG. The role of the anion gap in detecting and managing mixed metabolic acid–base disorders. Clin Endocrinol Metab. 1984;13:333–349.
12. Adrogué HJ, Madias NE. Management of life-threatening acid–base disorders. First of two parts. N Engl J Med. 1998;338:26–34.
13. Adrogué HJ, Madias NE. Management of life-threatening acid–base disorders. Second of two parts. N Engl J Med. 1998;338:107–111.
14. Abelow B. Understanding Acid–Base. Baltimore, MD: Williams & Wilkins, 1998:229.
15. Kearns T, Wolfson A. Metabolic acidosis. Emerg Med Clin North Am. 1989;7:823–835.
16. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med. 1988;318:594–599.
17. Hood FL, Tannen RL. Protection of acid–base balance by pH regulation of acid production. N Engl J Med. 1998;339:819–826.
18. Chernow B, ed. The Pharmacologic Approach to the Critically Ill Patient, 3rd ed. Baltimore, MD: Williams & Wilkins, 1994:965.

29 Alzheimer Disease

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LEARNING OBJECTIVES

LO

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

1. Describe the epidemiology of Alzheimer disease (AD) and its effects on society.
2. Describe the pathophysiology, including genetic and environmental factors that may be associated with AD.
3. Detail the clinical presentation of the typical patient with AD.
4. Describe the clinical course of the disease and typical patient outcomes.
5. Explain how nonpharmacologic therapy is combined with pharmacologic therapy for patients with AD.
6. Recognize and recommend treatment options for disease-specific symptoms as well as behavioral/noncognitive symptoms associated with AD.
7. Educate patients and/or caregivers about the expected outcomes for patients with AD, and provide contact information for support/advocacy agencies.

INTRODUCTION

KEY CONCEPT

Alzheimer disease (AD) is characterized by progressive cognitive decline including memory loss, disorientation, and impaired judgment and learning. Currently, it is diagnosed by exclusion of other potential causes for dementias. There is no single symptom unique to AD; therefore, diagnosis relies on a thorough patient history. The exact pathophysiologic mechanism underlying AD is not entirely known, although certain genetic and environmental factors may be associated with the disease. There is no cure for AD; however, drug treatment can slow symptom progression.

Family members of AD patients can be profoundly affected by the increased dependence of their loved ones as the disease progresses. Advocacy organizations, such as the Alzheimer Association, can provide early education and social support for both the patient and family. The Alzheimer Association has developed a list of common warning signs, which include memory loss, difficulty completing familiar tasks, disorientation, problems with word finding, misplacing things, impaired judgment, social withdrawal, and changes in mood.[1]

EPIDEMIOLOGY AND ETIOLOGY

LO 1

AD is the most common type of dementia, affecting an estimated 5.5 million Americans in 2017.[2] The majority (5.3 million) are 65 years and older. Various classifications of dementia include dementia of the Alzheimer type, vascular dementia, and dementia due to human immunodeficiency virus (HIV) disease, head trauma, Parkinson disease, Huntington disease, Pick disease, or Creutzfeldt-Jakob disease.[3] This chapter addresses only Alzheimer type dementia.

The prevalence of AD increases with age. Of those affected, one in ten are 65 years of age or older, and one in three are 85 years of age or older.[2] It is projected that by 2050, there will be a threefold increase in prevalence due to a population increase in persons older than 65 years.[2] The severity of AD also correlates with increasing age and is classified as mild, moderate, or severe. Other risk factors for AD include family history, female gender, and vascular risk factors such as diabetes, hypertension, heart disease, and current smoking.[4] It is unknown how factors such as environment contribute and interact with the genetic predisposition for AD.

The mean survival time of persons with AD is approximately 4 to 8 years from symptom onset. However, age at diagnosis, severity of AD, and other medical conditions affect survival time.[5] Although AD does not directly cause death, it is associated with an increase in risk factors that often contribute to death, such as senility, sepsis, stroke, pneumonia, dehydration, and decubitus ulcers.

The etiology of AD is unknown; however, genetic factors may contribute to errors in protein synthesis resulting in the formation of abnormal proteins involved in pathogenesis.[6] Early onset (AD prior to age 60) accounts for approximately 1% of all AD. This type is usually familial and follows an autosomal dominant pattern in approximately 50% of cases. Mutations in three genes, presenilin 1 on chromosome 14, amyloid precursor protein (APP) on chromosome 21, and presenilin 2 on chromosome 1, lead to an increase in the accumulation of amyloid beta (Aβ) in the brain, resulting in oxidative stress, neuronal destruction, and the clinical syndrome of AD.[7,8]

In late-onset AD, genetic susceptibility is more sporadic, and it may be more dependent on environmental factors.[6] The apolipoprotein E (apo E) gene on chromosome 19 has been identified as a strong risk factor for late-onset AD. Of the three variants of apo E, carriers of two or more of the apo E4 allele have an earlier onset of AD (~6 years earlier) compared with noncarriers.[6] Only 50% of AD patients have the apo E4 allele, thus indicating it is only a susceptibility marker.

PATHOPHYSIOLOGY

LO 2

KEY CONCEPT Pathologic hallmarks of the disease in the brain include **neurofibrillary tangles** (NFTs) (made up of abnormally phosphorylated tau (τ) protein) and **neuritic plaques** (primarily composed of insoluble forms of Aβ). Accumulation of these toxic forms results in neurodegeneration. In early stages of the disease, neurodegeneration of areas responsible for cholinergic transmission results in a cholinergic deficit. As the disease progresses, widespread neurodegeneration causes imbalance in all neurotransmitter systems. These are primarily located in brain regions involved in learning, memory, and emotional behaviors such as the hippocampus within the medial temporal lobe of the cerebral cortex, basal forebrain, and amygdala.[9]

Tangles

NFTs interfere with neuronal function and their presence has been correlated with the severity of dementia.[10] Unfortunately, NFTs are insoluble even after cell death and they cannot be removed once established, thus prevention is key. The neurons that provide most of the cholinergic innervation to the cortex are prominently affected.[11]

Plaques

The Aβ protein is present in neuritic plaques in a nontoxic, soluble form in human brains. In AD, conformational changes occur that render it insoluble and cause it to deposit into amorphous diffuse plaques associated with dystrophic neuritis.[12] Over time, these deposits become compacted into plaques, and the Aβ protein becomes fibrillary and neurotoxic. Inflammation occurs secondary to clusters of astrocytes and microglia surrounding these plaques.

Acetylcholine

In AD, the plaques and tangles damage **acetylcholine** (Ach) pathways, leading to a shortage of Ach and learning and memory impairment.[13] The basis of current pharmacologic treatment of AD has been to improve cholinergic neurotransmission in the brain. Blocking acetylcholinesterase, the enzyme that degrades Ach in the synaptic cleft, leads to an increased level of Ach with a goal of stabilizing neurotransmission.[13] This process is flawed as cholinergic cell loss appears to be a secondary consequence of AD pathology and not the disease producing event. Cholinergic neurons are only one of the many neuronal pathways affected in AD.

Glutamate

Glutamate is the primary excitatory neurotransmitter in the central nervous system; it is involved in memory, learning, and neuronal plasticity. It affects cognition through facilitation of connections with cholinergic neurons in the cerebral cortex and basal forebrain.[14] In AD, one type of glutamate receptor, *N*-methyl-D-aspartate (NMDA), is less prevalent than normal. There also appears to be overactivation of unregulated glutamate signaling. This results in a rise in calcium ions that induce secondary cascades, which lead to neuronal death and an increased production of APP.[13] The increased production of APP is associated with higher rates of plaque development and hyperphosphorylation of τ protein.[14] Current treatment of AD includes selective inhibition of NMDA receptor-mediated excitotoxicity.

Cholesterol

Increased cholesterol concentrations have also been associated with AD. Cholesterol increases β-amyloid protein synthesis, which can lead to plaque formation.[13] Also, the apo E4 allele is thought to be involved in cholesterol metabolism and is associated with higher cholesterol levels.[13]

Cerebrovascular Pathologies

Cerebrovascular pathologies are common pathologies with age-related cognitive decline along with AD pathologies. Although criteria are still being evaluated to understand the levels of cerebrovascular pathologies that contribute to cognitive impairment, epidemiological studies have found that the presence of vascular and metabolic risk factors during midlife are most strongly associated with risk of cognitive impairment and dementia.[15] Studies have found that antihypertensive treatment can be beneficial in reducing the risk of dementia.[16] Longitudinal studies are needed to study the evolution of cerebrovascular pathologies in those at higher risk of cardiovascular disease starting at midlife.

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT The diagnosis of AD is established following an extensive history and physical examination, and by ruling out other potential causes of dementia. Currently, there are biological

Clinical Presentation and Diagnosis of Alzheimer Disease

General

The diagnosis of AD is primarily made by medical and psychiatric history, neurological examination, formal memory testing, interview of caregivers and family members, and laboratory and imaging data.

Signs and Symptoms

- Cognitive, which occur gradually: memory loss, problems with language, disorientation to time and place, poor or decreased judgment, problems with learning and abstract thinking, misplacing things
- Noncognitive: Changes in mood, behavior, or personality, or loss of initiative
- Functional: Difficulty performing familiar tasks

Tests

- Neuropsychological tests such as the Folstein Mini-Mental State Examination
- MRI or CT to measure changes in brain size and volume in the medial temporal lobe/hippocampus and rule out stroke, brain tumor, or cerebral edema

Laboratory Tests

- Tests to exclude possible causes of dementia: depression screen, vitamin B_{12} and folate levels, thyroid function tests (thyroid-stimulating hormone and free triiodothyronine and thyroxine), complete blood count, and chemistry panel[17]
- Other diagnostic tests to consider for differential diagnosis: erythrocyte sedimentation rate, urinalysis, toxicology, chest x-ray, heavy metal screen, HIV testing, and CSF examination

Table 29–1

***DSM-5* Diagnostic Criteria for Major Neurocognitive Disorders**

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function and
   2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
B. Cognitive deficits interfere with independence in everyday activities
C. Cognitive deficits do not occur exclusively in the contest of delirium
D. Cognitive deficits are not better explained by another mental disorder

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Washington, DC: American Psychiatric Association;2013:602–603, with permission.

markers available to assist in diagnosis, but they are not currently used in routine practice. Further research is needed to improve brain, imagining, cerebrospinal fluid (CSF), and other AD biomarkers for routine clinical diagnostic use. The clinical presentation and diagnosis of AD is based on history, signs and symptoms, and laboratory and/or imaging tests.

LO 3

AD is a progressive disease that, over time, affects multiple areas of cognition. The American Psychiatric Association recently updated the criteria for AD in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*). See Tables 29–1, 29–2, and 29–3 for full criteria.[3]

Table 29–2

***DSM-5* Diagnostic Criteria for Mild Neurocognitive Disorder**

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
   1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function and
   2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing, or in its absence, another quantified clinical assessment
B. Cognitive deficits do not interfere with capacity for independence in everyday activities
C. Cognitive deficits do not occur exclusively in the context of delirium
D. Cognitive deficits are not better explained by another mental disorder

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Washington, DC: American Psychiatric Association;2013;605; with permission.

Table 29–3

***DSM-5* Diagnostic Criteria for Major or Mild Neurocognitive Disorder Due to Alzheimer Disease**

A. Criteria are met for major or mild neurocognitive disorder
B. Insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired)
C. Criteria are met for either probable or possible Alzheimer disease as follows:
   For Major Neurocognitive Disorder:
   Probable Alzheimer disease is diagnosed if either of the following is present; otherwise possible Alzheimer disease should be diagnosed.
   1. Evidence of a causative Alzheimer disease genetic mutation from family history or genetic testing
   2. All three of the following are present:
      a. Clear evidence of decline in memory and learning and at least one other cognitive domain
      b. Steadily progressive gradual decline in cognition, without extended plateaus
      c. No evidence of mixed etiology

   For Mild Neurocognitive Disorder:
   Probable Alzheimer disease: diagnosed if there is evidence of a causative Alzheimer disease genetic mutation from either genetic testing or family history
   Possible Alzheimer disease: diagnosed if there is no evidence of a causative Alzheimer disease genetic mutation from either genetic testing or family history, and all three of the following are present:
   1. Clear evidence of decline in memory and learning
   2. Steadily progressive, gradual decline in cognition, without extended plateaus
   3. No evidence of mixed etiology
D. Disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systematic disorder

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, Washington, DC: American Psychiatric Association;2013;611; with permission.

Patient Encounter Part 1

A man presents at the clinic with his 75-year-old mother complaining that his mother's memory is worsening. He complains that his mother is continuing to forget things, including paying the bills and emptying the cat's litter box. Three months ago, she was started on rivastigmine 4.6 mg/24 hours, which was titrated to 9.5 mg/24 hours. Her son organizes a weekly pillbox and helps administer the medications. The son asks if there is anything else his mother could take to help her memory.

What education points about Alzheimer disease would you provide to the son?

Where would you recommend the son find more information about Alzheimer disease?

How would you address the son's question regarding the pharmacologic management of his mother's Alzheimer disease?

Clinical Course and Typical Patient Outcomes

LO 4

AD has a gradual onset and is slowly progressive, with episodic memory, executive function, visuospatial function, and word-finding difficulties being affected early on. Impairment in motor, behavioral, and sensory functioning occurs later in the illness. During the final stages, patients are not aware of the events occurring around them and are dependent on others.

TREATMENT

Desired Outcomes

KEY CONCEPT Treatment is focused on delaying disease progression and preservation of functioning as long as possible. Secondary goals include treating psychiatric and behavioral symptoms that may occur during the course of the disease.

General Approach to Treatment

KEY CONCEPT The current gold standard of treatment for cognitive symptoms includes pharmacologic management with a cholinesterase (ChE) inhibitor and/or an NMDA antagonist. There are four agents approved for the treatment of AD, but none are curative or known to directly reverse the disease process, donepezil, rivastigmine, galantamine, and memantine. Additionally, psychiatric and behavioral symptoms that occur during the course of the disease should be treated as they occur.

Treatment of AD includes education, communication, and planning with the patient's family/caregiver. Treatment options, legal and financial decisions, and course of the illness should be discussed with the patient and family members. The clinician's emphasis should be on helping to maintain a therapeutic living environment while minimizing the burden of care resulting from the disease.

Nonpharmacologic Therapy

LO 5

The life of a patient with AD must become progressively more simple and structured as the disease progresses, and the caregiver must learn to keep requests and demands on the patient simple. Basic principles in the treatment of patients with AD are shown in Table 29–4.

Pharmacologic Therapy

▶ *Conventional Pharmacologic Treatment for Cognitive Symptoms*

ChE Inhibitors (Donepezil, Rivastigmine, and Galantamine) Guidelines recommend the use of ChE inhibitors as a valuable treatment for AD and the use of memantine for moderate to severe AD.[17] The few head-to-head studies comparing the ChE inhibitors conclude that there are no major differences in clinical outcomes. The selection of one ChE over another should be based on differences in mechanisms of action, adverse reactions, titration schedules, potential drug interactions, and patient and caregiver preference.[18] ChE inhibitors provide only modest benefit which should be communicated to the patient and caregiver.

Table 29–4

Basic Principles in the Management of Patients with AD

- Using a gentle, calm approach to the patient
- Giving reassurance when needed
- Empathizing with the patient's concerns
- Using distraction and redirection
- Maintaining daily routines
- Providing a safe environment
- Providing daytime activities
- Avoiding overstimulation
- Using familiar decorative items in the living area
- Bringing abrupt declines in function and the appearance of new symptoms to professional attention

Table 29–5

Treatment Algorithm for Cognitive Symptoms of AD

1. Patient diagnosed with AD
2. Assess all comorbid medical disorders and drug therapies that may affect cognition
3. Rule out comorbid depression
4. Evaluate for pharmacotherapy based on illness stage
   a. Mild AD: Cholinesterase inhibitor
   b. Moderate to severe AD: Cholinesterase inhibitor, memantine, or combination cholinesterase inhibitor and memantine
3. Deteriorating Mini Mental State Exam (MMSE) score > 2–4 points after 1 year: Change to a different cholinesterase inhibitor
4. Stable MMSE: Continue regimen
5. Treat behavioral/noncognitive symptoms associated with AD as they arise

Treatment should begin as early as possible after diagnosis.[19] Table 29–5 provides a recommended treatment algorithm. Patients should be switched to another ChE inhibitor from their initial ChE inhibitor if they show an initial lack of efficacy, initially respond but then lose clinical benefit, or experience safety/tolerability issues. This switch should not be attempted until the patient has been on a maximally tolerated dose for 3 to 6 months. The switch should also be based on realistic expectations of the patient and/or caregiver.[20] ChE inhibitor should be discontinued in patients who experience poor tolerance or adherence, who do not improve after 6 months at optimal dosing, who fail attempts at monotherapy with at least two agents or combination therapy, who continue to deteriorate at the pretreatment rate, who have dramatic clinical deterioration following initiation of treatment, or who deteriorate to the point where there is no significant effect on quality of life. Patients with an MMSE score less than 10 may also benefit from discontinuation of medication; however, this has not been substantially proven in clinical studies.[21]

LO 6

Donepezil Donepezil is a piperidine ChE inhibitor that reversibly and noncompetitively inhibits centrally active acetylcholinesterase.[22] A dose of 10 mg/day has demonstrated efficacy in patients with either mild to moderate or moderate to severe forms of AD, while the 23-mg dose is also approved for patients with moderate to severe disease. The 23-mg dose showed a small improvement in cognitive symptoms compared to the 10 mg/day dose; however, there was no improvement in overall functioning, and there was a higher incidence of adverse effects.[23] Table 29–6 describes dosing strategies for all of the approved agents for AD. The most frequent adverse effects are mild to moderate gastrointestinal symptoms.[22,24–27] Others include headache, dizziness, syncope, bradycardia, and muscle weakness. Table 29–7 compares their major side effects and monitoring parameters.[1,22,24–29]

Only a small number of drug interactions have been reported with donepezil. Monitoring for increased peripheral side effects is advised when adding a cytochrome P450 (CYP) 2D6 or 3A3/4 inhibitor to donepezil treatment. Also, inducers of CYP2D6 and 3A4 could increase the rate of elimination of donepezil.[22]

Table 29–6

Dosing Strategies for Cognitive Agents

	Donepezil (Aricept)	Rivastigmine (Exelon)	Galantamine (Razadyne)	Memantine (Namenda)[a]
Starting dose	5 mg daily in the evening	1.5 mg twice daily or 4.6 mg/24 hour applied daily (patch)	4 mg twice daily or 8 mg daily in the morning	5 mg daily or 7 mg daily (ER formulation)
Maintenance dose	5–23 mg daily	3–6 mg twice daily or 9.5 mg/24 hour applied daily (patch)	8–12 mg twice daily or 16–24 mg daily	10 mg twice daily or 28 mg daily (ER formulation)
Time between dose adjustments	4–6 weeks between 5 and 10 mg increment; 3 months between 10 and 23 mg increment	2 weeks for oral and 4 weeks for patch	4 weeks	1 week
Dosage adjustments for renal or hepatic impairment	None	Moderate to severe renal impairment, mild to moderate hepatic impairment, or low body weight (< 50 kg): consider maximum dose of 4.6 mg/24 hour	Do not exceed 16 mg for moderately impaired hepatic or renal function; do not administer in severe renal or hepatic impairment	Severe renal impairment: target maintenance dose of 5 mg twice daily or 14 mg daily

[a]Forest Pharmaceuticals, Inc. has discontinued the sale of all configurations of Namenda. They will continue to sell oral solution of Namenda as well as once-daily Namenda XR. Namzaric, a fixed-dose combination of extended-release memantine and donepezil (14/10 mg and 28/10 mg), was recently approved.

Aricept®[package insert]. Teaneck, NJ: Eisai; 2016.

Exelon® [package insert]. East Hanover, NJ: Novartis; 2016.

Razadyne ER/Razadyne® [package insert]. Titusville, NJ: Ortho-McNeil Neurologics; 2015.

Namenda® [package insert]. St. Louis, MO: Forest Pharmaceutica, Inc.; 2016.

Namenda XR® [package insert]. St. Louis, MO: Forest Pharmaceutica, Inc.; 2014.

Namzaric® [package insert]. Cincinnati, OH: Forest Pharmaceuticals, Inc.; 2015.

Table 29–7

Adverse Effects for Currently Approved Medications for Alzheimer Disease[a]

Adverse Event	Donepezil 5–10 mg/day (%) (*n* = 747)	Donepezil 23 mg/day (%) (*n* = 963)	Rivastigmine 6–12 mg/day (%) (*n* = 1189)	Galantamine IR 16–24 mg/day (%) (*n* = 1040)	Memantine IR 5–20 mg/day (%) (*n* = 940)	Memantine XR 28 mg/day (%) (*n* = 341)
Nausea	11	12	47	24	NR	NR
Vomiting	5	9	31	13	3	2
Diarrhea	10	8	19	9	NR	5
Headache	10	4	17	8	6	6
Dizziness	8	5	21	9	7	5
Muscle cramps	6	NR	NR	NR	NR	NR
Insomnia	9	3	9	5	NR	NR
Fatigue	5	2	9	5	2	3
Anorexia	4	5	17	9	NR	NR
Depression	3	NR	6	7	NR	3
Abnormal dreams	3	NR	NR	NR	NR	NR
Weight decrease	3	5	3	7	NR	NR
Abdominal pain	NR	NR	13	5	NR	2
Rhinitis	NR	NR	4	4	NR	NR

[a]Caution is urged in making comparisons between drugs based on these data because different clinical trials often collect adverse event data using different methodologies.

NR, not reported.

Aricept® [package insert]. Teaneck, NJ: Eisai; 2016.

Exelon® [package insert]. East Hanover, NJ: Novartis; 2016.

Razadyne ER/Razadyne® [package insert]. Titusville, NJ: Ortho-McNeil Neurologics; 2015.

Namenda® [package insert]. St. Louis, MO: Forest Pharmaceutica, Inc.; 2016.

Namenda XR® [package insert]. St. Louis, MO: Forest Pharmaceutica, Inc.; 2014.

Namzaric® [package insert]. Cincinnati, OH: Forest Pharmaceuticals, Inc.; 2015.

Rivastigmine Rivastigmine, approved for the treatment of mild to moderate AD, has central activity for both acetylcholinesterase and butyrylcholinesterase, which could potentially lead to broader efficacy.[27]

Rivastigmine is available as an oral formulation and a patch. If the patient is taking less than 6 mg/day orally, the 4.6 mg/24 hour patch is recommended if switching from oral form to the patch. If the patient is taking 6 to 12 mg/day orally, the 9.5 mg/24 hour patch is recommended. The first patch should be applied on the day following the last oral dose.[24]

Cholinergic side effects are common, but they are usually well tolerated if the recommended dosing schedule is followed. If side effects cause intolerance, several doses can be held, and then dosing can be restarted at the same or next lower dose. Drugs that induce or inhibit CYP450 metabolism are not expected to alter rivastigmine metabolism.[24]

Galantamine Galantamine, approved for the treatment of mild to moderate AD, is a ChE inhibitor, which elevates Ach in the cerebral cortex.[27] It also modulates the nicotinic Ach receptors to increase Ach release from surviving presynaptic nerve terminals. Galantamine may also increase glutamate and serotonin levels, but whether this brings additional benefit is unknown.

CYP3A4 and 2D6 are the major metabolizing enzymes, and pharmacokinetic studies with inhibitors of these enzymes have shown increased galantamine concentrations or reductions in clearance. Similar to donepezil, if inhibitors are given concurrently with galantamine, increased cholinergic side effects should be monitored.[27]

NMDA Receptor Antagonist Memantine is a noncompetitive antagonist of the NMDA type of glutamate receptors that are located throughout the brain. NMDA receptors regulate activity throughout the brain by controlling the amount of calcium that enters the nerve cell, a process essential for establishing an environment required for information storage. Overstimulation of the NMDA receptor by excessive glutamate allows too much calcium into the cell, disrupting information processing. Blocking NMDA receptors with memantine may protect neurons from the effects of excessive glutamate without disrupting normal neurotransmission.[22,27]

Memantine is approved to treat moderate to severe AD. It can be given as monotherapy or in combination with ChE inhibitors. Only modest benefit can be anticipated with the utilization of memantine. Memantine is not indicated for mild AD, and current evidence does not support its use in mild AD.[30] Adverse reactions associated with memantine include constipation, confusion, dizziness, headache, coughing, and hypertension. Closer monitoring should be done if memantine is given concurrently with a ChE inhibitor.

In vitro studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, 2A6, 2C9, 2D6, 2E1, and 3A4, and that no pharmacokinetic interactions with drugs metabolized by these enzymes should be expected.[26,27]

Future Therapies KEY CONCEPT Future therapies for AD may include disease-modifying therapies. Current investigations involving the amyloid hypothesis are evaluating various compounds in the secondary prevention of AD. Mechanisms by which these compounds are thought to work include[7]:

- Reducing levels of brain Aβ or manipulating its configuration
- Targeting τ proteins
- Targeting inflammatory approaches
- Addressing insulin resistance in the brain

Recent studies of bapineuzumab and solanezumab, humanized monoclonal antibody targeting the Aβ, failed to demonstrate a significant change in the Alzheimer Disease Assessment Scale (ADAS-cog11) in phase 3 clinical trials.[31,32]

Patient Encounter Part 2

The patient returns to the clinic in 6 months. She has been receiving 9.5 mg/24 hours of rivastigmine. Her memory symptoms have slowed in their decline, but recently she has been agitated at bedtime and talking to her deceased sister. The son is particularly concerned about the symptoms and wants to know what he could do to help. The patient's record is as follows:

PMH: Diabetes mellitus since age 51, it was well controlled until last year when she became confused about when to take her medication; hypertension treated for 23 years and well controlled; has been hypotensive on a few occasions recently during physicals; osteopenia, last bone mineral density test 12 months ago (T-score = –1.2); on therapy; hypercholesterolemia, last cholesterol panel 12 months ago showed well-controlled levels in normal range; on therapy

FH: Father died of myocardial infarction at age 76; mother died of breast cancer at age 79

SH: Lives with wheelchair-bound husband; son lives across street and checks in daily; denies drinking alcohol or smoking

Meds: Metformin 500 mg orally twice daily; insulin glargine 18 units subcutaneously at bedtime; hydrochlorothiazide 25 mg orally once daily in the morning; lisinopril 20 mg orally once daily in the morning; calcium carbonate and vitamin D 600 mg/200 international units orally twice daily with lunch and dinner; atorvastatin 10 mg orally once daily with dinner; rivastigmine 9.5 mg/24 hours

ROS: (+) Weight loss of 6.3 kg (14 lb) since last visit; (–) N/V/D, change in appetite, heartburn, chest pain, or shortness of breath

PE:

VS: BP 111/72 mm Hg supine, P 79 beats/min, RR 16 breaths/min, T 37°C (98.6°F)

Gen: Poorly groomed, thin woman looks stated age

Neuro: Folstein Mini-Mental State Exam score 20/30; disoriented to month, date, and day of week, clinic name and floor; poor registration with impaired attention and short-term memory; good language skills but problems with commands

CT Scan: Mild-to-moderate generalized cerebral atrophy

What do you recommend with regard to her current rivastigmine treatment?

What nonpharmacologic and pharmacologic interventions could be recommended for the agitation and psychosis?

► *Nonconventional Pharmacologic Treatment*

Nonconventional treatments have historically been used as adjunctive treatments of AD. Vitamin E was previously

recommended because of its antioxidant properties, but a meta-analysis suggested that greater than 400 IU/day should be avoided due to an increased all-cause mortality.[33] There is insufficient data supporting efficacy for nonsteroidal anti-inflammatory drugs (NSAIDs); gastritis, GI bleeds, and increased cardiovascular events are associated with their use.[34] Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) should be reserved for those who have other indications for their use.[35] Until Ginkgo biloba has a more standardized manufacturing process and its long-term safety and efficacy are established, it should be recommended with caution.[36] The medical food caprylidene (AC-1202, Axona) is a medium chain triglyceride approved for the dietary management of metabolic processes associated with mild to moderate AD.[37] Reduced neuronal metabolism of glucose has been associated with AD, and ketone bodies can potentially be used as an alternative energy source for AD patients.[37] Caprylidene is converted by the liver into the ketone body β-hydroxybutyrate (BHB). BHB crosses the blood–brain barrier and can be utilized by neurons as a potential energy source to generate adenosine triphosphate (ATP) and increase pools of Ach.[38] Tramiprosate (homotaurine), or Alzhemed, demonstrated early promise in the treatment of AD, but phase III trials were disappointing. Homotaurine is naturally occurring in seaweed and thought to interfere with amyloid plaque formation and subsequent degeneration of neuronal cells. It is available as a dietary supplement Vivimind™ or ActiveMind™ for age-associated memory impairment.[39]

With the growing body of evidence that brain vascular disease plays a role in the progression of dementia, guidelines support monitoring blood pressure, glucose, cholesterol, and homocysteine, and initiation of appropriate interventions.[40] Adherence to the Mediterranean Diet or Dietary Approaches to Stop Hypertension diet may reduce the risk of cognitive impairment or decline.[41] Additionally, physical activity is an important component of vascular brain health and has been shown in some short-term studies to be associated with a reduced risk of cognitive impairment as well.[41]

Treatment of Behavioral Symptoms

LO 6

KEY CONCEPT Treatment of behavioral symptoms should begin with nonpharmacologic treatments but may also include antipsychotic agents and/or antidepressants. Nonpharmacologic recommendations for treatment include[42]:

- Music
- Videotapes of family members
- Audiotapes of the voices of caregivers
- Walking and light exercise
- Sensory stimulation and relaxation

Clinical trials have reported modest benefit in managing behavioral symptoms with ChE inhibitors and memantine, although the long-term benefits have not been demonstrated to date. Antipsychotics are also frequently used for neuropsychiatric symptoms associated with AD. A meta-analysis concluded that only 17% to 18% of dementia patients demonstrated treatment response to atypical antipsychotics.[43] A double-blind, placebo-controlled trial of olanzapine, quetiapine, or risperidone for the treatment of psychosis, aggression, or agitation in patients with AD showed that adverse effects offset the benefits in the efficacy of atypical antipsychotics.[44]

In April 2005, the US Food and Drug Administration (FDA) issued a statement requiring black-box warnings on all antipsychotics stating that elderly people with dementia-related psychosis treated with an antipsychotic are at an increased risk of death compared with those treated with placebo. Fifteen of 17 trials investigating olanzapine, aripiprazole, quetiapine, and risperidone in elderly demented patients with behavioral disorders showed an increase in mortality compared with the placebo-treated groups (1.6–1.7 times increased risk of death). Causes for these deaths were heart-related events (heart failure and sudden death) and infections (mostly pneumonia). Readers are referred to Chapter 37 for additional information on antipsychotics.

Antipsychotics are not approved for the treatment of elderly patients with dementia-related psychosis. Therefore, it is important to individually assess and balance the risk versus benefit of antipsychotic use in this population. Both the American Society of Consultant Pharmacists and the American Psychiatric Association have published statements regarding the use of antipsychotics to treat agitation and psychosis in dementia.[45,46]

Depressive symptoms occur in as many as 50% of patients with AD and can be difficult to differentiate from symptoms of dementia. Symptoms of depression should be documented for several weeks prior to initiating therapy for depression with AD.[7] The selective serotonin reuptake inhibitors are most commonly used based on their side-effect profile and evidence of efficacy.[7] Indications for the use of antidepressants include depression characterized by poor appetite, insomnia, hopelessness, anhedonia, withdrawal, suicidal thoughts, and agitation. A recent trial suggested a lack of benefit of sertraline and mirtazapine compared with placebo and an increased risk of adverse effects.[47] Readers are referred to Chapter 38 for more information on antidepressants.

Other miscellaneous therapies for AD include benzodiazepines for anxiety, agitation, and aggression. However, their routine use is not advised because of the increase in falls.[7] Mood stabilizer anticonvulsants, carbamazepine, valproic acid, or gabapentin may be used as alternatives, but the current evidence is conflicting.[48] Buspirone has shown benefit in treating agitation and aggression in a limited number of patients with minimal adverse effects.[49] In open-label and controlled studies, selegiline decreased anxiety, depression, and agitation.[50] Finally, trazodone has been shown to decrease insomnia, agitation, and dysphoria, and it has been used to treat sundowning in AD patients.

GENOMICS

KEY CONCEPT At this time, there are no specific recommendations regarding the choice of medications or dosing regimens for the current treatments for AD based on genotype or other biomarkers.

Patient Encounter Part 3

The patient returns to the clinic for follow-up 1 year later. Her son states her memory has continued getting worse. Her current MMSE is 16/30. The addition of risperidone 0.5 mg at bedtime helped with her agitation. Her son would like to know if there are any other choices to help treat his mom.

What changes to the patient's current medications would you recommend?

Patient Care Process

Collect Information:

- Assess the type, frequency, and duration of cognitive and noncognitive symptoms.
- Review any available diagnostic data from the medical and psychiatric history including interviews from family, neuropsychologic testing, CT and MRI, and other labs (ie, vitamin deficiencies, thyroid function tests, complete blood counts, and chemistry panel).
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.
- Identify allergies to medications and other substances.

Assess the Information:

- Determine whether the patient has any other disease state (ie, depression) or is taking any medications that could contribute to cognitive changes in the elderly.
- Document current cognitive and noncognitive symptoms present in the patient.
- Assess the current regimen for appropriateness, effectiveness, adverse effects, drug interactions, appropriate dosing, and medication adherence (see Table 29–7).

Develop a Care Plan:

- Select an appropriate ChE inhibitor to avoid drug–drug interactions and adverse effects and in consideration of cost and patient preference (see Tables 29–6 and 29–7).
- Develop a plan to monitor cognitive response to treatment over time.
- Select appropriate medications for behavior symptoms if lifestyle modifications do not achieve goals.

Implement the Care Plan:

- If needed, provide patients and caregivers information about lifestyle modification, and refer them to support when needed.
- Be a resource and give continuous support to the patient and caregivers throughout the long course of the disease.
- Educate patient and caregivers on what to expect from pharmacotherapy.

Follow-up: Monitor and Evaluate:

- Follow up at needed intervals to assess effectiveness and safety of therapy. Review medical history and physical examination findings, lab tests, and results of other diagnostic tests.
- Monitor pharmacotherapy initiation (see Table 29–6), and regularly evaluate the patient for the presence of adverse drug reactions, drug allergies, drug–drug and drug–disease interactions, and adherence.
- If symptoms progress, consider stopping/switching the ChE inhibitor. Switch if there is initial lack of efficacy, loss of clinical benefit, or if poor tolerability develops. Discontinue if there is poor adherence, 6 months with no clinical improvement, or if there is continued deterioration at pretreatment rates.
- Continue to offer support to the patient and caregiver.

OUTCOME EVALUATION

- The success of therapy is measured by the degree to which the care plan decreases the pretreatment rate of cognitive deterioration, preserves the patients' functioning, and treats psychiatric and behavioral symptoms. The primary outcome measure is thus subjective information from the patient and the caregiver, although the MMSE can be a helpful tool. There are no physical examination or laboratory parameters to evaluate the success of therapy.
- Develop a plan to assess the effectiveness of the ChE inhibitor in slowing the deterioration of cognitive functioning after an appropriate interval (every 3–6 months).
- Assess improvement in quality-of-life measures such as ability to function independently and for slowing of memory deterioration (every 3–6 months).
- Evaluate functional performance, mood, and behaviors.
- Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions at appropriate intervals (soon after drug initiation or change and every 3–6 months).

CONCLUSION

AD is a progressive deterioration of cognitive abilities usually with behavioral disturbances and personality changes in the later stages of the disease. In an effort to help prepare patients and their caregivers for the inevitable, the Alzheimer Association has developed 10 quick tips on "Living with Alzheimer disease" and they can also provide many resources for patients and caregivers. Access the association at:

Alzheimer Association
Contact Center: 1-800-272-3900
TDD access: 1.312.335.8882
Website: www.alz.org
E-mail: info@alz.org
National office: 225 N. Michigan Ave., Fl. 17
Chicago, IL 60601–7633

LO 7

Abbreviations Introduced in This Chapter

Ach	Acetylcholine
Aβ	Amyloid beta
AD	Alzheimer disease
apo E	Apolipoprotein E
APP	Amyloid precursor protein
BHB	β-Hydroxybutyrate
ChE	Cholinesterase
CSF	Cerebrospinal fluid
CYP	Cytochrome P450
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
HIV	Human immunodeficiency virus
MMSE	Mini-Mental State Examination
NMDA	*N*-Methyl-D-aspartate
NFTs	Neurofibrillary tangles
NSAID	Nonsteroidal anti-inflammatory drug
τ	Tau protein

REFERENCES

1. 10 Early Signs and Symptoms of Alzheimer's. Alzheimer's Association. Available from: http://www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp. Accessed May 7, 2018.
2. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer Disease in the United States (2010–2050) estimated using the 2010 census. Neurology. 2013;80(19):1778–1783.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013:591–643.
4. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology. 2005;65:545–551.
5. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: a 15-year epidemiological study. Arch Neurol. 2005;62:779–784.
6. Kamboh MI. Molecular genetics of late-onset Alzheimer's disease. Ann Hum Genet. 2004;68:381–404.
7. Haas C. Strategies, development, and pitfalls of therapeutic options for AD. J Alzheimers Dis. 2012;28:241–281.
8. Golanski E, Hulas-Bigoszewskak, Sieruta M, et al. Earlier onset of Alzheimer's disease: risk polymorphisms within PRNP, PRND, CYP46, and APOE genes. J Alzheimers Dis. 2009;17:359–368.
9. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004;430:631–639.
10. Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. American Psychiatric Association Guideline Watch (October 2014): practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Washington, DC: American Psychiatric Press; 2014.
11. Cacabelos R, Fernandez-Novoa L, Lombardi V, Kubota Y, Takeda M. Molecular genetics of Alzheimer's disease and aging. Methods Find Exp Clin Pharmacol. 2005;27:1–573.
12. Yankner BA, Lu T. Amyloid beta-protein toxicity and the pathogenesis of Alzheimer's disease. J Biol Chem. 2009;284:4755–4759.
13. Pietrzik C, Behl C. Concepts for the treatment of Alzheimer's disease: molecular mechanisms and clinical application. Int J Exp Pathol. 2005;86:173–185.
14. Mishizen-Eberz AJ, Rissman RA, Carter TL, Ikonomovic MD, Wolfe BB, Armstrong DM. Biochemical molecular studies of NMDA receptor subunits NR1/2A/2B in hippocampal subregions throughout progression of Alzheimer's disease pathology. Neurobiol Dis. 2004;15:80–92.
15. Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. Alzheimers Dement (Amst). 2017;7:69–87.
16. Iadecola C, Yaffe K, Biller J, et al; American Heart Association Council on Hypertension, Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; Stroke Council. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. Hypertension. 2016;68:e67–e94.
17. Alexopoulos GS, Jeste DV, Chung H, Carpenter D, Ross R, Docherty JP. The expert consensus guideline series. Treatment of dementia and its behavioral disturbances. Introduction: Methods, commentary, and summary. Postgrad Med. 2005; No:6–22.
18. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006:CD005593.
19. Hogan DB, Bailey P, Black S, et al. Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia. CMAJ. 2008;179:1019–1026.
20. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr Med Res Opin. 2003;19(8):707–714.
21. Ehret MJ, Chamberlin KW. Current practices in the treatment of Alzheimer disease: where is the evidence after the phase III trials? Clin Ther. 2015;37:1604–1616.
22. Aricept® [package insert]. Teaneck, NJ: Eisai; 2016.
23. Farlow MR, Salloway S, Tatriot PN, et al. Effectiveness and tolerability of high dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: a 24-week, randomized, double-blind study. Clin Ther. 2010;32:1234–1251.
24. Exelon® [package insert]. East Hanover, NJ: Novartis; 2016.
25. Razadyne ER/Razadyne® [package insert]. Titusville NJ: Ortho-McNeil Neurologics; 2015.
26. Namenda® [package insert]. St. Louis, MO: Forest Pharmaceutica, Inc.; 2016.
27. Namenda XR® [package insert]. St. Louis, MO: Forest Pharmaceutica, Inc.; 2014.
28. Namzaric® [package insert]. Cincinnati, OH: Forest Pharmaceuticals, Inc.; 2015.
29. Sadowsky CH, Galvin JE. Guidelines for the management of cognitive and behavioral problems in dementia. J Am Board Fam Med. 2012;25(3):350–366.
30. Schneider LS, Dogerman KS, Higgins JP, McShane R. Lack of evidence for the efficacy of memantine in mild Alzheimer's disease. Arch Neurol. 2011;68:991–998.
31. Doody RS, Thomas, RG, Farlow M, et al; Alzheimer's Disease Cooperative Study Steering Committee; Solznezumab Study Group. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. NEJM. 2014;370:311–321.
32. Salloway S, Sperling R, Fox NC, et al; Bapineuzumab 301 and 302 Clinical Trial Investigators. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. NEJM. 2014;370:322–333.
33. Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2005;142:37–46.
34. Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen versus placebo on Alzheimer's disease progression. JAMA. 2003;289:2819–2826.
35. Cooper JL. Dietary lipids in the etiology of Alzheimer's disease. Drugs Aging. 2003;20:399–418.
36. Dekosky ST, Williamson JD, Fitzpatrick AL, et al; Ginkgo Evaluation of Memory (GEM) Study Investigators. Ginkgo biloba for prevention of dementia: a randomized controlled trial. JAMA. 2008;300:2253–2262.
37. Shan RC. Medical foods for Alzheimer's disease. Drugs Aging. 2011;28:421–428.
38. Axona® [product information]. Bloomfield, CO: Accera, 2012.
39. Herrman N, Chau SA, Kircanski I, Lanctot KL. Current and emerging drug treatment options for Alzheimer's disease: a systematic review. Drugs 2011;71:2031–2065.
40. Gorelick PB, Scuteri A, Black SE, et al; American Heart Association Stroke Council; Council on Epidemiology and Prevention; Council on Cardiovascular Nursing; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:2672–2713.
41. de Bruijn RFAG, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. BMC Med. 014;12:130.
42. Cummings J. Drug therapy: Alzheimer's disease. N Engl J Med. 2004;351:56–67.

43. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia. Meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006;14:191–210.
44. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med. 2006;355:1525–1538.
45. The American Psychiatric Association Practice Guidelines on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia. Available from: http://ajp.psychiatryonline.org/doi/pdf/10.1176/appi.ajp.2015.173501. Accessed July 14, 2018.
46. The Use of Antipsychotic Medications in Nursing Home Residents-Questions and Answers. Available from: http://www.nyshfa.org/files/2013/06/ASCP-QnA-AntipsychoticsFinal.pdf. Accessed July 14, 2018.
47. Banerjee S, Hellier J, Dewey M, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomized, multicentre, double-blind, placebo-controlled trial. Lancet. 2011;378:403–411.
48. Passmore MJ, Gardner DM, Polak Y, Rabheru K. Alternatives to atypical antipsychotics for the management of dementia-related agitation. Drugs Aging. 2008;25:381–398.
49. Sakuye KM, Camp CJ, Ford PA. Effects of buspirone on agitation associated with dementia. Am J Geriatr Psychol. 1993;1:82–84.
50. Tariot PN, Cohen RM, Sunderland T, et al. L-deprenyl in Alzheimer's disease. Arch Gen Psychol. 1987;44:427–433.

30 Multiple Sclerosis

Melody Ryan

LEARNING OBJECTIVES

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

1. Identify risk factors for multiple sclerosis (MS).
2. Distinguish between forms of MS based on patient presentation and disease course.
3. Compare and contrast MS disease-modifying treatment choices for a given patient.
4. Determine appropriate symptomatic treatment choices for a given patient.
5. Develop a monitoring plan for a patient placed on specific medications.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS). *Multiple* describes the number of CNS lesions, and *sclerosis* refers to the demyelinated lesions, today called plaques.

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

LO 1

Approximately 2.3 million people worldwide have MS.[1] Diagnosis usually occurs between 20 and 50 years, affecting at least twice as many women as men.[1] Whites and people of northern European heritage are more likely to develop MS.[1] Risk factors include family history of MS, autoimmune diseases, or migraine; personal history of autoimmune diseases or migraine; and cigarette smoke exposure.

Etiology

The cause of MS is unknown, but may be genetic, environmental, or both. Genetic risks may explain up to 35% of cases.[2] Environmental theories involve infectious agents or decreased patient or maternal vitamin D serum concentrations or other infectious exposures.[2,3]

PATHOPHYSIOLOGY

While the causative agent of MS is unclear, the result is the development of an autoimmune disorder with areas of CNS inflammation and degeneration.

Inflammation

An unknown antigen presented by the major histocompatibility complex (MHC) class II molecules causes T-cells to become autoreactive (Figure 30–1). Autoreactive T-cells enter lymphatic tissues to expand. Upon a signal involving sphingosine-1-phosphate, T-cells reenter the circulation.[4] Once activated, T-cells cause blood–brain barrier breakdown and enter the CNS. These T-cells come into contact with antigen-presenting cells (APCs) and proliferate and differentiate. Th1 cells secrete cytokines that enhance macrophage and microglial cells that attack myelin.[4]

B-cells cross damaged sections of the blood–brain barrier where autoreactive T-cells trigger B-cells to form myelin autoantibodies. These inflammatory processes probably cause relapses.[4]

Degeneration

Axonal injury and transection disrupts nerve signals. Growing evidence suggests cytotoxic T-cells cause axonal injury early in disease.[4] Axonal loss is likely responsible for MS progression.[4]

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis

LO 2

Clinically isolated syndrome (CIS) is a focal demyelinating event in the CNS, often optic neuritis or myelopathy, in a patient not known to have MS.[7] CIS has approximately 60% rate of conversion to clinically definite MS over 4 years.[8] This definite diagnosis is made when dissemination in time and space is demonstrated. KEY CONCEPT The McDonald criteria are used to show dissemination in time by more than one clinical attack and dissemination in space by an attack at a different body site.[9] Evidence from magnetic resonance imaging (MRI) and/or **oligoclonal immunoglobulin G bands** can help fulfill these time and space criteria and facilitate earlier diagnosis and treatment (Figure 30–2).[9] KEY CONCEPT MS is classified into relapsing and progressive disease (Figure 30–3). Progressive MS diagnosis is more difficult because there are often no clinical attacks. Diagnosis requires 1 year of disease progression and two of the following: dissemination in space on MRI of the brain, dissemination in space on MRI of the spinal cord, and positive cerebrospinal fluid (CSF) (oligoclonal immunoglobulin G bands or elevated immunoglobulin G index).[9] MS is the most common cause of young adult disability (impaired walking, fine motor movements, sight, cognitive dysfunction, mood disorders, pain) and reduces life expectancy by 10 to 12 years.[10]

TREATMENT

Desired Outcomes and General Approach to Treatment

The goal of treatment is preventing permanent neurologic damage. There are three approaches to treatment. KEY CONCEPT First, treat acute relapses with corticosteroids to speed recovery.

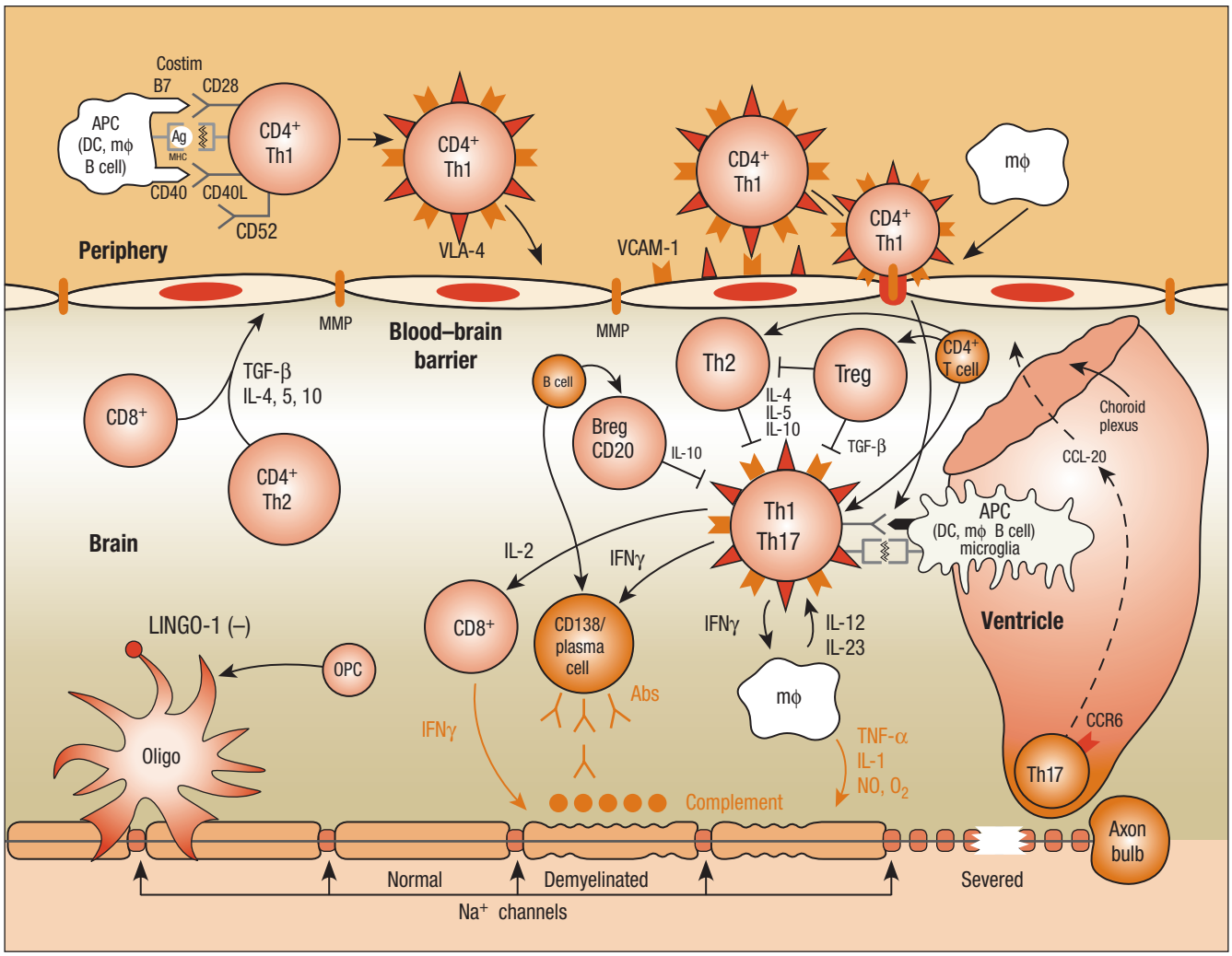


FIGURE 30–1. Autoimmune theory of the pathogenesis of multiple sclerosis (MS). In MS, the immunogenic cells tend to be more myelin-reactive, and these T-cells produce cytokines mimicking a Th1-mediated proinflammatory reaction. T-helper cells ($CD4^+$) appear to be key initiators of myelin destruction in MS. These autoreactive $CD4^+$ cells, especially of the T-helper cell type 1 (Th1) subtype, are activated in the periphery, perhaps following a viral infection. The activation of T- and B-cells requires two signals. The first signal is the interaction between MHC and APC (macrophage, dendritic cell, and B-cell). The second signal consists of the binding between B7 on the APC and CD28 on the T-cell for T-cell activation. Similarly, CD40 expressed on APCs and CD40L expressed on T-cells interact to signal the proliferation of B-cells within the blood–brain barrier following the entry to T-cells. The T-cells in the periphery express adhesion molecules on their surfaces that allow them to attach and roll along the endothelial cells that constitute the blood–brain barrier. The activated T-cells also produce MMP that help to create openings in the blood–brain barrier, allowing entry of the activated T-cells past the blood–brain barrier and into the CNS. Once inside the CNS, the T-cells produce proinflammatory cytokines, especially interleukins (ILs) 1, 2, 12, 17, and 23, tumor necrosis factor-α (TNF-α), and interferon-γ (INF-γ), which further create openings in the blood–brain barrier, allowing entry of B-cells, complement, macrophages, and antibodies. The T-cells also interact within the CNS with the resident microglia, astrocytes, and macrophages, further enhancing production of proinflammatory cytokines and other potential mediators of CNS damage, including reactive oxygen intermediates and nitric oxide. The role of modulating, or downregulating, cytokines such as IL-4, IL-5, IL-10, and transforming growth factor-β (TGF-β) also has been described. These cytokines are the products of $CD4^+$, $CD8^+$, and Th1-cells. New pathogenic mechanisms involve, but are not limited to, receptor-ligand mediated T-cell entry via choroid plexus (CCR6-CCL20 axis), coupling of key receptor-ligands for inhibition of myelination/demyelination (LINGO-1/NOGO66/p75 or TROY complex, Jagged-Notch signaling). (Ag, antigens; APC, antigen presenting cell; DC, dendrite cell; IgG, immunoglobulin G; MΦ, macrophage; Na^+, sodium ion; MMP, matrix metalloproteinases; MHC, major histocompatibility complex; OPC, oligodendrocyte precursor cell; VLA, very late antigen; VCAM, vascular cell adhesion molecule.) (From Bainbridge JL, Miravalle A, Wong PS. Multiple sclerosis. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017, with permission.)

Clinical Presentation of MS[5,6]

MS symptoms depend on the location of lesions within the CNS and thus can be nonspecific. Myelin increases the speed of nerve impulse transmission; demyelination slows the speed. No impulses can be transmitted if the axon is transected. The primary symptoms of MS are caused by this delay or cessation of impulses. The secondary symptoms of MS result from the primary symptoms.

Primary Symptoms	Frequency of Occurrence (%)	Related Secondary Symptoms
Urinary symptoms	70	
Incontinence		Decubitus ulcers
Urinary retention		Urinary tract infections
Spasticity	70–80	Falls, care difficulties, pain, gait problems
Visual symptoms		
Optic neuritis	70	Falls, care difficulties
Bowel symptoms	39–73	
Incontinence		Decubitus ulcers
Constipation		Pain
Depression	50	Suicide
Anxiety	36	
Cognitive deficits	43–70	Decline in work or social performance, care difficulties
Fatigue	92	Effects on employment and social roles
Uhthoff phenomenon	80	
Sexual dysfunction		
Erectile dysfunction	50–90	
Female sexual dysfunction	40–85	
Tremor	80	Inability to perform activities of daily living
Pain	86	
Trigeminal neuralgia		
Lhermitte sign		
Dysesthetic pain	14–29	
Impaired gait	64	

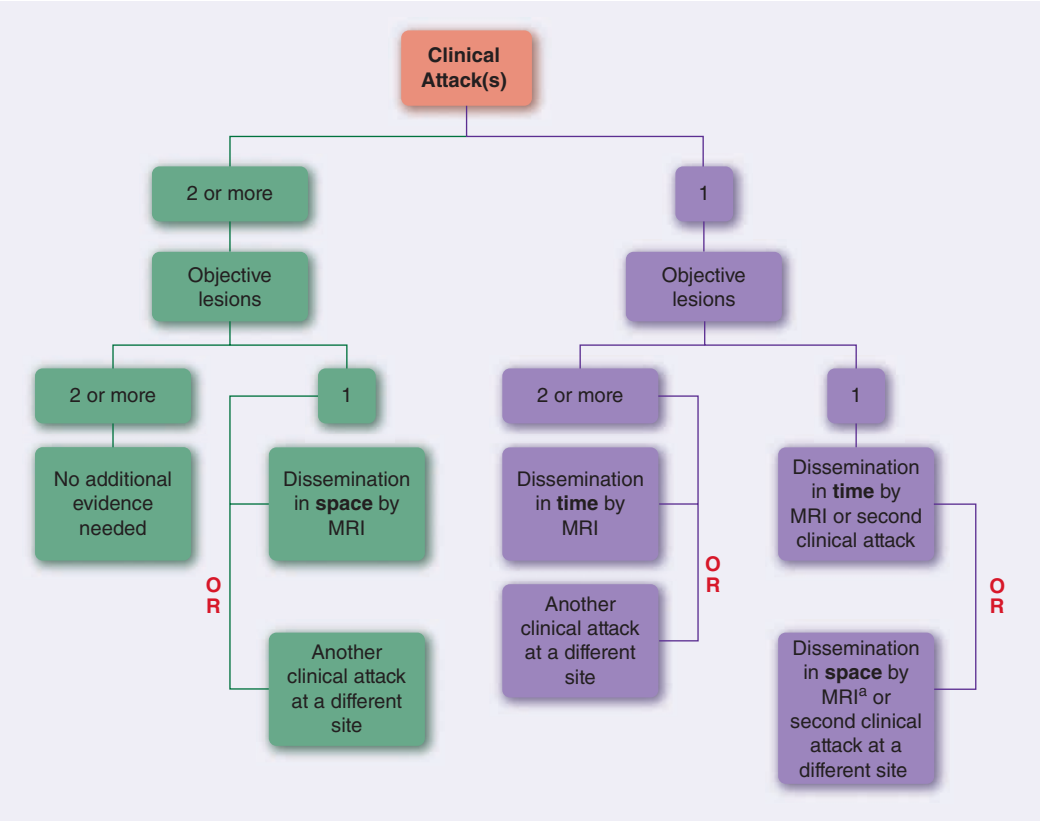


FIGURE 30–2. McDonald diagnostic criteria for MS.[9] An attack is defined as a patient-reported or objectively observed event typical of an acute inflammatory demyelinating event in the CNS with a duration of at least 24 hours in the absence of fever or infection. MRI evidence of dissemination over time is a new T2-weighted lesion after the initial clinical event or the simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time. [a]Dissemination in space by MRI evidence of one or more T2-weighted lesions in at least two of the following areas: periventricular, juxtacortical, infratentorial, spinal cord.

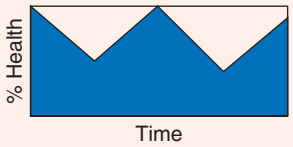
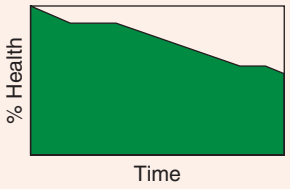
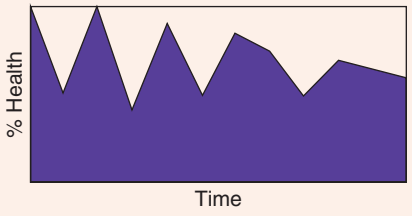
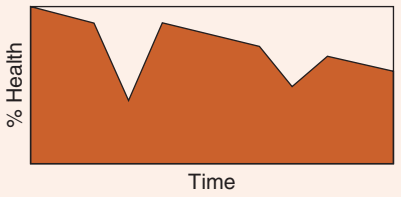
MS Type	Definition	Patients Affected	Example
Relapsing remitting	Episodes of acute worsening of neurologic function (relapses) followed by a varying degree of recovery, with a stable course between attacks (remissions)	85%	
Primary progressive	Gradual, nearly continuous, worsening with minor fluctuations but no distinct relapses	10%	
Secondary progressive	Initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus	50% of relapsing remitting patients within 10 years of diagnosis	
Progressive relapsing	Progressive disease from onset, with clear acute relapses, with or without recovery, with periods between relapses characterized by continuing progression	5%	

FIGURE 30–3. Clinical patterns of MS.

KEY CONCEPT Second, disease-modifying therapies decrease the number of relapses, prevent permanent neurologic damage, and prevent disability. KEY CONCEPT Third, symptomatic treatments improve quality of life by minimizing problematic symptoms.

Pharmacologic Treatment

▶ *Treatment of Acute Relapses with Corticosteroids*

Pharmacology and Mechanism of Action Corticosteroids prevent inflammatory cytokine activation, inhibit T- and B-cell activation, and prevent immune cells from entering the CNS.[11] Corticosteroids hasten functional recovery.[11] Equivalence of IV and oral dosage forms has been demonstrated.[12]

Adverse Effects The most common adverse effects are taste change, flushing, gastrointestinal upset, insomnia, and mood disturbance.[13]

Dosing and Administration Methylprednisolone is given 1000 mg/day IV or orally as one dose for 3 days.[12] Oral prednisone 1250 mg/day provides an equivalent dose. Recovery is equivalent with or without a subsequent oral corticosteroid taper.[14]

▶ *Outcome Evaluation*

- Monitor for symptom improvement
- Educate regarding adverse effects

Disease-Modifying Therapies

LO 3

Agents indicated for MS are shown in Table 30–1. These immunomodulators reduce annualized relapse rates (ARRs) 30% to 70%.[15–30] Almost all agents are indicated for relapsing forms of MS and many may be used for CIS. Ocrelizumab is the first agent approved for primary progressive MS. KEY CONCEPT There is no consensus on the best medication for initial therapy. Figure 30–4 suggests a treatment approach. Agents below are ordered according to place in therapy.

▶ *β-Interferons*

Pharmacology and Mechanism of Action β-Interferons decrease T-cell activation, thereby decreasing cytokine secretion;

Patient Encounter Part 1

A 33-year-old white woman visits the emergency department today with complaints of decreased sensation on the right side of her body that developed over several hours. She reports over the last 2 to 3 years she has had periodic changes in her visual acuity that resolve spontaneously over weeks. She has also noticed heat intolerance that seems to lead to stumbling when she walks and a few falls.

What information is suggestive of multiple sclerosis (MS)?

What risk factors does she have for MS?

What additional information or testing would assist in making the diagnosis of MS?

What treatment could be provided to her for the current acute event?

Table 30–1

Disease-Modifying Therapies

Drug	Dose	Route	Frequency	Selected Adverse Effects	Black Box Warnings
Interferon β-1a (Avonex)	Initial 7.5 mcg for 1 week, then 15 mcg for 1 week, then 22.5 mg for 1 week, then 30 mcg	IM	Weekly	Flu-like symptoms 61% Anemia 8% Neutralizing antibody formation 2%–18.9%	None
Interferon β-1a (Rebif)	22 mcg or 44 mcg Initial 20% increase over 4 weeks to final dose	SQ	Three times/week	Flu-like symptoms 28% Injection site reactions 66% Leukopenia 22% Increased AST/ALT 17%–27% Neutralizing antibody formation 16.5%–35.4%	None
Interferon β-1b (Betaseron, Extavia)	Initial 0.0625 mg, increase over 6 weeks to 0.25 mg	SQ	Every other day	Flu-like symptoms 60%–76% Injection site reactions 50%–85% Asthenia 49% Menstrual disorder 17% Leukopenia 10%–16% Increased AST/ALT 4%–19% Neutralizing antibody formation 27.3–53.3%	None
Peginterferon β-1a (Plegridy)	Initial 63 mcg, 94 mcg day 15, 125 mcg day 29	SQ	Every 2 weeks	Injection site reactions 62% Flu-like symptoms 47% Neutralizing antibody formation < 1%	None
Glatiramer acetate (Copaxone, Glatopa)	20 mg 40 mg (Copaxone only)	SQ SQ	Daily Three times/week	Injection site reaction 90% Systemic reaction 15% Alopecia 61% Menstrual disorders 61% Urinary tract infection 32% Leukopenia 19% GGT increase 15% Injection site atrophy 2%	None
Teriflunomide (Aubagio)	7 or 14 mg	By mouth	Daily	Increased AST 12%–14% Alopecia 10%–13% Diarrhea 15%–18% Decreased white blood cell and platelet counts 10%–15%	Hepatotoxicity Teratogenicity
Dimethyl fumarate (Tecfidera)	Initial 120 mg for 1 week, then 240 mg	By mouth	Twice daily	Flushing 30% Gastrointestinal effects 25% Leucopenia/lymphopenia 4%–10% Influenza viral infections 13% Diarrhea 12% Cough 10% Bradycardia 4%	None
Fingolimod (Gilenya)	0.5 mg	By mouth	Daily	ALT/GGT/AST elevations 15% Hypertension 8% Lymphopenia 7%	None
Natalizumab (Tysabri)	300 mg	IV	Every 4 weeks	Headache 38% Fatigue 27% Arthralgia 19% Urinary tract infection 20%	Progressive multifocal leukoencephalopathy

(*Continued*)

Table 30–1

Disease-Modifying Therapies (*Continued*)

Drug	Dose	Route	Frequency	Selected Adverse Effects	Black Box Warnings
Ocrelizumab (Ocrevus)	Course 1: 300 mg Other courses: 600 mg	IV	Course 1: once, then once 2 weeks later Other courses: every 6 months	Infection 58%–70% Infusion reactions 34%–40%	None
Alemtuzumab (Lemtrada)	Course 1: 12 mg/day Course 2: 12 mg/day	IV	Course 1: Daily for 5 days Course 2: Daily for 3 days 12 months after course 1	Infusion reaction 92% Infections 71% Thyroid disorders 34% Diarrhea 12% Blood in urine 8% Dyspnea 8%	Autoimmunity Infusion reactions Malignancies
Mitoxantrone (Novantrone)	12 mg/m^2 up to 140 mg/m^2 (maximum lifetime dose)	IV	Infuse over 30 minutes every 3 months	Nausea 76% Arrhythmia 3%–18% Cardiotoxicity 2.7% Alopecia 61% Menstrual disorders 61% Urinary tract infection 32% Leukopenia 19% Increased GGT 15%	Bone marrow suppression Cardiotoxicity Secondary acute myelogenous leukemia

Rommer PS, Zettl UK, Kieseier B, et al. Requirements for safety monitoring of approved multiple sclerosis therapies: an overview. Clin Exper Immunol. 2013;175:397–407.

Galetta SL, Markowitz C. U.S. FDA-approved disease-modifying treatments for multiple sclerosis: review of adverse effect profiles. CNS Drugs. 2005;29:239–252.

Calabresi PA, Kieseier BC, Arnold DL, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. Lancet Neurol. 2014;13:657–665.

Govindappa K, Sathish J, Park K, Kirkham J, Pirmohamed M. Development of interferon beta-neurtralising antibodies in multiple sclerosis-a systematic review and meta-analysis. Eur J Clin Pharmacol. 2015;72:1287–1298.

Subei AM, Ontaneda D. Risk mitigation strategies for adverse reactions associated with the disease modifying drugs in multiple sclerosis. CNS Drugs 2015;29:759–771.

prevent upregulation of adhesion molecules on activated T-cells, limiting T-cells access to the CNS; suppress matrix metalloproteinases (MMPs), maintaining the integrity of the blood–brain barrier; decrease microglial proliferation, preserving myelin; promote formation of Th2 cells rather than Th1 cells, decreasing inflammation; and increase neural growth factor production, assisting in repair of the CNS.[15,34]

Efficacy in Patients with Relapsing Remitting MS (RRMS) β-Interferons reduce relapses by about one-third versus placebo.[15] CIS treatment resulted in fewer patients developing clinically definite MS compared with placebo.[15]

Efficacy in Patients with Secondary Progressive MS Who Experience Relapses β-Interferons reduce the risk of relapses, but do not slow progression.[16] Treatment is most effective if clinical relapses or MRI inflammatory activity are present.[16]

Adverse Effects Adverse effects are common with β-interferons (Tables 30–1). Flu-like symptoms (fever, fatigue, muscle aches, malaise, and chills) begin a few hours postinjection and dissipate within 24 hours.[17] Injection site reactions range from redness to necrosis. There are preventive and treatment measures for these reactions (Table 30–2). Because of conflicting data, it is difficult to determine if β-interferons cause depression; however, providers should monitor and assess for depression because patients with MS do commonly develop depression during the course of the disease.[33] Antibodies to β-interferons can reduce effect.[15] **Neutralizing antibodies** develop 6 to 18 months after initiation, can form against any β-interferon, and are cross-reactive (Table 30–3).[15,34] There are no standardized recommendations for neutralizing antibody testing.[15]

▶ *Glatiramer Acetate*

Pharmacology and Mechanism of Action Glatiramer acetate binds to MHC class II, blocking the activation of T-cells, and activates Th2 cells, preventing inflammation. Activated Th2 cells secrete brain-derived neurotrophic factor, which may be neuroprotective.[19]

Efficacy Glatiramer acetate reduces relapses by 28% compared with placebo, but does not prevent sustained progression of RRMS.[20] It is used in CIS to prevent conversion to clinically definite MS.[19]

Adverse Effects Patients report injection site reactions (see Table 30–2). Icing the injection site preinjection and postinjection and/or topical anesthetics improve these reactions. A postinjection reaction may yield a systemic effect (flushing, chest tightness, palpitations, anxiety, and shortness of breath). If this occurs, it is self-limited to 15 minutes, close in time to the injection and recurrence is infrequent. Doses may be reduced by

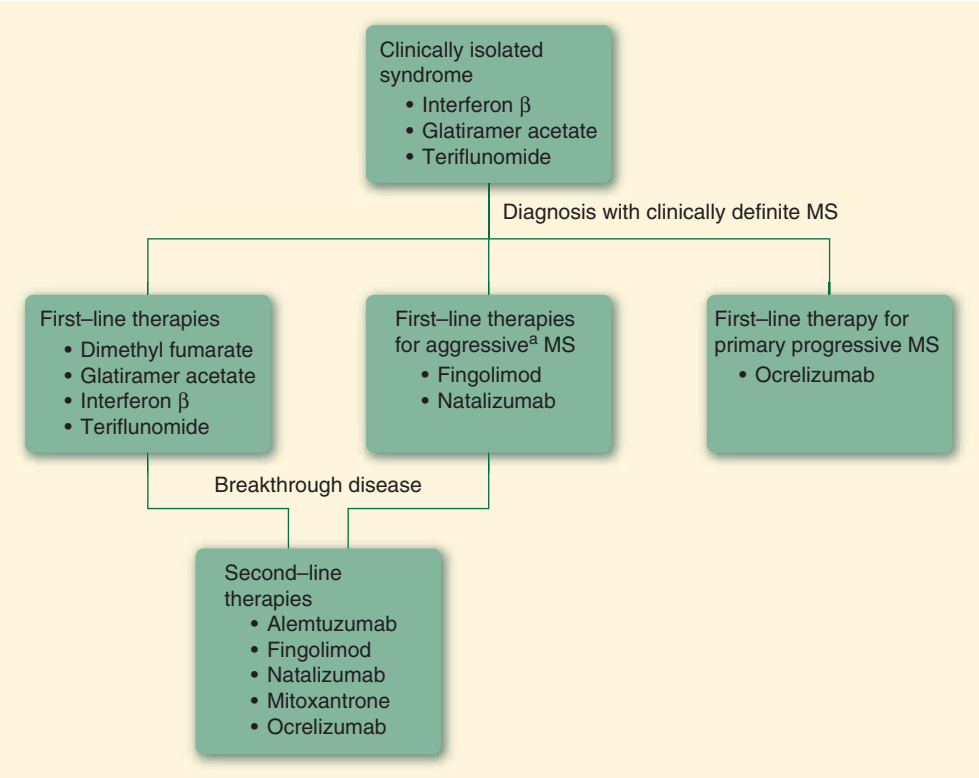


FIGURE 30–4. Treatment algorithm for CIS and MS.[31] [a]A definition of aggressive multiple sclerosis has been proposed as follows: two or more relapses in the preceding year and two or more gadolinium-enhancing lesions on brain MRI scans or a significant T2 lesion burden.[32]

75% for the week following the reaction, then increased by 25% per week to the full dose.[17]

▶ *Teriflunomide*

Pharmacology and Mechanism of Action Teriflunomide has a cytostatic effect on rapidly dividing B- and T-cells by inhibiting *de novo* pyrimidine synthesis and it inhibits T-cell activation, entry to the CNS, and secretion of proinflammatory cytokines.[21]

Pharmacokinetics Half-life of teriflunomide is 2 weeks, taking 3 months to achieve steady-state concentrations. Teriflunomide inhibits CYP2C8 and induces CYP1A2 and CYP2C9.

Table 30–2

β-Interferon Adverse Effects Prevention or Treatment Strategies

Flu-Like Symptoms	Injection Site Reaction
Inject dose in the evening Begin at ¼ dose for 2 weeks of treatment, then increase by 25% every 2 weeks to full dose Use ibuprofen 200 mg or acetaminophen 325–650 mg before and 6 and 12 hours after injection	Bring medication to room temperature Ice injection site before and after injection Rotate injection sites Inject in buttocks or abdomen Use an autoinjection device If severe, use hydrocortisone 1% cream If necrotic: temporarily discontinue; consult dermatologist; do not use topical corticosteroids

Efficacy Teriflunomide reduces relapse rate and progression of disease for relapsing forms of MS.[21] It also prevents CIS from converting to clinically definite MS.[22]

Adverse Effects Teriflunomide is generally well tolerated. Rare, but serious, adverse effects include hepatotoxicity, skin reactions, peripheral neuropathy, infections, and teratogenicity.[21]

▶ *Dimethyl Fumarate*

Pharmacology and Mechanism of Action Dimethyl fumarate shifts cytokine production from a proinflammatory state to an anti-inflammatory state, prevents macrophage entry into the CNS by an unknown mechanism, and stabilizes transcription factor nuclear (erythroid-derived 2) related factor which may reduce oxidative stress.[23]

Efficacy Dimethyl fumarate reduced relapses approximately 50% compared to placebo. It slowed RRMS progression in some studies.[23]

Adverse Effects Dimethyl fumarate causes a transient, dose-dependent flushing sometimes with itching that is likely due to histamine release. The incidence of this reaction decreases after the first month and may be improved by slower dose titration, administration with food, and/or H2-blocking antihistamines.[23] Gastrointestinal adverse effects may be lessened with a slow dose increase and administration with food.[23]

▶ *Fingolimod*

Pharmacology and Mechanism of Action Fingolimod is a sphingosine 1-phosphate receptor modulator. It retains T-cells in lymphoid tissues, depleting peripheral blood and CNS lymphocytes. Fingolimod binds to brain sphingosine 1-phosphate receptors, reducing inflammatory cytokines.[24]

Table 30–3

Monitoring Disease-Modifying Therapies

Therapy	Tests	Frequency
All Therapies	EDSS, MSFC, neurologic examination	Baseline, every 3 months for 2 years; then every 6 months
β-Interferons	CBC with differential, bilirubin, electrolytes, AST, ALT, GGT, alkaline phosphatase, depression/suicidal ideation	Baseline, 1, 3, and 6 months; then every 3 months
	Thyroid function tests	Baseline and every 6 months in patients with a history of thyroid dysfunction
Teriflunomide	CBC, screen for tuberculosis, pregnancy testing	Baseline
	ALT, AST, bilirubin	Baseline and monthly for first 6 months
	Blood pressure	Baseline; then periodically
Dimethyl fumarate	CBC, ALT, AST, alkaline phosphatase, bilirubin	Baseline and every 6 months
Fingolimod	Varicella zoster immunity evaluation and/or vaccination and FEV_1, pregnancy test	Baseline
	CBC, ALT, AST, bilirubin	Baseline and every 6 months
	Pulse and blood pressure	Baseline; observe in clinical area for 6 hours after initial dose with hourly monitoring
	Ophthalmology evaluation	Baseline; 3–4 months; then as needed
	Dermatologic evaluation	Baseline; then as needed
	Electrocardiogram	Baseline and 6 hours after initial dose
Natalizumab	HIV, CBC, AST, ALT, MRI	Baseline; repeat MRI at 6 months; then yearly
	MRI, CSF JC virus	Periodically and at onset of new neurologic symptoms
	Anti-JC virus antibody index	Baseline and every 6 months
Ocrelizumab	Hepatitis B screening	Baseline
	Infection assessment	Prior to every infusion
Alemtuzumab	Thyroid function	Baseline, every 3 months until 48 months after last infusion
	CBC with differential, serum creatinine, urinalysis with cell counts	Baseline, monthly until 48 months after last infusion
	Varicella zoster immunity evaluation and/or vaccination, tuberculosis screening, hepatitis B and C screening	Baseline
	Vital signs	Baseline, during, and 2 hours after infusion
	Skin examination	Baseline and yearly
Mitoxantrone	CBC, bilirubin, AST, ALT, alkaline phosphatase, pregnancy test	Before each infusion
	Echocardiogram/MUGA scan	Baseline; prior to each infusion, and yearly after stopping mitoxantrone

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; FEV_1, forced expiratory volume during one second; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; JC, John Cunningham; MRI, magnetic resonance imaging scan; MSFC, multiple sclerosis functional composite; MUGA, multigated acquisition scan.

Rudick RA, Goelz SE. Beta-interferon for multiple sclerosis. Exp Cell Res. 2011;317:1301–1311.

Rommer PS, Zettl UK, Kieseier B, et al. Requirements for safety monitoring of approved multiple sclerosis therapies: an overview. Clin Exper Immunol. 2013;175:397–407.

Scott LJ. Glatiramer acetate: a review of its use in patients with relapsing-remitting multiple sclerosis and in delaying the onset of clinically definite multiple sclerosis. CNS Drugs. 2013;27:971–988.

LaMantia L, Munari LM, Lovati R. Glatiramer acetate for multiple sclerosis. Cochrane Database Syst Rev. 2010;5: CD004678. DOI: 10.1002/14651858.CD004678.pub2.

Brunetti L, Wagner ML, Maroney M, Ryan M. Teriflunomide for the treatment of relapsing multiple sclerosis: a review of clinical data. Ann Pharmacother. 2013;47:1153–1160.

Linker RA, Gold R. Dimethyl fumarate for treatment of multiple sclerosis: mechanism of action, effectiveness, and side effects. Curr Neurol Neurosci Rep. 2013;13:394.

Willis MA, Cohen JA. Fingolimod therapy for multiple sclerosis. Semin Neurol. 2013;33:37–44.

Hoepner R, Faissner S, Salmen A, Gold R, Chan A. Efficacy and side effects of natalizumab therapy in patients with multiple sclerosis. J Cent Nerv Syst Dis. 2014;6:1–49.

Martinelli Boneschi F, Vacchi L, Rovaris M, Capra R, Comi G. Mitoxantrone for multiple sclerosis. Cochrane Database Syst Rev. 2013;5:CD002127. DOI: 10.1002/14651858.CD002127.pub3.

Hegen H, Auer M, Deisenhammer F. Predictors of response to multiple sclerosis therapeutics in individual patients. Drugs 2016;76:1421–1445.

Subei AM, Ontaneda D. Risk mitigation strategies for adverse reactions associated with the disease modifying drugs in multiple sclerosis. CNS Drugs 2015;29:759–771.

Pharmacokinetics Fingolimod has a half-life of 8 to 9 days (steady-state concentrations achieved in 1–2 months).[24]

Efficacy Treatment reduced the ARR to 0.18 compared with 0.40 for placebo. It also slowed RRMS progression.[24]

Adverse Effects Fingolimod reduces circulating lymphocytes by about 75%; therefore, infections and malignancies are concerns.[24] Sphingosine 1-phosphate receptors modulation causes first-dose bradycardia, macular edema, and reduced forced vital capacity.[24] Fingolimod is contraindicated in patients with myocardial infarctions, unstable angina, stroke, transient ischemic attacks, or some types of congestive heart failure within the past 6 months or in patients with many types of atrioventricular block, prolonged QT interval, or who are taking class Ia or III antiarrhythmic medicines.[24] Baseline and first-dose monitoring is required (see Table 30–3); monitoring must be repeated if therapy is interrupted.[24]

▶ *Natalizumab*

Pharmacology and Mechanism of Action Natalizumab is a α_4-integrin antagonist. It binds to $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, preventing lymphocyte migration into the CNS and inflammation, and inhibits binding of α_4-positive leukocytes to fibronectin and osteopontin, decreasing the activation of leukocytes within the CNS.[25]

Efficacy Treatment with natalizumab reduced relapses in RRMS by 68% at 1 year and disability by 42% at 2 years versus placebo.[25]

Adverse Effects Hypersensitivity reactions (itching, dizziness, fever, rash, hypotension, dyspnea, chest pain, and anaphylaxis) may occur within 2 hours of administration and requires treatment discontinuation. A separate infusion reaction (headache, dizziness, fatigue, nausea, sweats, and rigors) may occur within 2 hours of dosing.[17] Histamine 1 and 2 receptor blockers prevent these symptoms, and discontinuation is not required. A serious, but rare, adverse effect is progressive multifocal leukoencephalopathy (PML). PML, caused by the John Cunningham (JC) polyomavirus virus, is rapidly progressive and often results in death or permanent disability. Though most associated with natalizumab, PML has been reported in patients treated with dimethyl fumarate, fingolimod, and alemtuzumab.[17] Specific recommendations are to test for JC virus, avoid natalizumab in immunocompromised patients; carefully assess for immune compromise in patients previously treated with immunosuppression, radiation therapy, or chemotherapy; use only as monotherapy, and carefully monitor patients.[17] Vigilance is paramount because PML can mimic MS symptoms.[25]

KEY CONCEPT These concerns lead to the recommendation that natalizumab be reserved for patients with rapidly advancing disease who have failed other therapies.

Antinatalizumab antibodies develop in 9% to 12% of patients. If patients have antibodies 6 months after start of therapy, relapse rates, disability, and hypersensitivity reactions increase.[25]

▶ *Ocrelizumab*

Pharmacology and Mechanism of Action Ocrelizumab is a monoclonal antibody approved for treatment of relapsing or primary progressive MS. Ocrelizumab depletes B-cells.[26]

Efficacy In RRMS, ocrelizumab treatment lowered ARR and disability progression compared with interferon β.[27] In primary-progressive MS, fewer patients had confirmed disability progression compared with placebo.[28]

Adverse Effects Infusion reactions (pruritus, rash, erythema, bronchospasm, dyspnea, flushing, hypotension, pyrexia, headache, nausea, and tachycardia) are seen in 34% to 40% of patients given ocrelizumab.[27,28] Premedication with corticosteroids and antihistamines is required and antipyretics considered before each infusion. Ocrelizumab is contraindicated in patients with active hepatitis B infections.

▶ *Alemtuzumab*

Pharmacology and Mechanism of Action Alemtuzumab is a monoclonal antibody that eliminates circulating B- and T-cells. Repopulation of these cells takes 8 to 35 months.[29]

Efficacy Treatment reduced relapse rates compared to interferon β with 77% of patients relapse-free for 2 years.[29]

Adverse Effects Infusion-associated reactions (headache, rash, pyrexia, nausea, itching, and fatigue) occur in more than 90% of patients, requiring pretreatment with methylprednisolone and often antihistamines and antipyretics.[33] Acyclovir co-treatment is required due to risk of herpesvirus infections. Secondary autoimmune diseases can also develop.[29] Because of these safety concerns, alemtuzumab is generally reserved for patients who have failed two therapies. Neutralizing antibodies are present in up to 94% of patients, but do not seem to decrease efficacy.

▶ *Mitoxantrone*

Pharmacology and Mechanism of Action Mitoxantrone is an anthracenedione antineoplastic. It causes apoptosis in T-cells and APCs, preventing initial T-cell activation; inhibits DNA and RNA synthesis, decreasing proliferation of T-cells, B-cells, and macrophages; decreases cytokine release, preventing inflammation; and inhibits macrophages, preventing myelin degradation.[30]

Efficacy Mitoxantrone reduces the relapse rate and attack-related MRI outcome measures and MS progression.[30] KEY CONCEPT Because of its potential for significant toxicities, mitoxantrone is reserved for patients with rapidly advancing disease who have failed other therapies.

Adverse Effects Bluish discoloration of the sclera and urine lasts 24 hours or more postinfusion.[17] Amenorrhea may be permanent and lead to infertility.[30] Cardiotoxicity is a serious adverse effect. Mitoxantrone is contraindicated in patients with cardiomyopathy, even if asymptomatic. Cyclooxygenase-2 inhibitors potentially worsen cardiac toxicity and should be avoided.[30] Maximum lifetime dose of mitoxantrone is 140 mg/m^2.

▶ *Issues with Self-Injected Disease-Modifying Therapies*

Adherence KEY CONCEPT Adherence to injectable medications is a significant problem, with 22% to 59% discontinuation. Realistic therapy expectations, higher educational levels, and higher self-efficacy improve adherence; depression and cognitive problems lower adherence.[35]

Patient Education Refer to Table 30–4 for patient self-injection education.

▶ *Other Therapy Considerations*

Pregnancy Because MS affects women of childbearing age, the teratogenicity of medications is concerning. Although none of the disease modifying therapies is recommended for use during pregnancy, pregnancy registry analysis demonstrates no adverse outcomes with interferon β, glatiramer acetate, and natalizumab.[36] Sphingosine 1-phosphate receptors are important

Table 30–4

Self-Injection Patient Education

Keep supplies together and out of reach of children/pets
Allow medication to warm to room temperature
Wash hands
Choose injection site, rotating among sites
Ice area (≤ 15 minutes) prior to injection, if desired
Clean site with alcohol or soap/water
Administer injection
Ice site (≤ 15 minutes) after injection, if desired

in fetal formation; thus fingolimod should be discontinued for at least 2 months before conception. Mitoxantrone and teriflunomide are contraindicated during pregnancy, and teriflunomide is contraindicated for men who have sexual intercourse with women who may become pregnant.[36] Because of the long half-life of teriflunomide, accelerated elimination with cholestyramine or activated charcoal is recommended for women who wish to become pregnant.[36]

Vaccinations Patients taking alemtuzumab, fingolimod, mitoxantrone, ocrelizumab, or teriflunomide should not receive live attenuated virus vaccines.[21,25,37] Vaccines may be less effective while on several disease-modifying therapies; they should be given 6 weeks before therapy starts. Vaccines should be held for 4 to 6 weeks after a mitoxantrone dose.[21,25]

▶ *Outcome Evaluation*

LO 5

- Assess symptom changes periodically (every 3–12 months).
- In β-interferon-treated patients with frequent relapses, test for neutralizing antibodies.
- Monitor medication-specific adverse effects (see Tables 30–1 and 30–3).
- Assess adherence.
- Assess disability with the Expanded Disability Status Scale[38] or the Multiple Sclerosis Functional Composite Score.[39]

▶ *Symptomatic Therapies*

LO 4

Symptoms most unique to MS are fatigue, spasticity, impaired ambulation, and pseudobulbar affect. Treatment of other symptoms such as urinary incontinence, pain, depression, cognitive impairment, and sexual dysfunction is addressed elsewhere in this text and does not differ in MS.

Fatigue There are nonpharmacologic and pharmacologic strategies for coping with fatigue (Table 30–5).[40]

Spasticity Spasticity treatment goals are patient specific. For ambulatory patients, reducing spasticity may improve mobility and decrease pain. For bed-bound patients, treating spasticity may relieve pain and facilitate care. Physical therapy is a nonpharmacologic treatment for spasticity.[41]

KEY CONCEPT MS patients must be treated with agents specific for upper motor neuron spasticity (Table 30–6).[41] MS spasticity is classified as focal (one muscle group) or generalized. Botulinum toxin may benefit focal spasticity.[41] Systemic medications are used for generalized spasticity. No conclusion can be reached regarding efficacy superiority of one agent.[41]

Patient Encounter Part 2

PMH: She reports over the last 2 to 3 years she has had periodic changes in her visual acuity that resolve spontaneously over weeks. She has also noticed heat intolerance that seems to lead to stumbling when she walks and a few falls.

FH: Both parents alive and well. Younger sister with an episode of optic neuritis.

SH: Elementary school teacher. Divorced. She smokes 1 pack/day. She drinks 2 to 3 alcoholic beverages/week. She does not use illicit drugs.

Allergies: NKDA

Meds: None

ROS: (–) HA, SOB, chest pain, cough

PE:

VS: 122/76, P 76, RR 20, T 36°C (96.8°F)

Skin: Warm, dry

HEENT: Right pupillary response to light is sluggish, decreased visual acuity right eye

CV: RRR, normal S1 and S2, no m/r/g

Chest: CTA

Abd: Soft, NT/ND

Neuro: A & O × 3; CN II-XII intact.

Motor: Paresthesia to touch and decreased pin sensation on right side. Mild vibratory sense loss in distal right leg. Tandem gait mildly unstable.

Labs: WNL

Imaging: T2-weighted MRI shows two enhancing T2-weighted lesions in left cortex and a nonenhancing T2-weighted lesion on the right optic nerve.

Given this additional information, what is your assessment of this patient's condition?

Identify your treatment goals for this patient.

What pharmacologic alternatives are available for this patient?

Impaired Ambulation Nonpharmacological treatment includes assistive devices, physical therapy, and/or exercise. Extended-release dalfampridine is indicated for improvement in walking speed. This potassium channel blocker prolongs action potentials, improving conduction in demyelinated neurons.[42] Not all patients

Patient Encounter Part 3

Based on the information available, create a care plan for this patient's MS. The plan should include (a) a statement of the drug-related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

Table 30–5

Pharmacologic and Nonpharmacologic Fatigue Treatments

Nonpharmacologic	Pharmacologic	Renal Dosing
Appropriate rest-to-activity ratio Use assistive devices to conserve energy Environmental modifications to make activities efficient	*First-line therapy:* Amantadine 100 mg orally every morning and early afternoon	CrCl 30–50 mL/min (0.50–0.84 mL/s): 100 mg/day CrCl 15–29 mL/min (0.25–0.49 mL/s): 100 mg every other day CrCl < 15 mL/min (0.25 mL/s): 200 mg every 7 days
Cooling strategies to avoid fatigue caused by elevations in core body temperature	*Second-line therapy:* Methylphenidate 10–20 mg every morning and noon	
Regular aerobic exercise Lower extremity muscle resistance training Stress management		

CrCl, creatinine clearance.

From Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Mult Scler Int. 2014;2014:798285.

respond to this agent; response can be assessed at 2 months.[42] Urinary tract infections, insomnia, dizziness, headache, nausea, asthenia, back pain, and balance disorder all occur frequently with dalfampridine.[42] Seizures are an uncommon adverse effect; therefore, patients with seizure disorders should not receive dalfampridine.[42]

Pseudobulbar Affect Ten percent of patients with MS develop pseudobulbar affect, which is characterized by inappropriate laughing or crying and can lead to social isolation.[43] A combination of dextromethorphan and quinidine is a treatment for pseudobulbar affect. Dextromethorphan prevents the release of excitatory neurotransmitters. Low-dose quinidine blocks first-pass metabolism of dextromethorphan and increases serum concentrations. Episodes decrease 49% with this treatment.[43]

LOS

▶ *Outcome Evaluation*

- Assess symptom improvement/recurrence.
- Assess quality of life.
- Monitor adverse effects.
- Monitor adherence.

Table 30–6

Antispasticity Agents

Place in Therapy	Medication	Mechanism of Action	Dose
First-line	Baclofen	Presynaptic and postsynaptic γ-aminobutyric acid type B receptor agonist	5 mg orally three times daily; increase by 5 mg/dose every 3 days; maximum 80 mg/day *Renal dysfunction:* Dose reduction
	Tizanidine	Centrally acting α_2-receptor agonist	2 mg orally three times daily; increase gradually by 2 mg at each dose every 1–4 days; maximum 36 mg/day *Hepatic and renal dysfunction:* Dose reduction
Second-line	Dantrolene	Direct inhibitor of muscle contraction by decreasing the release of calcium from skeletal muscle sarcoplasmic reticulum	25 mg orally daily; increase to 25 mg three to four times daily after 7 days; then increase by 25 mg every 4–7 days; maximum 400 mg/day
	Diazepam	γ-aminobutyric acid agonist	2–10 mg orally three to four times daily *Cirrhosis:* Reduce dose by 50%
Third-line	Intrathecal baclofen	Presynaptic and postsynaptic γ-aminobutyric acid type B receptor agonist	Titrated individually; usual range: 62–749 mcg/day
Focal spasticity	Botulinum toxin	Prevents release of acetylcholine in the neuromuscular junction	Individualized

Data from Gold R, Oreja-Guevera C. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity guidelines. Expert Rev Neurother. 2013;13(suppl 12):55–59.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and care.

Assess the Information:

- Based on physical examination and review of systems, determine whether patient is experiencing an MS exacerbation currently. Determine presence of symptoms such as urinary incontinence.
- Based on the medical history and MRI findings, determine the following. Does the patient have CIS? Has the patient had MS relapses? Does patient have aggressive MS (Figure 30–4)? Is patient pregnant? Does patient want to become pregnant?
- Review available laboratory tests.
- Based on the medication history, has patient been treated with any MS medications or immunosuppressants previously? Is patient experiencing adverse effects from current therapy?
- If patient is receiving disease-modifying or symptomatic pharmacotherapy, assess efficacy, safety, and patient adherence. Are there any significant drug interactions?

Develop a Care Plan:

- If patient is having relapses, select corticosteroids.
- Select disease-modifying therapy (Table 30–1, Figure 30–4), considering:
  - Route of administration
  - Frequency of administration
  - Adverse effect profile
  - Cost, including insurance preauthorization needs

Implement the Care Plan:

- Obtain baseline laboratory studies (Table 30–2).
- Educate patient regarding self-injection, if necessary (see Table 30–4), and adherence.
- Initiate needed symptomatic treatments.
- Address any concerns about MS and management.
- Refer patient to the National MS Society for information, newsletters, and local support groups (www.nationalmssociety.org).
- Instruct patient to contact clinician for any sudden symptom changes indicating relapse or adverse effects.

Follow-up: Monitor and Evaluate:

LOS

- Monitor patient for efficacy and adverse effects of disease-modifying and symptomatic therapies (Table 30–2).
- Obtain MRI annually or more frequently as dictated by symptoms and selected therapy.
- Assess adherence with medications.
- Monitor quality of life, disability, and further symptom development.

Abbreviations Introduced in This Chapter

ALT	Alanine aminotransferase
APC	Antigen-presenting cell
ARR	Annualized relapse rate
AST	Aspartate aminotransferase
CBC	Complete blood count
CIS	Clinically isolated syndrome
CNS	Central nervous system
CrCl	Creatinine clearance
CSF	Cerebrospinal fluid
DC	Dendrite cell
EDSS	Expanded Disability Status Scale
FEV_1	Forced expiratory volume in 1 second
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IL	Interleukin
INF	Interferon
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
Mϕ	Macrophage
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
MUGA	Multiple-gated acquisition
OPC	Oligodendrocyte precursor cell
PML	Progressive multifocal leukoencephalopathy
RRMS	Relapsing remitting multiple sclerosis
TGF	Transforming growth factor
Th1	T-helper-1 cells
Th2	T-helper-2 cells
TNF	Tumor necrosis factor
VCAM	Vascular cell adhesion molecule
VLA	Very late antigen

REFERENCES

1. Who gets MS? (epidemiology). National Multiple Sclerosis Society. Available from: http://www.nationalmssociety.org/What-is-MS/Who-Gets-MS. Accessed July 16, 2018.
2. Hauser SL, Chan JR, Oksenberg JR. Multiple sclerosis: prospects and promise. Ann Neurology. 2013;75:317–327.
3. Huynh JL, Casaccia P. Epigenetic mechanisms in multiple sclerosis: implications for pathogenesis and treatment. Lancet Neurol. 2013;12:195–206.
4. Aktas O, Kieseier B, Hartung HP. Neuroprotection, regeneration and immunomodulation: broadening the therapeutic repertoire in multiple sclerosis. Trends Neurosci. 2010;33:140–152.
5. Smakoff LM, Goodman AD. Symptomatic management in multiple sclerosis. Neurol Clin. 2011;29:449–463.

6. Toosy AT, Mason DF, Miller DH. Optic neuritis. Lancet Neurol. 2014;13:83–99.
7. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis. The 2013 revisions. Neurol. 2014;83:278–286.
8. Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: a large multicentre study. Mult Sclerosis J. 2015;28:1013–1024.
9. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162–173.
10. Hurwitz BJ. Analysis of current multiple sclerosis registries. Neurology. 2011;76(suppl 1):S7–S13.
11. Burton JM, O'Connor PSW, Hohol M, Beyene J. Oral versus intravenous steroids for treatment of relapses in multiple sclerosis (review). Cochrane Database Syst Rev. 2012;12:1–66.
12. Le Page E, Veillard D, Laplaud D, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. Lancet 2015;386:974–981.
13. Jongen PJ, Stavrakaki I, Voet B, et al. Patient-reported adverse effects of high-dose intravenous methylprednisolone treatment: a prospective web-based multi-center study in multiple sclerosis patients with a relapse. J Neurol. 2016;263:1641–1651.
14. Perumal JS, Caon C, Hreha S, et al. Oral prednisone taper following intravenous steroids fails to improve disability or recovery from relapses in multiple sclerosis. Eur J Neurol. 2008;15:677–680.
15. Rudick RA, Goelz SE. Beta-interferon for multiple sclerosis. Exp Cell Res. 2011;317:1301–1311.
16. La Mantia L, Vacchi L, De Pietrantonj C, et al. Interferon beta for secondary progressive multiple sclerosis. Cochrane Database Syst Rev. 2012:1–60.
17. Rommer PS, Zettl UK, Kieseier B, et al. Requirements for safety monitoring of approved multiple sclerosis therapies: an overview. Clin Exper Immunol. 2013;175:397–407.
18. Calabresi PA, Kieseier BC, Arnold DL, et al; ADVANCE Study Investigators. Pegylated interferon β-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. Lancet Neurol. 2014;13:657–665.
19. Scott LJ. Glatiramer acetate: a review of its use in patients with relapsing-remitting multiple sclerosis and in delaying the onset of clinically definite multiple sclerosis. CNS Drugs. 2013;27:971–988.
20. LaMantia L, Munari LM, Lovati R. Glatiramer acetate for multiple sclerosis. Cochrane Database Syst Rev. 2010;5:CD004678.
21. Brunetti L, Wagner ML, Maroney M, Ryan M. Teriflunomide for the treatment of relapsing multiple sclerosis: a review of clinical data. Ann Pharmacother. 2013;47:1153–1160.
22. Miller A, Wolinski J, Kappos L, et al. TOPIC main outcomes: efficacy and safety of once-daily oral teriflunomide in patients with clinically isolated syndrome [abstract]. Mult Scler J. 2013; 19(suppl 1):22.
23. Linker RA, Gold R. Dimethyl fumarate for treatment of multiple sclerosis: mechanism of action, effectiveness, and side effects. Curr Neurol Neurosci Rep. 2013;13:394.
24. Willis MA, Cohen JA. Fingolimod therapy for multiple sclerosis. Semin Neurol. 2013;33:37–44.
25. Hoepner R, Faissner S, Salmen A, Gold R, Chan A. Efficacy and side effects of natalizumab therapy in patients with multiple sclerosis. J Cent Nerv Syst Dis. 2014;6:1–49.
26. Sorensen PS, Blinkenberg M. The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects. Ther Adv Neurol Disord. 2016;9:44–52.
27. Hauser SL, Bar-Or G, Comi G, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376:221–234.
28. Montalban X, Hauser SL, Kappos L, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med. 2017;376:209–220.
29. Dorr J, Baum K. Alemtuzumab in the treatment of multiple sclerosis: patient selection and special considerations. Drug Des Devel Ther. 2016;10:3379–3386.
30. Martinelli Boneschi F, Vacchi L, Rovaris M, Capra R, Comi G. Mitoxantrone for multiple sclerosis. Cochrane Database Syst Rev. 2013;5:CD002127.
31. Sorensen PS. New management algorithms in multiple sclerosis. Curr Opin. 2014;27:246–259.
32. Perumal J, Gauthier S, Nealson N, Vartanian. A practice definition of aggressive onset multiple sclerosis [abstract]. Mult Scler J. 2012;18(suppl 4):55–277.
33. Subei AM, Ontaneda D. Risk mitigation strategies for adverse reactions associated with the disease modifying drugs in multiple sclerosis. CNS Drugs 2015;29:759–771.
34. Govindappa K, Sathish J, Park K, Kirkham J, Pirmohamed M. Development of interferon beta-neurtralising antibodies in multiple sclerosis-a systematic review and meta-analysis. Eur J Clin Pharmacol. 2015;72:1287–1298.
35. Menzin J, Caon C, Nichols C, White LA, Friedman M, Pill MW. Narrative review of the literature on adherence to disease-modifying therapies among patients with multiple sclerosis. J Manag Care Pharm. 2013;19:S24–S40.
36. Houtchens M. Multiple sclerosis and pregnancy. Clin Obstet Gynecol. 2013;56:342–349.
37. Pelligrino P, Carnovale C, Perrone V, et al. Efficacy of vaccination against influenza in patients with multiple sclerosis: the role of concomitant therapies. Vaccine. 2014;32:4730–4735.
38. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33(11):1444–1452.
39. Cutter GR, Baier ML, Rudick RA, et al. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain 1999;122:871–882.
40. Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. Mult Scler Int. 2014;2014:798285.
41. Gold R, Oreja-Guevera C. Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity guidelines. Expert Rev Neurother. 2013;13(suppl 12):55–59.
42. Bethoux F. Gait disorders in multiple sclerosis. Continuum. 2013;19:1007–1032.
43. Schoedel KA, Morrow SA, Sellers EM. Evaluating the safety and efficacy of quinidine/dextromethorphan in the treatment of pseudobulbar affect. Neuropsychiatr Dis Treat. 2014;10:1161–1174.

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31 Epilepsy

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LEARNING OBJECTIVES

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

1. Describe the epidemiology and social impact of epilepsy.
2. Define terminology related to epilepsy, including seizure, convulsion, and epilepsy.
3. Describe the basic pathophysiology of seizures and epilepsy.
4. Differentiate and classify seizure types given a description of the clinical presentation of the seizure and electroencephalogram.
5. Identify key therapeutic decision points and therapeutic goals in the treatment of epilepsy.
6. Discuss nonpharmacologic treatments for epilepsy.
7. Recommend an appropriate pharmacotherapeutic regimen with monitoring parameters for the treatment of epilepsy.
8. Devise a plan for switching a patient from one antiepileptic regimen to a different regimen.
9. Manage potential drug interactions with antiepileptic drugs (AEDs).
10. Determine when and how to discontinue AED therapy.
11. Educate a patient or caregiver on epilepsy and pharmacotherapy for this disorder.

EPIDEMIOLOGY

LO 1

Epilepsy is a disorder that afflicts approximately 2 million individuals in the United States, with an age-adjusted prevalence of approximately 4 to 7 cases per 1000 persons.[1] The incidence of epilepsy in the United States is estimated at 35 to 75 cases per 100,000 persons per year.[2,3] In developing countries, the incidence is higher at 100 to 190 cases per 100,000 persons per year. About 8% of the US population will experience a **seizure** during their lifetime. New-onset seizures occur most frequently in infants younger than 1 year and in adults after age 55.[2]

SOCIAL IMPACT

LO 1

Epilepsy has a profound impact on a patient's life. Due to restrictions on driving, individuals who have recently had a seizure face major impediments to engaging in simple activities.[4] Fifty percent of patients with epilepsy report cognitive and learning difficulties.[5,6] Underemployment and unemployment are major concerns for individuals with epilepsy, due to limited transportation options, cognitive and learning difficulties, and seizures, resulting in problems paying for health care. Additionally, the social stigma of embarrassment or injury due to seizures in public results in isolation of the patient.[7]

Patients with epilepsy often depend on caregivers to assist with medications, transportation, and ensuring the patient's safety, so they should be informed about treatments and managing seizures.

ETIOLOGY

In approximately 80% of patients with epilepsy, the underlying etiology is unknown.[8] The most common causes of epilepsy are head trauma and stroke. Developmental and identifiable genetic defects cause about 5% of cases. Genetic causes are presumed in up to 25% of patients but are often unproven. Brain tumors, central nervous system (CNS) infections, and neurodegenerative diseases are other common causes. Human immunodeficiency virus infection and neurocysticercosis infection are also important causes.

Isolated seizures can be caused by stroke, CNS trauma, CNS infections, metabolic disturbances (eg, hyponatremia, hypoglycemia), and hypoxia. Failure to correct these causes may lead to the development of epilepsy. Drugs commonly associated with causing seizures are tramadol, bupropion, theophylline, select antidepressants and antipsychotics, amphetamines, cocaine, imipenem, lithium, excessive doses of penicillins or cephalosporins, and sympathomimetics or stimulants.

PATHOPHYSIOLOGY

Seizures

LO 3

Regardless of the underlying etiology, all seizures involve a sudden electrical disturbance of the cerebral cortex. A population of neurons fires rapidly and repetitively for seconds to minutes. Cortical electrical discharges become excessively rapid, rhythmic, and synchronous. This phenomenon is presumably related to an excess of excitatory neurotransmitter action, a failure of inhibitory neurotransmitter action, or a combination of the two. In individual patients, it is usually impossible to identify which neurochemical factors are responsible.

Neurotransmitters

The primary excitatory neurotransmitter is glutamate.[9] When glutamate is released from a presynaptic neuron, it attaches to postsynaptic receptors. The result is opening of membrane

channels allowing sodium or calcium to flow into the neuron, depolarizing it and transmitting an excitatory signal.[10] Many antiepileptic drugs (AEDs) (eg, phenytoin, carbamazepine, lamotrigine) work by blocking the release of glutamate or blocking sodium or calcium channels.[11] At usual doses, these drugs only halt the excessive rapid neuronal firing characteristic of seizures, and do not affect normal brain function.

The primary inhibitory neurotransmitter is **γ-*aminobutyric acid* (GABA)**. It attaches to neuronal membranes and opens chloride channels. Chloride flow into the neuron causes hyperpolarization and less excitability. This mechanism is probably critical for suppressing seizure activity. Barbiturates and benzodiazepines primarily enhance the action of GABA.

Cortical function is modulated by many other neurotransmitters, but their role in epilepsy is poorly understood.

Neuronal Mechanisms

Seizures originate in a group of neurons with abnormal electrical behavior, presumably due to an imbalance of neurotransmitter function.[11] In individual neurons, firing is excessively prolonged and repetitive. Instead of firing a single action potential, these neurons stay depolarized too long, firing many action potentials. This long, abnormal depolarization is called a *paroxysmal depolarizing shift (PDS)*.

Excessive electrical discharges can spread to adjacent neurons or distant ones connected by fiber tracts.[12] The seizure spreads to other areas by recruiting neurons into uncontrolled firing patterns. Recruited neurons may be normal but are diverted from their normal functioning to participate in the excessive discharges. The area of spread determines the clinical manifestations of the seizure.

Nearly all seizures stop spontaneously, because inhibitory mechanisms overcome abnormal excitation.

Epilepsy

LO 2

Epilepsy is a disease where individuals have at least 2 unprovoked seizures more than 24 hours apart, 1 unprovoked seizure with at least a 60% probability of another seizure in the next 10 years, or diagnosis of an epilepsy syndrome.[13] Practically, this implies a permanent change in cortical function, rendering neurons more likely to participate in a seizure discharge, epileptogenesis.

Epilepsy may develop days, months, or years after a brain insult. A small group of abnormal neurons causes adjacent or connected normal neurons to gradually become abnormal. When a network of abnormal neurons becomes sufficiently large, it causes an excessive firing pattern for at least several seconds: a seizure. This hyperexcitable network of neurons is the seizure focus.

If the change in cortical electrical characteristics is permanent, why do seizures not occur all the time? The occurrence of an individual seizure depends on an interplay of environmental and internal brain factors that intermittently result in loss of the normal mechanisms that control abnormal neuronal firing. It is impossible to determine what triggers a specific seizure.

Epilepsy may remain stable, decrease in severity, or worsen over time. Repeated seizures may cause further damage to the cortex and loss of neurons. Reorganization of connections between groups of neurons may strengthen excitatory connections and weaken inhibitory connections.

Epilepsy is associated with an increased mortality rate, from injuries with seizures or sudden death.[14] Early control of epileptic seizures may reduce permanent changes in brain function, although this hypothesis is unproven.

Genetic Factors

Patients with seizures may be concerned that their children or other family members will inherit epilepsy. Patients with acquired causes of seizures, such as head trauma or stroke, will not transmit epilepsy. Most patients with inherited epilepsy have generalized onset epilepsy, and develop seizures during childhood.[15,16] Complex inheritance patterns are usually seen, indicating the likely involvement of several abnormal genes or other factors for seizures to occur in offspring. Most patients can be reassured that their children and siblings are unlikely to develop epilepsy.

SEIZURE CLASSIFICATION AND PRESENTATION

General Principles

Careful diagnosis and identification of seizure types is essential to proper treatment of epilepsy. The International League Against Epilepsy (ILAE) recently revised the classification of seizures (**Table 31–1**).[17] The new system integrates the concept of onset of seizures with their clinical presentation. Classification of epileptic seizures emphasizes electroencephalographic (EEG) findings combined with the clinical symptoms of the seizure events. Clinical presentation of seizures varies widely depending on the region and the amount of brain involved in the seizure.

LO 4

Generalized Seizures

If the entire cerebral cortex is involved in the seizure from the onset, the seizure is classified as **generalized seizures**. There are multiple types of generalized seizures. Two major categories of generalized seizures are motor, seizures that involve involuntary muscle activity, and nonmotor, seizures without involuntary muscle activity. In these seizures, the EEG demonstrates involvement of the entire brain from the onset of the seizure.

Focal Seizures

When the seizure begins in a localized area of the brain, it is defined as **focal seizures**. There are two main types of focal seizures, aware or impaired awareness. Focal seizures can be further categorized as motor and nonmotor. The EEG demonstrates that the seizure begins in a small region of the brain. Additionally, focal seizures can spread to involve the entire brain.

Unknown-Onset Seizures

Individuals whose seizures are classified as **unknown-onset** have seizures where the distinction between generalized and focal cannot be made. In these seizures, the EEG is unclear as to the start of the seizure.

Epilepsy Syndromes

Currently, there are no officially recognized epilepsy syndromes. Epilepsy syndromes that are often described in publications include **juvenile myoclonic epilepsy (JME)**, **Lennox–Gastaut syndrome (LGS)**, **mesial temporal lobe epilepsy (MTLE)**, **severe myoclonic epilepsy of infancy (SMEI)**, and **infantile spasms (West syndrome)**.

Table 31–1

ILAE 2017 Classification of Seizure Types[17]

Focal Onset[a,b]				
Aware[c]	Impaired Awareness[d]	Generalized Onset[a,g]	Unknown Onset	Unclassified
Motor		**Motor**	**Motor**	
Automatisms		Tonic-clonic	Tonic-clonic	
Atonic[e]		Clonic	Epileptic spasms	
Clonic		Tonic	**Nonmotor**	
Epileptic spasms[e]		Myoclonic	Behavior arrest	
Hyperkinetic		Myoclonic-tonic-clonic		
Myoclonic		Myoclonic-atonic		
Tonic		Atonic		
Nonmotor		Epileptic spasms		
Autonomic		**Nonmotor (absence)[h]**		
Behavior arrest		Typical		
Cognitive		Atypical		
Emotional		Myoclonic		
Sensory		Eyelid myoclonia		
Focal to bilateral tonic-clonic[f]				

[a]The word "onset" is assumed when the seizure type begins with focal, generalized, or absence.

[b]Formerly partial seizures.

[c]Formerly simple partial seizures.

[d]Formerly complex partial seizures.

[e]Do not have a level of awareness specified.

[f]Formerly secondary generalized seizures.

[g]Formerly primary generalized seizures.

[h]Formerly absence seizures.

DIAGNOSIS

A correct and accurate diagnosis is essential prior to starting pharmacotherapy. KEY CONCEPT A distinction between a single seizure and epilepsy must be made, and other seizure-like disorders (eg, syncope, psychogenic, nonepileptic events, anxiety attacks, cardiac arrhythmias, hypoglycemia, transient ischemic attacks, tics, and complicated migraine headaches) should be ruled out. Seizures are typically brief spells, lasting less than 5 minutes. However, prolonged seizures lasting greater than or equal to 5 minutes or occurring one after another without recovery in between are status epilepticus, which requires immediate medical attention (Chapter 32).

A proper diagnostic workup of a patient presenting with seizures includes the following elements:

- Complete neurologic examination
- EEG
- Laboratory tests (complete blood count [CBC], complete serum chemistry which includes liver function tests [LFTs])
- Neuroimaging (preferably magnetic resonance imaging [MRI])

Many of the tests are done to rule out other causes of seizures (eg, infection, electrolyte imbalance), and in most patients will be normal. Often the EEG appears normal between seizures. Sleep deprivation, photic stimulation, prolonged (> 20 minutes) EEG recording, and 24-hour EEG monitoring with video correlation can be done to capture seizure or seizure-like activity on the EEG.

TREATMENT

Desired Outcomes

LOS The ultimate outcome goal for any patient with epilepsy is the elimination of all seizures without adverse effects from treatment. An effective treatment plan allows the patient to live a normal lifestyle with complete control of seizures. The treatment should enable the patient to drive, perform well in school, hold a reasonable job, and function effectively in the family and community. However, 30% to 50% of patients are not able to fully achieve these outcomes. In these cases, the goal of therapy is to provide a tolerable balance between reduced seizure frequency and/or severity and medication adverse effects, enabling the individual to have a lifestyle as nearly normal as possible.

General Approach to Treatment

Once it is concluded that the patient has epilepsy, the type of seizure must be determined.

KEY CONCEPT Selection of appropriate pharmacotherapy depends on distinguishing, identifying, and understanding different seizure types. Without an accurate classification of the seizure type, it is possible to select a medication that is ineffective or even harmful to the patient.

KEY CONCEPT Prior to starting pharmacologic therapy, it is essential to determine the risk of having a subsequent seizure. If there is an underlying treatable cause, such as hyponatremia or a CNS infection, the risks of another seizure and the development

Clinical Presentation and Diagnosis of Epilepsy

General

Typically, health care providers are not able to observe a patient's seizures, and for most types of seizures, the patient has no memory of the event. It is important to obtain a careful history from the patient and any individuals who witness the seizures.

Common Descriptions of Seizures

The clinical presentation of seizures varies from patient to patient depending on the portion of brain involved in the seizure. Events tend to be stereotypical for an individual patient.

Patients who experience seizures may complain of paroxysmal spells of

- Blanking-out spells, lapses in memory, periods of altered consciousness
- Warnings or auras consisting of various sensations or automatic, uncontrolled movements
- Daydreaming
- Jerks, shoulder shrugs, sudden chills of spine
- Falling out

Associated Symptoms

- Incontinence, usually of urine
- Tongue biting
- Traumatic injuries, usually associated with falling during a seizure

Diagnosis

Description of events: The patient and any witnesses to the seizures should be carefully interviewed to obtain a full and complete description of typical seizures.

Neurologic examination: Usually, the neurologic physical examination is completely normal. Any neurologic deficits identified should be fully investigated because seizures do not usually cause permanent, detectable neurologic deficits.

Electroencephalogram (EEG): A routine EEG can be helpful if epileptiform discharges are seen. However, the EEG may be normal between seizures, and most routine EEGs are not performed during a seizure. Maneuvers such as sleep deprivation, photic stimulation, hyperventilation, or prolonged monitoring can help expose EEG changes consistent with epilepsy.

Neuroimaging (preferably an MRI of the brain): Imaging of the brain is important to rule out obvious causes of seizures such as stroke or tumors. An MRI scan is also helpful in detecting mesial temporal sclerosis, a finding often associated with mesial temporal epilepsy and predictive of positive surgical outcomes.

Video EEG monitoring: A procedure consisting of continuous video monitoring of the patient with a simultaneous EEG. Usually a patient is monitored in the hospital for 4 to 5 days. This procedure is used to determine if the patient is truly having seizures, to determine the specific type of seizures the patient is having, and to localize the area of the brain that is the origin of the seizures.

of epilepsy are very small. In these cases, the only necessary pharmacotherapy is to correct the underlying problem and possibly use an AED short-term. Risk factors for repeated seizures in patients without an underlying disorder include[18]

- Structural CNS lesion
- Abnormal EEG
- Partial seizure type
- Positive family history
- Postictal motor paralysis

If no risk factors are present, the risk of another seizure is 10% to 15%. However, if two or more risk factors are present, the risk of another seizure is 100%. If the estimated risk is over 70%, an epilepsy diagnosis is plausible. When sufficient evidence is available to determine the patient has seizures and is at risk for another seizure, pharmacotherapy is usually started (Table 31–2). The patient or caregiver should be in agreement with the plan, be willing to take the medication, and be able to monitor seizure frequency and adverse drug effects. KEY CONCEPT Mechanisms of action, effectiveness for specific seizure types, common adverse effects, and potential drug interactions are key elements in selecting a medication. Other patient factors such as gender, concomitant drugs, age, economic factors, and lifestyle also need to be considered.

Nonpharmacologic Therapy

LO 6

Nonpharmacologic treatments for epilepsy include surgery, vagal nerve stimulation, and dietary modifications. For some patients, surgery is the treatment approach with the greatest probability of eliminating seizures. The most common surgery for epilepsy is temporal lobectomy. When the seizure focus can be localized and it is in a region of the brain that is not too close to critical areas, such as those responsible for speech or muscle control, surgical removal of the focus can result in 80% to 90% of patients becoming seizure free.[19] Other surgical procedures that are less likely to make a patient seizure free include corpus callosotomy and extratemporal lesion removal.

Vagal nerve stimulation is another nonpharmacologic approach to treating all types of seizures.[20] The unit that generates an intermittent electrical current is placed under the skin in the chest. A wire is tunneled under the skin to the left vagus nerve in the neck and delivers a small electrical stimulus to the vagus nerve. This efficacy of this treatment is essentially equivalent to starting a new medication, with fewer than 10% of refractory patients becoming seizure free. Vagal nerve stimulation is usually reserved for patients who do not respond to several drugs and are not surgical candidates. Finally, deep brain stimulation devices are approved for individuals with seizures refractory to other treatments. Some AED therapy is usually continued in patients with devices.

Another nonpharmacologic treatment is the ketogenic diet.[21] This diet produces a keto-acidotic state through the elimination of nearly all carbohydrates. The diet consists of high dietary fats (eg, butter, heavy cream, fatty meats) and low protein with no added sugar. Daily urinalysis for ketones is performed to ensure the patient remains in ketosis. Any inadvertent consumption of sugar results in the diet needing to be reinitiated. Clinicians must be vigilant in maintaining the diet, by determining the sugar or

Table 31–2

Evidence-Based Selection of Antiepileptic Drugs for Initial Monotherapy Treatment of Epilepsy[a]

Seizure Type	Drugs
Generalized onset: Motor	Carbamazepine (except myoclonic) Lamotrigine Levetiracetam Oxcarbazepine (except myoclonic) Perampanel Phenobarbital Phenytoin Topiramate Valproate
Generalized onset: Nonmotor (Absence)	Clobazam Clonazepam Ethosuximide (preferred) amotrigine Topiramate Valproate Zonisamide
Focal onset: Motor and nonmotor	Carbamazepine Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Phenobarbital Phenytoin Topiramate Valproate

[a]Adapted from: Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults [Internet], [cited 2018 July 10]. http://www.sign.ac.uk/assets/sign143.pdf.

National Institute for Clinical Excellence. Epilepsies: diagnosis and management [Internet], [cited 2017 Nov 10]. https://www.nice.org.uk/guidance/cg137/chapter/Appendix-E-Pharmacological-treatment.

French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2005;62:1252–1260.

carbohydrate content of medications the patient is taking. This diet is typically used only in children with difficult-to-control seizures. In certain patients, the diet can be extremely effective, resulting in complete seizure control and reduction of AEDs. However, it is difficult to maintain, and palatability of the diet, growth retardation, and hypercholesterolemia are concerns. Less stringent diets, such as a modified Adkins diet, may produce seizure control similar to a rigorous ketogenic diet.

Pharmacologic Therapy

▶ *Special Considerations*

Use of AEDs presents some unique challenges due to their pharmacokinetic and pharmacodynamic properties.

Michaelis–Menten Metabolism Phenytoin metabolism is capacity limited. Michaelis–Menten pharmacokinetics occurs when the maximum capacity of hepatic enzymes to metabolize the drug is reached within the normal dose range. The clinical significance is that small changes in doses result in large changes in serum concentrations. Too large a dose change may result in concentration-related toxicity or breakthrough seizures. Individual differences in metabolism result in differing relationships between dose and serum concentrations. These differences can be defined only by careful use of serum concentration and dosing data. There are numerous schemes for determining appropriate dosage adjustments of phenytoin, but for routine clinical practice, dosage adjustments for adults with normal protein binding of phenytoin and a steady-state serum concentration can be made using the following plan:

- For serum concentrations less than 7 mcg/mL (mg/L; 28 μmol/L), the total daily dose is increased by 100 mg.
- For serum concentrations of 7 to 12 mcg/mL (mg/L; 28–48 μmol/L), the total daily dose is increased by 50 mg.
- For serum concentrations more than 12 mcg/mL (mg/L; 48 μmol/L), the total daily dose is increased by no more than 30 mg.[22]

Protein Binding Some AEDs, especially phenytoin and valproate, are highly bound to plasma proteins. When interpreting a reported concentration for these drugs, it is important to remember the value represents the total (ie, bound and unbound) concentration in the blood. Because of differences in the metabolism of these drugs, the clinical effects of altered protein binding are different.

Normally, 88% to 92% of phenytoin is bound to plasma protein, leaving 8% to 12% as unbound. The unbound component produces the clinical effect in the CNS, produces dose-related side effects in the CNS and at other sites, distributes to other peripheral sites, and gets metabolized. Certain patient groups have decreased protein binding, resulting in an increased unbound percentage of drug. These patient groups include:

- Those with kidney failure
- Those with hypoalbuminemia
- Neonates
- Pregnant women
- Those taking multiple highly protein-bound drugs
- Patients in critical care settings

Due to the Michaelis–Menten metabolism of phenytoin, alterations in its protein binding result in increased concentration-related adverse effects. In patients with suspected changes in protein binding, it is useful to measure unbound phenytoin concentrations.

When valproate protein binding is altered, the risk for severe dose-related adverse effects is less compared with phenytoin. Michaelis–Menten metabolism is not a factor with valproate, so hepatic enzymes are able to efficiently metabolize the additional unbound portion.

Autoinduction Carbamazepine is a potent inducer of hepatic microsomal enzymes. It increases the rate of metabolism for many other drugs, and the rate of its own metabolism. Hepatic enzymes become maximally induced over several weeks, necessitating a small initial dose of carbamazepine that is increased over time to compensate for the enzyme induction (Table 31–3). Most dosage regimens for carbamazepine use a starting dose that is 25% to 30% of the typical maintenance dose of 15 mg/kg/day. The dosage is increased weekly until the target maintenance dose is achieved within 3 to 4 weeks. Titration of the carbamazepine dose reduces the risk for severe dose-related adverse effects.

▶ *Drug Selection and Seizure Type*

LO 7 The key to selecting effective pharmacotherapy is to base the decision on the seizure type. Several consensus treatment

Patient Encounter 1: New-Onset Seizures

MN, a 22-year-old man, is seen by his physician due to a series of unexplained episodes. He has no memory of these events. Friends say that he stares, speaks incoherently, and fumbles with his clothes.

His physical examination is completely normal, and no focal neurologic deficits were observed. An MRI was ordered and reported as left mesial temporal sclerosis. An EEG shows occasional left frontal temporal spike waves.

What additional information is needed to make a decision about pharmacotherapy?

How should this information be used to make choices concerning AED therapy?

He remembers several weeks ago that when he woke up in the morning, his muscles ached all over and there was some blood in his mouth and on his pillow.

Is pharmacotherapy indicated?

If it is indicated, what drug should be used and how should it be started?

What adverse effects are important to monitor?

Six months later, he still is having 1 to 2 episodes a month of similar symptoms.

What adjustments in pharmacotherapy should be made at this point?

Is it possible for him to discontinue AED therapy at some time in the future?

guidelines from the Scottish Intercollegiate Guidelines Network (SIGN), the National Institute for Clinical Excellence (NICE) in the United Kingdom, the American Academy of Neurology (AAN), and ILAE all link seizure type to the selection of pharmacotherapy (Table 31–2).[23–26] Table 31–2 summarizes recommendations from these treatment guidelines and US Food and Drug Administration (FDA) approved indications.

For initial treatment of absence seizures, ethosuximide is preferred. In absence and myoclonic seizures, carbamazepine, oxcarbazepine, gabapentin, tiagabine, and pregabalin should be avoided due to association with worsening of these seizure types.

KEY CONCEPT AED therapy should usually be initiated carefully using a titration schedule to minimize adverse events. Moderate target doses are chosen until the patient's response can be further evaluated in the clinic. If seizures continue, the dose is increased gradually until the patient becomes seizure free or adverse effects appear. For some drugs like lamotrigine, specific titration guidelines are established by the manufacturer.

Treatment of refractory seizures (ie, unresponsive to at least two first-line AEDs) is somewhat different. Combinations of drugs may be useful in patients with difficult to control seizures. All AEDs, except ethosuximide, are effective in combination therapy for partial seizures.

▶ Complications of Pharmacotherapy

LO 10

Adverse effects of AEDs are frequently dose limiting or cause a drug to be discontinued. Two types of adverse effects occur with AEDs: serum concentration-related and idiosyncratic (Table 31–3). Concentration-related adverse effects occur with increasing frequency and severity as the dose or serum concentration of a drug is increased. Common concentration-related adverse effects include sedation, ataxia, and diplopia. Adverse effects should be considered in the selection of AED. For example, if a patient has a job that requires mental alertness, it is best to choose an AED that is less likely to cause sedation (eg, lamotrigine, levetiracetam).

Idiosyncratic adverse effects are not dose or concentration related and almost always result in the AED being discontinued. Typically, these types of reactions will occur during the first 6 to 12 months of taking the AED. Rash is the most common of these. Prior to initiating carbamazepine, genetic testing for human leukocyte antigen (HLA) HLA-B*1502 and HLA-A*3101 should be done. Polymorphisms of these HLA genes are associated with increased risk of severe skin reactions in patients of Asian descent. Likewise with phenytoin, genetic polymorphisms of HLA-B*1502 and the CYP 2C9*3 have been associated with increased risk of severe skin reactions. Severe skin, hepatic, or hematological reactions occur rarely, but are potentially life-threatening. The AED should be discontinued immediately when these reactions occur. Carbamazepine, phenytoin, phenobarbital, valproate, lamotrigine, oxcarbazepine, and felbamate are most likely to cause reactions. There is a possibility of cross-reactivity for these adverse effects, especially for carbamazepine, phenytoin, phenobarbital, and oxcarbazepine.

▶ Chronic Adverse Effects

Because AEDs are administered for long periods of time, adverse effects due to prolonged drug exposure are of concern. Some chronic adverse effects associated with AEDs include peripheral neuropathy and cerebellar atrophy. Other chronic adverse effects are extensions of acute adverse effects, for example, weight gain.

Osteoporosis is a major chronic adverse effect of several drugs.[27,28] Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, and valproate decrease bone mineral density, after 6 months of treatment. The risk of osteoporosis due to chronic AED use is comparable to the risk with chronic use of glucocorticosteroids. Patients taking carbamazepine, oxcarbazepine, phenytoin, phenobarbital, or

Patient Encounter 2: Managing Chronic Adverse Reactions

JP, a 45 year-old woman, has been taking oxcarbazepine 600 mg/day for 15 years. Her seizures are well controlled on this regimen, and she works as a public health nurse. She expresses concern about taking the oxcarbazepine for so long.

What chronic adverse effects are important to monitor in this patient?

How should monitoring for these adverse effects be done?

What measures can be taken to prevent these adverse effects?

Table 31–3

Characteristics of Common AEDs

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Brivaracetam (Briviact)	Modulate synaptic vesicle protein 2A	*Maintenance Dose*: 50–100 mg twice daily	*Half-life*: 9 hours *Apparent volume of distribution*: 0.5 L/kg *Protein binding*: 17.5% *Primary elimination route*: Hepatic	Not established	Ataxia, dizziness, fatigue, somnolence	Angioedema, bronchospasm, suicidal behavior and ideation,
Carbamazepine (Tegretol and generic, Tegretol XR, generic), Carbatrol, Epitol, Equetro	Fast sodium channel inactivation	*Maintenance dose*: Titrate dosage to target over 3–4 weeks Adults: 800–1200 mg/day in divided doses Children: 20–30 mg/kg/day as a divided dose Intravenous: Indicated for oral replacement therapy at 70% of the total oral maintenance dose divided into four equal doses given every 6 hours	*Half-life*: 10–25 hours with chronic dosing *Apparent volume of distribution*: 0.8–1.9 L/kg *Protein binding*: 67%–81% *Primary elimination route*: Hepatic	4–12 mcg/mL (mg/L; 17–51 µmol/L)	Diplopia, drowsiness, nausea, sedation	Aplastic anemia, hyponatremia, leukopenia, osteoporosis, rash
Clobazam (Onfi)	Enhance GABA	Weight < 30 kg, start 5 mg/day, titrate to 20 mg/day in divided doses Weight > 30 kg start 10 mg/day in divided doses, titrate to 40 mg/day in divided doses CYP 2C19 poor metabolizers: start 5 mg/day, titrate to 10–20 mg/day, maximum dose 40 mg/day	*Half-life*: 10–50 hours *Apparent volume of distribution*: ~0.9 L/kg *Protein binding*: ~90% *Primary elimination route*: Hepatic; metabolized to active metabolite that is further metabolized by CYP 2C19	Not established	Sedation, somnolence, lethargy, pyrexia, irritability, drooling, aggression	
Clonazepam (Klonopin, generic)	Enhance GABA activity	*Maintenance dose*: Initiate at 0.5 mg one to three times daily, titrate dose to effectiveness, usually 3–5 mg daily in two or three divided doses Pediatric dosing in children < 10 years or < 30 kg: Initiate at 0.01–0.03 mg/kg/day in 2–3 divided doses, titrate dose to effectiveness	*Half-life*: 30–40 hours *Apparent volume of distribution*: 3.2 L/kg *Protein binding*: 47%–80% *Primary elimination route*: Hepatic	Not established	Ataxia, memory impairment, sedation, slowed thinking	
Eslicarbazepine (Aptiom)	Fast sodium channel inactivation	*Maintenance dose*: Adults: Initiate at 400 mg daily and titrate in increments of 400–600 mg daily to a maintenance dose of 800–1600 mg daily Pediatrics: Initial, incremental increases, and maintenance dose based on body weight	*Half-life*: 13–20 hours in adults *Apparent volume of distribution*: 0.85–0.9 L/kg *Protein binding*: < 40% *Primary route of elimination*: Renal	Not established	Ataxia, dizziness, diplopia, drowsiness, sedation, nausea, vomiting	

(*Continued*)

Table 31–3

Characteristics of Common AEDs (*Continued*)

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Ethosuximide (Zarontin, generic)	Modulate calcium channels	*Maintenance dose*: Initiate at 250 mg twice daily and titrate to 500–1000 mg twice daily	*Half-life*: 60 hours *Apparent volume of distribution*: 0.6–0.7 L/kg *Protein binding:* None *Primary elimination route*: Hepatic	40–100 mcg/mL (mg/L; 283–708 µmol/L)	Ataxia, sedation	Hepatotoxicity, neutropenia, rash
Felbamate (Felbatol)	Inhibit glutamate activity	*Maintenance dose*: 1200–3600 mg/day in three or four divided doses	*Half-life*: Monotherapy: 20 hours Concurrent enzyme inducers: 11–16 hours *Apparent volume of distribution*: 0.7–0.8 L/kg *Protein binding*: 25%–35% *Primary elimination route*: Hepatic	Not established	Anxiety, insomnia, nausea	Anorexia, aplastic anemia, headache, hepatotoxicity, weight loss
Gabapentin (Neurontin, generic)	Modulate calcium channels and enhance GABA activity	*Maintenance dose*: Adults: 900–3600 mg/day in three or four divided doses Pediatrics: Age 3–4 Initial dose 10–15 mg/kg/day, titrate to a maximum of 50 mg/kg/day divided in divided three doses; age 5–11 initial dose 10–15 mg/kg/day titrate to maximum of 50 mg/kg/day in three divided doses; age > 12 Initial dose 300 mg thrice daily titrate to a maximum of 360 mg/day divided in three doses Renal dosing: CrCl 30–50 mL/min (0.50–0.84 mL/s) decrease by 25% and give twice daily; CrCl 10–29 mL/min (0.17–0.49 mL/s) decrease dose by 25% and give once daily; CrCl < 10 mL/min (0.17 mL/s) decrease dose 25% and give every other day	*Half-life*: 5–7 hours (proportional to creatinine clearance) *Apparent volume of distribution*: 0.6–0.8 L/kg *Protein binding*: < 10% *Primary elimination route*: Renal	Not established	Drowsiness, sedation	Peripheral edema, weight gain

Lacosamide (Vimpat)	Slow sodium channel inactivation; modulate collapsin response; mediator protein-2	*Maintenance dose*: 200–400 mg/day; start at 100 mg/day in two divided doses and titrate upward according to response	*Half-life*: Approximately 13 hours *Volume of distribution*: 0.6 L/kg *Protein binding*: < 15% *Primary elimination route*: 40% renal 60% hepatic	Not established	Ataxia, dizziness, diplopia, headache, nausea, vomiting	PR interval prolongation
Lamotrigine (Lamictal, Lamictal XR, generic)	Fast sodium channel inactivation	*Initial dose*: With valproate 25 mg every other day for 2 weeks, then 25 mg daily for 2 weeks, then 25 mg twice daily for a week, increase by 25 mg/day every week until maintenance dose of 150 mg/day is achieved; without enzyme inhibitor or inducer 25 mg daily for 2 weeks, then 25 mg twice daily for 2 weeks, then increase by 25 mg daily every week maintenance dose of at least 200 mg/day is achieved; with enzyme inducer 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks, then increase by 100 mg/day every week until maintenance dose of 300–500 mg/day is achieved *Maintenance dose*: 150–800 mg/day in two or three divided doses Pediatric: age 2–12 with valproate 0.15 mg/kg/day for 2 weeks, then 0.3 mg/kg/day for 2 weeks, then increase by 0.3 mg/kg/day every week until maintenance dose of 1–5 mg/kg/day achieved; without inhibitor or inducer 0.3 mg/kg/day for 2 weeks, then 0.6 mg/kg/day for 2 weeks, then increase by 0.6 mg/kg/day weekly until maintenance dose of 4.5–7.5 mg/kg/day achieved; with inducer 0.6 mg/kg/day in two divided doses for 2 weeks, then 1.2 mg/kg/day in two divided doses for 2 weeks, then increase by 1.2 mg/kg/day weekly until maintenance dose of 5–15 mg/kg/day is achieved	*Half-life*: Monotherapy: 24 hours Concurrent enzyme inducers: 12–15 hours Concurrent enzyme inhibitors: 55–60 hours *Apparent volume of distribution*: 1.1 L/kg *Protein binding*: 55% *Primary elimination route*: Hepatic	Not established	Ataxia, drowsiness, headache, insomnia, sedation	Rash

(*Continued*)

Table 31–3

Characteristics of Common AEDs (*Continued*)

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Levetiracetam (Keppra, Keppra XR, generic)	Modulate synaptic vesicle protein	*Adult Maintenance dose*: 1000–3000 mg/day. Start at 1000 mg/day and titrated upward as indicated by response *Pediatric*: 1–6 months 7 mg/kg twice daily titrate by 7 mg/kg twice daily every 2 weeks to maintenance dose of 21 mg/kg twice daily; 6 months to 4 years 10 mg/kg twice daily then increase by 10 mg/kg twice daily every 2 weeks to maintenance dose of 25 mg/kg twice daily; 4–16 years 10 mg/kg twice daily then increase by 30 mg/kg twice daily Renal failure: CrCl 50–80 mL/min (0.84–1.33 mL/s) 500–1000 mg twice daily, CrCl 30–50 mL/min (0.50–0.84 mL/s) 250–750 mg twice daily, CrCl < 30 mL/min (0.50 mL/s) 250–500 mg twice daily, End stage on dialysis 500–1000 mg daily	*Half-life*: 6–8 hours *Apparent volume of distribution*: 0.5–0.7 L/kg *Protein binding*: < 10% *Primary elimination route*: 70% renal 30% hepatic	Not established	Somnolence, dizziness	Depression
Perampanel (Fycompa)	Antagonist of glutamate receptors on postsynaptic neurons	*Maintenance dose*: without CYP3A4 inducers 8–12 mg once daily. Start at 2 mg once daily, increase by 2 mg/day increments to desired response With CYP3A4 inducers Start at 4 mg once daily, increase by 2 mg/day increments to desire response with maximum dose of 12 mg daily	*Half-life*: 105 hours *Apparent volume of distribution*: 0.7–1.5 L/kg *Protein binding*: 95%–96% *Primary elimination route*: Hepatic	Not established	Ataxia, dizziness, drowsiness, somnolence	Suicidal behavior and ideation, agitation, hostility, aggression, hypersensitivity reactions
Oxcarbazepine (Trileptal, generic)	Fast sodium channel inactivation	*Maintenance dose*: 600–1200 mg/day. Start at 300 mg twice daily and titrated upward as indicated by response Pediatric dosing *Maintenance dose*: 20 kg 300–450 mg twice daily; 25–30 kg 450–600 mg twice daily; 35–40 kg 450–750 mg twice daily; 40–50 kg 600–750 mg twice daily; 50–55 kg 600–900 mg twice daily; 60–65 kg 600–1050 mg twice daily Renal failure dosing CrCl < 30 mL/min (0.50 mL/s) starting dose of 150 mg twice daily and titrate at a slower rate to desired effect	*Half-life*: *Parent drug*: Approximately 2 hours *10-monohydroxy metabolite*: Approximately 9 hours *Apparent volume of distribution*: 0.5–0.7 L/kg *Protein binding*: 40% *Primary elimination route*: Hepatic	Not established	Diplopia, dizziness, somnolence	Hyponatremia, 25%–30% cross-sensitivity in patients with hypersensitivity to carbamazepine

Phenobarbital (Luminal, generic) Primidone (Mysoline, generic) gets metabolized to phenobarbital	Fast sodium channel inactivation	*Loading dose*: 10–20 mg/kg as single or divided IV infusion or orally in divided doses over 24–48 hours *Maintenance dose*: Adults: 1–4 mg/kg/day as a single or divided dose Children: 3–6 mg/kg/day as divided dose Neonates: 1–3 mg/kg/day as divided dose	*Half-life*: Adults: 49–120 hours Children: 37–73 hours Neonates: approximately 115 hours *Volume of distribution*: 0.7–1 L/kg *Protein binding*: Approximately 50% *Primary elimination route*: Hepatic	15–40 mcg/mL (mg/L; 65–172 µmol/L)	Ataxia, drowsiness, sedation	Attention deficit, cognitive impairment, hyperactivity, osteoporosis, passive-aggressive behavior
Phenytoin (Dilantin, Phenytek, generic)	Fast sodium channel inactivation	*Loading dose*: Adults: 15–20 mg/kg single IV dose or divided oral dose Infants younger than 3 months: 10–15 mg/kg single IV dose Neonates: 15–20 mg/kg single IV dose *Maintenance dose*: Adults: 5–7 mg/kg/day, as single or divided dose Children: 6–15 mg/kg/day, as divided dose Neonates: 3–8 mg/kg/day, as divided dose	*Half-life*: Follows capacity-limited or Michaelis–Menten pharmacokinetics. Half-life increases as the dose and serum concentration increases. *Volume of distribution*: Adults: 0.7 L/kg Children: 0.8 L/kg Neonates: 1.2 L/kg *Protein binding*: adults, children: 88%–92% Neonates: 65% *Primary elimination route*: Hepatic	10–20 mcg/mL (mg/L; 40–79 µmol/L) total concentration 1–2 mcg/mL (mg/L; 4–8 µmol/L) unbound concentration	Ataxia, diplopia, drowsiness, sedation	Anemia, gingival hyperplasia, hirsutism, lymphadenopathy, osteoporosis, rash
Pregabalin (Lyrica)	Modulate calcium channels	*Maintenance dose*: Initiate at 150 mg/day in two or three divided doses and titrate to a maximum dose of 600 mg/day Renal failure dosing CrCl > 60 mL/min (1.0 mL/s) 150–600 mg / day in 2–3 divided doses; CrCl 30–60 mL/min (0.50–1.0 mL/s) 75–300 mg/day in 2–3 divided doses; CrCl 15–30 mL/min (0.25–0.50 mL/s) 25–150 mg/day in 1–2 divided doses; CrCl < 15 mL/min (0.25 mL/s) 25–75 mg/day	*Half-life*: 6.3 hours, proportional to creatinine clearance *Apparent volume of distribution*: 0.5 L/kg *Protein binding*: Negligible *Primary elimination route*: Renal	Not established	Ataxia, blurred vision, dizziness, dry mouth, somnolence	Edema, weight gain

(*Continued*)

Table 31–3

Characteristics of Common AEDs *(Continued)*

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects	Idiosyncratic Adverse Effects
Rufinamide (Banzel)	Unknown, may enhance inactivation of sodium channels	*Maintenance dose*: Adults: 3200 mg/day; start at 400–800 mg/day in two divided doses and titrate upward according to response Children: 45 mg/kg/day or 3200 mg/day; start at 10 mg/kg/day in two divided doses and titrate upward according to response	*Half-life*: 6–10 hours *Apparent volume of distribution*: Approximately 0.7 L/kg, varies with dose *Protein binding*: 34% (27% to albumin) *Primary elimination route*: Hepatic	Not established	Dizziness, fatigue, headache, nausea, somnolence, vomiting	
Tiagabine (Gabitril, generic)	Enhance GABA activity	*Maintenance dose*: With concomitant hepatic enzyme inducers Initiate with 4 mg/day for 1 week, increase weekly by 4–8 mg/day in 2–3 divided doses with maximum dose of 56 mg/day Without concomitant hepatic enzyme inducers Initiate with 2–4 mg/day for 1 week, increase weekly by 2–4 mg/day to maintenance dose of 12–22 mg/day in 2–3 divided doses Pediatric dosing Age > 12 Initiate with 4 mg/day for 1 week, then 4 mg twice daily for 1 week, then titrate by 4–8 mg/day in 2–4 divided doses with maximum dose of 32 mg/day	*Half-life*: Monotherapy: 7–9 hours Concurrent enzyme inducers: 2.5–4.5 hours *Apparent volume of distribution*: 0.6–0.8 L/kg *Protein binding*: 96% *Primary elimination route*: Hepatic	Not established	Dizziness, somnolence, irritability, slowed thinking	
Topiramate (Topamax, generic) Qudexy, Trokendi, Topiragen	Fast sodium channel inactivation, inhibit glutamate activity, enhance GABA activity	*Maintenance dose*: 100–400 mg/day in two or three divided doses. Doses should be started at 25–50 mg/day and gradually titrated upward over 3–6 weeks to avoid excessive adverse effects Pediatric dosing Ages 2–16 Initiate at 5–9 mg/kg/day in two divided doses for 1 week, then titrate by 1–3 mg/kg/day every 1–2 weeks to desired response maximum dose of 400 mg/day	*Half-life*: Monotherapy: 21 hours Concurrent enzyme inducers: 11–16 hours *Apparent volume of distribution*: 0.55–0.8 L/kg *Protein binding*: 13%–17% *Primary elimination route*: 60% renal 40% hepatic	Not established	Ataxia, dizziness, drowsiness, slowed thinking	Acute glaucoma, metabolic acidosis, oligohidrosis, paresthesia, renal calculi, weight loss

Valproic acid/ divalproex sodium (Depakene, Depakote, Depakote ER, Depacon, generic), Stavzor	Fast sodium channel inactivation	*Loading dose*: 20–40 mg/kg *Maintenance dose*: Adults: 15–45 mg/kg/day in two to four divided doses Pediatric dosing: 5–60 mg/kg/day in two to four divided doses Do not administer to children < 2 years of age Doses of extended release products should be 8%–20% higher than immediate release products	*Half-life*: Adults: 8–15 hours Children: 4–15 hours Infants younger than 2 months: 65 hours *Volume of distribution*: 0.1–0.5 L/kg *Protein binding*: 90% (decreases with increasing serum concentrations) *Primary elimination route*: Hepatic	50–100 mcg/mL (mg/L; 346–693 µmol/L) Children may require concentrations up to 150 mcg/mL (mg/L; 1040 µmol/L)	Drowsiness, nausea, sedation, tremor	Hepatotoxicity, osteoporosis, pancreatitis, weight gain
Vigabatrin (Sabril)	Inhibits GABA transaminase	*Adults*: Initiate at 1000 mg/day in two divided doses, titrate up to 3000 mg/day *Children*: 1 month–2 years: 50 mg/kg/day in two divided doses *Renal failure*: CrCl 50–80 mL/min (0.84–1.33 mL/s), decrease dose by 25%; CrCl 30–50 mL/min (0.50–0.84 mL/s), decrease dose by 50%; CrCl 10–30 mL/min (0.17–0.50 mL/s), decrease dose by 75%	*Half-life*: 7.5 hours, proportional to creatinine clearance *Volume of distribution*: 1.1 L/kg *Protein binding*: negligible *Primary route of elimination*: Renal	Not established	Convulsion, dizziness, headache, nasopharyngitis, somnolence, weight gain	Vision loss and blindness
Zonisamide (Zonegran, generic)	Modulate sodium and calcium channels	*Maintenance dose*: 100–600 mg/day; start at 100 mg/day and titrated upward as indicated by response	*Half-life*: Approximately 63 hours *Apparent volume of distribution*: 1.45 L/kg *Protein binding*: 40% *Primary elimination route*: Hepatic	Not established	Dizziness, somnolence	Metabolic acidosis, oligohidrosis, paresthesia, renal calculi

GABA, γ-aminobutyric acid.

valproate more than 6 months should take supplemental calcium and vitamin D. Routine monitoring for osteoporosis should be performed every 2 years, and patients should be instructed on ways to protect themselves from fractures.

▶ *Practical Issues*

Comorbid Disease States Patients with epilepsy often have comorbid disease states. Care must be taken when treating comorbid conditions, as numerous drugs can interact with AED. These interactions necessitate close monitoring for changes in efficacy or increased toxicity, and dosage changes of other drugs may be necessary when an AED is added or removed. Patients with headaches need special attention in the selection of an AED. Agents known to prevent headache (eg, valproate and topiramate) may be preferred, and agents associated with increased headaches (eg, lamotrigine and felbamate) may be secondary or tertiary alternatives.

Depression is common in patients with epilepsy. Approximately 30% have symptoms of major depression at some point.[29] Patients with epilepsy should be routinely assessed for depression using a validated screening tool, and treatment initiated if necessary. Most AEDs can exacerbate depression, and patients should be warned to watch for mood changes. Some AEDs (eg, lamotrigine, carbamazepine, oxcarbazepine) may be useful in treating depression. If treatment for depression is necessary, an agent that is unlikely to increase seizures and does not interact with AEDs should be chosen. However, treatment with an appropriate antidepressant should not be withheld because of a small risk of increasing seizure frequency.

LO 8

Switching Drugs Changing from one AED to another can be a complex process. If the first drug is stopped too abruptly, breakthrough seizures may occur. KEY CONCEPT Changes in AED regimens should be done in a stepwise fashion, keeping in mind drug interactions that may be present and may necessitate dosage changes in concomitant drugs. Typically, the new drug is started at a low initial dose and gradually increased over several weeks. Once the new drug is at a minimally effective dose, the drug to be discontinued is gradually tapered while the dose of the new drug continues to be increased to the target dose. During a transition between drugs, patients should be cautioned about the possibility of increased seizures or adverse reactions.

LO 10

Stopping Therapy Epilepsy is generally considered to be a lifelong disorder requiring ongoing treatment. However, some patients who are seizure free may desire to discontinue their medications.[30,31] Patients who become seizure free following surgery for epilepsy may have medications slowly tapered starting 1 to 2 years after surgery. Many patients will choose to stay on at least one medication, following successful surgery, to ensure they remain seizure free. KEY CONCEPT Discontinuation of AEDs should be done gradually, only after the patient has been seizure free for 2 to 5 years and with careful consideration of factors predictive of seizure recurrence. They are

- No seizures for 2 to 5 years
- Normal neurologic examination
- Normal intelligence quotient
- Single type of partial or generalized seizure
- Normal EEG with treatment

Individuals who fulfill all of these criteria have a 61% chance of remaining seizure free after AEDs are discontinued. Additionally, there is a direct relationship between the duration of seizure freedom with medications and the chance of remaining seizure free after medications are withdrawn. Withdrawal of AEDs is done slowly, usually with a tapering dose over at least 1 to 3 months.

▶ *Dosing*

Dosing of AEDs is determined by general guidelines and response of the patient. Serum concentrations may be helpful in benchmarking a specific response. Therapeutic ranges that are often quoted are broad guidelines for dosing, but should never replace careful evaluation of the patient's response. In ambulatory patients, it is usually best to obtain AED concentrations immediately before a dose, preferably the first morning dose. Sufficient time should have elapsed for the AED to be at steady state when a concentration is measured. In acute care, concentrations may be measured more frequently to ensure proper dosing and check for alterations in AED pharmacokinetics (eg, altered protein binding, poor oral absorption, increased metabolism).

▶ *Drug Interactions*

LO 9

AEDs are associated with many different drug interactions.[32–35] Most interactions occur due to alterations in absorption, metabolism, and protein binding. Tube feedings and antacids are known to reduce the absorption of phenytoin and carbamazepine. Phenytoin, carbamazepine, and phenobarbital are potent inducers of various CYP450 isoenzymes, increasing the clearance of other drugs metabolized through these pathways (Table 31–4). In contrast, valproate is a CYP450 and UDP-glucuronosyltransferase (UGT) isoenzyme inhibitor and reduces the clearance of some drugs. Phenytoin and valproate are highly protein bound and can be displaced when taken together or with other highly protein-bound drugs. For example, when phenytoin and valproate are taken together, there may be increased dose-related adverse effects within several hours of dosing. This can be avoided by staggering doses or giving smaller doses more frequently during the day. Whenever a change in a medication regimen occurs, drug interactions should be considered and appropriate adjustments in dose of AEDs be made.

▶ *Special Populations*

KEY CONCEPT Children and women with epilepsy have unique problems related to the use of AEDs. In children, developmental changes occur rapidly, and metabolic rates are greater than those seen in adults. When treating a child, it is imperative to control seizures as quickly as possible to avoid interference with development of the brain and cognition. AED doses are increased rapidly, and frequent changes in the regimen are made to maximize seizure control. Due to rapid metabolic rates seen in children, doses of AEDs are typically higher on a milligram per kilogram basis compared with adults, and serum concentrations are used more extensively to help ensure an adequate trial of a drug has been given.

For women, the treatment of epilepsy poses challenges, including teratogenicity, breastfeeding, interactions between AEDs and hormonal contraceptives, and reduced fertility.[36–38] Recommendations are developed for managing women of childbearing potential and who are pregnant (Table 31–5). Several AEDs are implicated in causing birth defects.[39] Neural tube defects (eg, spina bifida, microcephaly, anencephaly) are associated most commonly with valproate and possibly carbamazepine. Additionally, valproate is associated with impaired cognitive development in children born to women taking valproate during pregnancy. Use of valproate should be

Table 31–4

Cytochrome P450 and AED Interactions

Enzyme	Substrate	Common Inducers	Common Inhibitors
CYP 1A2	Carbamazepine Perampanel	Carbamazepine Phenytoin Phenobarbital Rifampin	Cimetidine Ciprofloxacin Erythromycin Clarithromycin
CYP 2C9	Brivaracetam Phenobarbital[a] Phenytoin[a] Carbamazepine Valproate	Carbamazepine Phenytoin Phenobarbital Rifampin	Amiodarone Cimetidine Fluconazole Valproate
CYP 2C19	Brivaracetam[a] Phenobarbital Phenytoin Valproate Lacosamide		Felbamate Omeprazole Ticlopidine Topiramate Zonisamide
CYP 2D6	Zonisamide	Carbamazepine	
CYP 3A4	Carbamazepine[a] Perampanel[a] Tiagabine[a] Zonisamide[a]	Carbamazepine Phenytoin Phenobarbital Rifampin	Amiodarone Erythromycin Ketoconazole
Uridine diphosphate glucuronyl-transferase	Lamotrigine[a] Carbamazepine Valproate	Lamotrigine Phenobarbital Phenytoin Hormonal contraceptives	Valproate

[a]Primary route of metabolism.

avoided, if possible, in women of childbearing potential. All women of childbearing potential who take AEDs should take 1 to 4 mg daily of supplemental folic acid to reduce the risk of birth defects. Many AEDs are excreted in breast milk. However, infants were exposed to higher concentrations of AED in utero, so it is unclear if drugs in breast milk are harmful to the child. Decisions about breastfeeding are made on an individual basis.

Many AEDs induce hepatic microsomal enzyme systems and reduce the effectiveness of hormonal contraceptives. Women taking AEDs that may reduce the effectiveness of hormonal contraceptives should also use other forms of birth control. In contrast to these interactions, hormonal contraceptives induce glucuronidation of lamotrigine and valproate, and cause reductions in serum concentrations of these drugs during days of the cycle when hormones are taken; serum concentrations increase during days when hormones are not taken. Serum concentrations of many AEDs drop during pregnancy and dose increases based on frequent serum concentration monitoring is necessary. Due to induction or inhibition of sex hormone metabolism and changes in binding of hormones to sex hormone-binding globulin, some AEDs reduce fertility. Valproate has been associated with a drug-induced polycystic ovarian syndrome.

Table 31–5

Management of AEDs During Pregnancy

- Give supplemental folic acid 1–4 mg daily to all women of childbearing potential
- Use monotherapy whenever possible
- Use lowest doses that control seizures
- Continue pharmacotherapy that best controls seizures prior to pregnancy
- Monitor AED serum concentrations at start of pregnancy and monthly thereafter
- Adjust AED doses to maintain baseline serum concentrations
- Administer supplemental vitamin K during eighth month of pregnancy to women receiving enzyme-inducing AEDs
- Monitor postpartum AED serum concentrations to guide adjustments of drug doses
- Avoid valproate, if possible

Patient Encounter 3: Pregnancy

TC is a 22-year-old woman with epilepsy who comes to clinic for a routine visit. Her medications consist of oxcarbazepine and nonprescription antihistamines. She is sexually active and asks about birth control and concerns about becoming pregnant. Her seizures are well controlled and overall she is in good health.

What advice should be given regarding birth control?

What is the risk of birth defects if she gets pregnant while taking AEDs?

What can be done to limit the risk of birth defects?

What AEDs should generally be avoided in women of childbearing potential?

How should oxcarbazepine be managed when she becomes pregnant and after delivery?

Patient Encounter 4: Seizures in Older Adults

WB is a 78-year-old man who had several seizures after a stroke 2 years ago. He was started on levetiracetam at that time and continues to take it. His MRI is consistent with an old stroke and his EEG is reported as normal.

Should pharmacotherapy be continued in this patient?

If pharmacotherapy is discontinued, how should it be stopped?

How should the efficacy and toxicity be monitored in this patient?

Women who experience difficulties with fertility should seek the advice of health care professionals with expertise in fertility.

KEY CONCEPT Older adults have the highest incidence of newly diagnosed epilepsy and face unique challenges in treatment. The highest incidence of seizures and epilepsy is in individuals older than 65 years. Cerebrovascular disease, tumors, trauma, and neurodegenerative diseases are the primary causes of epilepsy in this age group. Diagnosis of epilepsy in older adults is difficult. This is due to the subtle symptoms of seizures, often compromised memory in the elderly, and the fact that many elderly live alone. Carbamazepine, lamotrigine, levetiracetam, topiramate, and gabapentin are effective in controlling seizures in older adults. Elderly patients are more sensitive to adverse events, so smaller doses tend to be used in this age group. Additionally, patients in this age group are at a greater risk for drug interactions due to the likelihood they are taking concomitant medications for other disease states.

OUTCOME EVALUATION

LO 10

KEY CONCEPT Patients receiving AEDs for seizures should be instructed on and have regular monitoring for seizure frequency, seizure patterns, acute adverse effects, chronic adverse effects, comorbid conditions, and possible drug interactions.

Efficacy

- Seizure counts are the standard way to evaluate the efficacy of treatment.
- Encourage patients to keep a seizure calendar that notes the time and day a seizure occurs and the type of seizure. Compare seizure counts on a monthly basis to determine the level of seizure control.

Toxicity

- Monitor acute toxicity of AEDs at every clinic visit.
- Question patients about common adverse effects of the AEDs they are receiving. Weigh the impact of acute adverse effects against the extent of seizure control. If it is determined, the adverse effects negatively impact the patient more than the extent of seizure control benefits the patient, adjust the therapeutic regimen. Continuously monitor chronic adverse effects of AEDs.

Comorbid Conditions

Routinely evaluate patients for signs and symptoms of depression.

Patient Care Process

Collect Information:

- Description of seizure events
- EEG report
- Neuroimaging report
- Laboratory results (eg, serum chemistry, complete blood count, renal function, hepatic function, toxicology screen, AED serum concentrations)
- History of prematurity or difficult delivery at birth, febrile seizures, head injury, infections of the central nervous system
- Family history of seizures or other neurological disorders
- Medication history
- Adherence to medications
- Allergies
- Social history (eg, employment, driving, living situation, recreational activities)

Assess the Information:

- Type of seizure
- Risk of a recurrent seizure
- Impact of potential pharmacotherapy on lifestyle
- Ability to adhere to medication regimen
- Need for modifying lifestyle (eg, ability to drive, modifications at work, avoidance of recreational activities that could result in harm with a seizure)

Develop a Care Plan:

- Determine optimal goals of pharmacotherapy
- Select medication that is effective for the seizure type, and minimizes the risk of adverse effects that negatively impact the patient's lifestyle; evaluate the risk of important drug interactions
- Design a dosing schedule to optimize adherence
- Identify important patient education points (eg, driving, safety, pregnancy, birth control, adherence)

Implement the Care Plan:

- Select and initiate the best medication for the patient at an appropriate starting dose
- Provide a medication titration schedule, if needed
- Assist patient to determine the best ways to monitor efficacy (eg, seizure frequency and severity) and adverse events
- Instruct patient on important patient education points (eg, driving, safety, pregnancy, birth control, adherence)

Follow-up: Monitor and Evaluate:

- Seizure frequency and severity
- Adverse events (eg dose-related, idiosyncratic, chronic)
- Serum concentrations, when appropriate
- Possible drug interactions
- Adherence

Abbreviations Introduced in This Chapter

AAN	American Academy of Neurology
AED	Antiepileptic drug
CBC	Complete blood count
CNS	Central Nervous System
CYP	Cytochrome P 450
EEG	Electroencephalograph
GABA	γ-aminobutyric acid
HLA	Human leukocyte antigen
ILAE	International League Against Epilepsy
JME	Juvenile myoclonic epilepsy
LFT	Liver function tests
LGS	Lennox-Gastaut syndrome
MRI	Magnetic resonance imaging
MTLE	Mesial temporal lobe epilepsy
NICE	National Institute for Clinical Excellence in the United Kingdom
PDS	Paroxysmal depolarizing shift
SIGN	Scottish Intercollegiate Guidelines Network
SMEI	Severe myoclonic epilepsy in infancy
UGT	Uridine 5′-diphospho-glucuronosyltransferase

REFERENCES

1. Bell GS, Neligan A, Sander JW. An unknown quantity-the worldwide prevalence of epilepsy. Epilepsia. 2014;55(7):958–962.
2. Zack MM, Kobau R. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy—United States, 2015. MMWR Morb Mortal Wkly Rep. 2017;66:821–825.
3. Shamansky SL, Glaser GH. Socioeconomic characteristics of childhood seizure disorders in the New Haven area: an epidemiologic study. Epilepsia. 1979;20:457–474.
4. Driver Information by State. Epilepsy Foundation. Available from: https://www.epilepsy.com/driving-laws. Accessed May 15, 2018.
5. Selassie AW, Wilson DA, Martz GU, Smith GG, Wagner JL, Wannamaker BB. Epilepsy beyond seizure: a population-based study of comorbidities. Epilepsy Res. 2014;108:305–315.
6. Atkinson P, Das KB, Chin RFM, et al. Cognition in school-aged children with "active" epilepsy: a population-based study. J Clin Experiment Neuropsych. 2015;37(4):429–438.
7. Hermann LK, Welter E, Berg AT, Perzynski AT, Van Doren JR, Sajatovic M. Epilepsy misconceptions and stigma reduction: current status in Western countries. Epilepsy Behav. 2016;60(7):165–173.
8. Fiest KM, Sauro KM, Wiebe S, Kwon CS, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. Neurology. Jan 2017;88(3):296–303.
9. Benke TA, Brooks-Kayal AR. Experimental models of seizures and mechanisms of epileptogenesis. In: Wyllie E, ed. Wyllie's Treatment of Epilepsy Principles and Practice, 5th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2011.
10. Jefferys JGR, Jiruska P. Basic mechanisms of seizure generation. In: Osorio I, Zaveri JP, Frei MG, Arthers S, eds. Epilepsy: The Intersection of Neurosciences, Biology, Mathematics, Engineering, and Physics. Boca Raton, FL: CRC Press a Taylor and Francis Group; 2011.
11. Matsumura N, Nakaki T. Isobolographic analysis of the mechanisms of action of anticonvulsants from a combination effect. Eur J Pharmacol. 2014;741:237–246.
12. Jessberger S, Parent JM. Adult neurogenesis in epilepsy. In: Seki T, Sawamoto K, Parent JM, Alvarez-Buylia A, eds. Neurogenesis in the Adult Brain II. Tokyo: Springer; 2011.
13. Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. Epilepsia. 2014;55(40:475–482.
14. Tian N, Shaw EC, Zack MM, Kobau R, Dykstra H, Covington TM. Cause-specific mortality among children and young adults with epilepsy: results from the U.S. National Child Death Review Case Reporting System. Epilepsy Behav. 2015;45:31–34.
15. Hantus S. Idiopathic generalized epilepsy syndromes of childhood and adolescence. In: Wyllie E, ed. Wyllie's Treatment of Epilepsy Principles and Practice. 5th ed. Philadelphia, PA: Wolters Kluwer/ Lippincott Williams & Wilkins; 2011.
16. Galanopoulou AS, Moshé SL. Neonatal and infantile epilepsy: acquired and genetic models. Cold Spring Harb Perspect Med. 2015;6:a022707.
17. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):522–530.
18. Berg AT. Risk of recurrence after a first unprovoked seizure. Epilepsia. 2008;49(1):13–18.
19. Jobst BC, Cascino GD. Resective epilepsy surgery for drug resistant focal epilepsy. JAMA 2015;313(3):285–293.
20. Wheless JW. Vagus nerve stimulation therapy. In: Wyllie E, ed. The Treatment of Epilepsy. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
21. Nordli DR, DeVivo DC. The ketogenic diet. In: Wyllie E, ed. The Treatment of Epilepsy. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
22. Privitera MD. Clinical rules for phenytoin dosing. Ann Pharmacother. 1993;27(10):1169–1173.
23. Scottish Intercollegiate Guidelines Network. Diagnosis and Management of Epilepsy in Adults. Available from: http://www.sign.ac.uk/assets/sign143.pdf. Accessed May 15, 2018.
24. National Institute for Health and Care Excellence. Epilepsies: Diagnosis and Management Clinical guidelines CG 137. National Institute for Health and Care Excellence. Available from: https://www.nice.org.uk/guidance/cg137/chapter/Appendix-e-pharmacological-treatment. Accessed May 15, 2018.
25. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2005;62:1252–1260.
26. French JA, Kanner AM, Bautista J, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology; Quality Standards Subcommittee of the American Academy of Neurology; American Epilepsy Society. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2005;62:1261–1273.
27. Shen C, Chen F, Zhang Y, Guo Y, Ding M. Association between use of antiepileptic drugs and fracture risk: a systematic review and meta-analysis. Bone. 2014;64:246–253.
28. Petty SJ, Wilding H, Wark JD. Oseoporosis associated with epilepsy and the use of anti-epileptics—a review. Curr Ostoeporos Rep. 2016;14:54–65.
29. van Ool JS, Snoeijen-Schouwenaars FM, Schelhaas HJ, Tan IY, Aldenkamp AP, Hendriksen JGM. A systematic review of neuropsychiatric comorbidities in patients with both epilepsy and intellectual disability. Epiepsy Behav. 2016;60:130–137.
30. Schmidt D, Loscher W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. Acta Neurol Scand. 2005;111(5):291–300.

31. Tsur VG, O'Dell C, Shinnar S. Initiation and discontinuation of antiepileptic drugs. In: Wyllie E, ed. The Treatment of Epilepsy. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
32. Zaccara G, Perucea E. Interactions between antiepileptic drugs and between antiepileptic drugs and other drugs. Epielptic Disord. 2014;16(4):409–431.
33. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)-part 1: pharmacokinetic and pharmacodynamics interactions between AEDs. Clin Pharmacokinet. 2013;52(11): 927–966.
34. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs)-part 2: pharmacokinetic and pharmacynamic interactions between AEDs and drugs used to treat non-epilepsy disorders. Clin Pharmaokinet. 2013;52(12):1045–1061.
35. Loddenkemper T, Glauser TA, Morita DA. Pharmacogenetics of antiepileptic medications. In: Wyllie E, ed. The Treatment of Epilepsy. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
36. Harden CL, Hopp J, Ting TY, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73:126–132.
37. Harden CL, Pennell PB, Koppel BS, et al. Practice parameter update: management issues for women with epileps—focus on pregnancy (an evidence-based review: vitamin K, folic acid, blood levels, and breatsfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73:142–149.
38. Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73:133–141.

32 Status Epilepticus

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LEARNING OBJECTIVES

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

1. Describe the pathophysiology of status epilepticus.
2. Explain the urgency of diagnosis and treatment of status epilepticus.
3. Recognize the signs and symptoms of status epilepticus.
4. Identify the treatment goals for a patient in status epilepticus.
5. Formulate an initial treatment strategy for a patient in generalized convulsive status epilepticus.
6. Compare the pharmacotherapeutic options for refractory status epilepticus.
7. Describe adverse drug events associated with the pharmacotherapy of status epilepticus.
8. Recommend monitoring parameters for a patient in status epilepticus.

INTRODUCTION

KEY CONCEPT **Status epilepticus** (SE) is a neurologic emergency that can lead to permanent brain damage or death. KEY CONCEPT SE is defined as continuous seizure activity lasting more than 5 minutes or two or more seizures without complete recovery of consciousness.[1] Refractory status epilepticus (RSE) is unresponsive to emergent (first-line) or urgent (second-line) therapy.

SE can present as nonconvulsive status epilepticus (NCSE) or generalized convulsive status epilepticus (GCSE). NCSE is characterized by persistent impaired consciousness without clinical seizure activity and is diagnosed with **electroencephalography** (EEG). GCSE is characterized by full-body motor seizures and involves the entire brain.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of SE in the United States is 12.5/100,000/year, with an in-hospital mortality rate of 9.2%,[2] and an estimated annual direct cost for inpatient admissions of $4 billion.[3] It occurs most frequently in males, African Americans, children, and the elderly.

KEY CONCEPT It is important to evaluate etiologies of SE for timely and optimal seizure control. Causes of SE include metabolic disturbances (eg, hyponatremia, hypernatremia, hyperkalemia, hypocalcemia, hypomagnesemia, hypoglycemia); central nervous system (CNS) disorders, infections, injuries; **hypoxia**; and drug toxicity (eg, theophylline, isoniazid, cyclosporine, cocaine). Chronic causes of SE include preexisting **epilepsy**, chronic alcoholism (withdrawal seizures), CNS tumors, and strokes.[4] In epileptics, the common causes of SE are anticonvulsant withdrawal or subtherapeutic levels.

PATHOPHYSIOLOGY

LO 1 Status epilepticus occurs when the brain fails to stop isolated seizures, due to a mismatch of neurotransmitters. **Glutamate**, the primary excitatory neurotransmitter, stimulates postsynaptic *N*-methyl-D-aspartate (NMDA) receptors, causing neuronal depolarization. Sustained depolarization causes neuronal injury and death.[5] The primary inhibitory neurotransmitter, **γ-aminobutyric acid** (GABA), opposes excitation by stimulating $GABA_A$ receptors, producing hyperpolarization and inhibition of the postsynaptic cell membrane. GABA-mediated inhibition diminishes with continuous seizure activity, causing a decreased response to GABA-receptor agonists.[6] Seizures lasting more than 30 minutes cause significant injury and neuronal loss because of excessive electrical activity and cerebral metabolic demand. Decreased $GABA_A$-receptor response and increasing neuronal injury with prolongation of seizure activity necessitates rapid control of SE.

LO 2

Systemic changes appear in two phases during SE. Phase I occurs during the first 30 minutes, and phase II occurs after 30 to 60 minutes.[7]

Phase I

LO 3 During phase I, autonomic activity increases, resulting in hypertension, tachycardia, hyperglycemia, hyperthermia, sweating, and salivation. Cerebral blood flow increases to preserve oxygen supply to the brain. Increases in sympathetic and parasympathetic stimulation with muscle hypoxia can cause ventricular arrhythmias, severe acidosis, and rhabdomyolysis which can lead to hypotension, shock, hyperkalemia, and acute kidney injury.

Phase II

After 30 to 60 minutes of continuous seizure activity, loss of cerebral autoregulation, decreased cerebral blood flow, increased intracranial pressure (ICP), and systemic hypotension occur. LO 7 Cerebral metabolic demand remains high; however, the body is unable to compensate, resulting in hypoglycemia, hyperthermia, respiratory failure, hypoxia, respiratory and metabolic acidosis, hyperkalemia, hyponatremia, and uremia. Motor activity may not be clinically evident during prolonged seizures, but electrical activity may still exist (ie, NCSE) requiring prompt recognition and aggressive treatment.

Patient Encounter 1, Part 1

A 79-year-old woman with a history of hypertension, diabetes, and arthritis was admitted with traumatic subdural hematoma after falling down a flight of stairs. She underwent surgery 2 days ago to evacuate the hematoma and is currently recovering in the intensive care unit (ICU). She was started on fosphenytoin for seizure prophylaxis upon admission along with her home medications. She has only one peripheral IV line and has very poor vascular access. Her nurse reports that a few minutes ago, she was alert and awake, but now she is unarousable and is having jerky, convulsive movements on both sides of her body. The doctor evaluates her and the jerky activity stops, but then starts again about 1 minute later. She never regained consciousness between these episodes. Her diagnosis is status epilepticus. Ht 165 cm (5'5"), Wt 147 kg (323 lbs).

What initial assessments should be performed?

What are some possible etiologies for her seizure?

What nonpharmacologic interventions are needed at this time?

CLINICAL PRESENTATION AND DIAGNOSIS

History

KEY CONCEPT When a patient presents with seizures, a thorough history is needed to determine the type and duration of previous seizure activity. This will help guide therapy and clarify necessary laboratory and diagnostic tests. Emergent treatment should not be delayed if seizure activity is diagnosed or is suspected based on the patient's family or emergency response personnel.

Physical Examination

Once clinical seizures are halted, a neurologic examination should evaluate the level of consciousness (coma, lethargy, or somnolence), motor function and reflexes (rhythmic contractions, rigidity, spasms, or posturing), and pupillary response. A physical examination can identify secondary injuries.

Clinical Symptoms

LO 3

Patients with SE usually present with generalized, convulsive, tonic-clonic seizures. They may also be hypertensive, tachycardic, febrile, and diaphoretic which resolve after seizure termination. A loss of bowel or bladder function, respiratory compromise, and nystagmus may also be observed. When seizure activity exceeds 30 to 60 minutes, muscle contractions may no longer be visible, necessitating an EEG to diagnosis SE. Twitching of the face, hands, or feet may be seen in these comatose patients with prolonged seizures.

Laboratory Parameters

KEY CONCEPT It is important to obtain a serum chemistry profile to help identify possible causes of SE, such as hypoglycemia, hyponatremia or hypernatremia, hypomagnesemia, and hypocalcemia; patients with renal and liver failure are at high risk as well. In febrile patients with elevated white blood count (WBC) counts, active infections should be considered and treated appropriately. Cultures from the blood, cerebrospinal fluid (CSF), respiratory tract, and urine should be collected once seizures are controlled. Computed tomography (CT) or magnetic resonance imaging (MRI) can rule out CNS abscesses, bleeding, or tumors, all of which may be a source of seizures. Order a blood alcohol level and urine toxicology screen to determine if SE is caused by alcohol withdrawal, illicit drug use, or a drug overdose. Serum drug levels should be obtained in an overdose situation to rule out toxicity. KEY CONCEPT Knowing the cause of SE will guide initial antiepileptic therapy and increase the probability of seizure termination.

In patients taking anticonvulsants, a baseline serum concentration can help determine if the concentration is below the desired range and whether a loading dose (LD) is needed. Albumin levels, and renal and liver function tests should also be utilized to assess therapy.

Hypoxia and respiratory or metabolic acidosis are common in patients with SE. Pulse oximetry and arterial blood gas (ABG) measurements are used to assess pulmonary status and determine the need for protection or supplemental oxygen. Metabolic acidosis may resolve without treatment after termination of clinical seizures.

Clinical Presentation of Status Epilepticus

General

- The patient may present with or without clinically noticeable seizures.

Symptoms

- Impaired consciousness, from lethargy to coma
- Disorientation after GCSE cessation
- Pain from associated injuries (eg, tongue lacerations, dislocated shoulder, head/facial trauma)

Signs

Phase I (≤ 30 minutes of SE):
Generalized convulsions
Hypertension, tachycardia
Fever and sweating
Muscle contractions, spasms
Respiratory compromise
Incontinence

Phase II (> 30 minutes of SE):
Respiratory failure with pulmonary edema
Cardiac failure (arrhythmias, shock)
Hypotension
Hyperthermia
Rhabdomyolysis and multiorgan failure

Laboratory Tests

- Hyperglycemia (phase I) and hypoglycemia (phase II) can occur
- Hyponatremia, hypernatremia, hyperkalemia, hypocalcemia, hypomagnesemia, and hypoglycemia can cause SE
- The white blood cell (WBC) count may slightly increase
- Abnormal arterial blood gases (ABGs) due to hypoxia and respiratory or metabolic acidosis
- Elevated serum creatinine will be present in renal failure patients
- Myoglobinuria can occur in patients with continuous seizures

Diagnostic Tests

EEG to confirm seizure activity

CT or MRI may reveal mass lesions or hemorrhage

Diagnostic Tests

EEG is required to identify SE in a comatose patient. Continuous EEG monitoring should be used in patients who remain unconscious after initial antiepileptic treatment, those receiving long-acting paralytic agents, or those requiring prolonged RSE therapy. Treatment should not be delayed while awaiting EEG results. CT and MRI scans are useful to identify traumatic injury, mass lesions, or evidence of infection as the cause of SE.

TREATMENT

Desired Outcomes

LO 4

KEY CONCEPT The goal of therapy is to terminate physical and electroencephalographic evidence of seizures, prevent recurrence, and minimize adverse drug events. Poor outcomes are associated with prolonged SE and refractory SE.[8] Complications of SE should also be treated.

General Approach

LO 5

The initial approach to SE involves removing the patient from harmful surroundings and ensuring maintenance of airway, breathing, and circulation. Benzodiazepines are the preferred initial drugs to stop acute seizure activity (emergent therapy), followed by an anticonvulsant (urgent therapy) for suppression of seizures. Medications are given intravenously (IV) for immediate onset of action, but if IV access is not available, select medications may be given rectally, intramuscularly (IM), buccally, or nasally. After seizures stop, clinicians must identify and treat underlying causes of the seizures, such as toxins, hypoglycemia, or brain injury. Patients with known seizure disorders should be evaluated for abrupt cessation of their medications, noncompliance, or drug interactions. Recent guidelines provide treatment algorithms for SE.[1,9]

Nonpharmacologic Treatment

Oxygen administration or intubation for mechanical ventilation should be performed in cases of hypoxia, and temperature management should be considered for febrile seizures. Specialists in neurology or epileptology should be consulted as appropriate. Admission to an intensive care unit (ICU) allows for aggressive treatment and monitoring.

Pharmacologic Treatment

▶ *Initial Treatment*

Hypoglycemia-induced SE is treated with IV dextrose. IV thiamine is given to alcoholics prior to administering any dextrose-containing solutions to prevent encephalopathy.

▶ *Benzodiazepines*

LO 5

KEY CONCEPT Initial or emergent drug therapy begins with IV administration of a benzodiazepine. This class of agents is highly effective in terminating seizures.[10,11] Intravenous bolus doses of diazepam, lorazepam, and midazolam have been used in SE because of their rapid effects on GABA receptors. Lorazepam is the preferred agent of most clinicians. When treating patients on chronic benzodiazepine therapy, consider using higher doses to overcome tolerance. Diazepam and lorazepam should be diluted 1:1 with normal saline before parenteral administration via peripheral veins to avoid vascular irritation from the propylene glycol diluent.

Diazepam Being extremely lipophilic, diazepam penetrates the CNS quickly, but rapidly redistributes into body fat and muscle. This results in a rapid decline in CNS levels and early recurrence of seizures. Doses can be given every 5 minutes until seizure activity stops or toxicities are seen (eg, respiratory depression). Diazepam can be administered as a rectal gel enabling nonmedical personnel to provide timely therapy at home or in public areas.[12] IM administration of diazepam is not recommended because of erratic absorption.

Lorazepam Less lipophilic than diazepam, lorazepam has a longer redistribution half-life, resulting in longer duration of action and decreased need for repeated doses. Both lorazepam and diazepam are effective in stopping seizures,[13] but lorazepam is currently preferred due to a longer duration of action. It can be redosed every 5 to 10 minutes (up to a maximum cumulative dose of 8 mg) until seizure activity stops or side effects such as respiratory depression occur. IM administration is not preferred due to slow and unpredictable absorption.

Midazolam Midazolam is water-soluble and can be administered intramuscularly,[14] buccally,[15,16] and nasally.[17,18] Compared to diazepam and lorazepam, it has less respiratory

Patient Encounter 1, Part 2

Physical examination, chart review, and recent laboratory studies reveal the following information:

PE:

VS: BP 178/92 mm Hg, HR 109 beats/min, RR 26 breaths/min, T 39.0°C (102.2°F)

CNS: Unresponsive, unarousable

CV: Sinus tachycardia; normal S1, S2; no murmurs, rubs, gallops

Pulm: Tachypneic; oxygen saturation 88% (0.88) on room air; no rhonchi, wheezes, rales

Abd: Deferred

Exts: Rhythmic tonic-clonic movements of all extremities

GU: Incontinent of urine and stool

HEENT: Persistent upward gaze

Current Medications: Fosphenytoin 100 mg PE IV every 8 hours; Famotidine 20 mg IV every 12 hours; Metoprolol 50 mg PO every 12 hours; Insulin glargine 25 units SQ at bedtime; Insulin aspart 5 units SQ with meals; Acetaminophen/hydrocodone 325 mg/5 mg tablet PO; Every 4 hours as needed for pain; Morphine 2 mg IVP every 2 hours as needed for pain

Labs: Sodium 129 mEq/L (mmol/L), potassium 4.1 mEq/L (mmol/L), phenytoin 2.7 mcg/mL (11 µmol/L), albumin 3.5 g/dL (35 g/L), chloride 105 mEq/L (mmol/L), carbon dioxide 12 mEq/L (mmol/L), blood urea nitrogen 10 mg/dL (3.6 mmol/L), serum creatinine 0.9 mg/dL (80 µmol/L), glucose 54 mg/dL (3.0 mmol/L); WBC $15 \times 10^3/mm^3$ ($15 \times 10^9/L$), hemoglobin 9.6 g/dL (96 g/L or 5.96 mmol/L), hematocrit 28% (0.28 volume fraction), platelets $235 \times 10^3/mm^3$ ($235 \times 10^9/L$), prothrombin time 12 seconds; international normalized ratio 1.1, activated partial thromboplastin time 28 seconds.

What is your assessment of the cause of this patient's condition?

What pharmacologic interventions are needed at this time?

Identify goals of therapy for this patient.

What therapies must be instituted next?

and cardiovascular side effects. Its short half-life requires that it be redosed frequently or administered as a continuous IV infusion. Liquid or injectable formulations can be given buccally or intranasally (0.3 mg/kg) in pediatric patients. Rapid breathing and increased secretions can interfere with nasal administration. A recent study in adults and children showed that IM midazolam was as safe and effective as IV lorazepam for prehospital termination of seizures.[18]

▶ *Anticonvulsants*

LO 5 KEY CONCEPT After administering the first dose of benzodiazepine, an anticonvulsant such as phenytoin, valproate sodium, or phenobarbital should be started to prevent further seizures (urgent therapy). Anticonvulsants must not be given as first-line therapy since they are infused relatively slowly to avoid adverse effects, delaying their onset of action. If the underlying cause of the seizures has been corrected (eg, hypoglycemia) and seizure activity has ceased, an anticonvulsant may be unnecessary. This may be reasonable when patients become alert and oriented or if an EEG confirms absence of seizure activity.

After the LD of the anticonvulsant is administered, maintenance doses should be initiated to ensure that therapeutic levels are sustained. Chronic and idiosyncratic side effects and potential drug interactions should be considered if the patient continues anticonvulsant therapy. Drugs should be adjusted for any hepatic or renal dysfunction. Table 32–1 summarizes the doses used in SE, and Table 32–2 is an example algorithm for treatment of patients in SE.

Phenytoin The most widely used anticonvulsant for urgent treatment of SE is phenytoin. It is available in its original form or as a prodrug, fosphenytoin, which is the most commonly used dosage form. Doses are infused no faster than 50 mg/min due to risks of hypotension or arrhythmias. Continuous monitoring of electrocardiogram (ECG) and blood pressure is recommended. Maintenance doses can be started 12 hours after the LD. Phenytoin should not be infused with other medications because of stability concerns (it is soluble in propylene glycol and compatible only in 0.9% sodium chloride solutions). It should not be given IM due to its alkalinity.

LO 7

Patient Encounter 2, Part 1

A 19-year-old man admitted for two reported episodes of intermittent jerking in his left arm that were witnessed by his mother this morning. He is nonresponsive at the time of these episodes and does not remember anything during that period of time. He does not take any medications and has no drug allergies. One week ago, he was seen in the emergency department for confusion and difficulty walking after being hit in the head with a soccer ball. At that time, a head CT scan showed no hemorrhage and he was diagnosed with a mild traumatic brain injury. While the nurse is taking his vital signs, he becomes confused and then unarousable with jerky movements on the left side of his body. His diagnosis is status epilepticus after this seizure activity does not stop over the next 5 minutes.

VS: BP 111/75 mm Hg, HR 108 beats/min, RR 21 breaths/min, T 37.0°C (98.6°F), Wt 68 kg (150 lb), Ht 178 cm (5′10″).

What is the most likely cause of this patient's SE?

What are possible treatment options at this time?

How would you optimize his outcome?

LO 7 **Extravasation** of phenytoin can cause local tissue discoloration, edema, pain, and sometimes necrosis (purple glove syndrome). Oral loading is not recommended due to the limitations of single dose absorption (ie, doses > 400 mg are not fully absorbed) and delayed peak concentrations when given orally. Obese patients require larger LDs due to a larger volume of distribution (V_d).[19] A dosing weight (DW) can be calculated using total body weight (TBW) and ideal body weight (IBW): DW = IBW + 1.33(TBW – IBW). V_d can be calculated as follows: V_d = 0.7 L/kg × DW (in kg). An LD can then be calculated using V_d and a target concentration: LD = $C_{target} \times V_d$.

Fosphenytoin Fosphenytoin is a water-soluble, phosphoester prodrug that is rapidly converted to phenytoin in the body. It is compatible with most IV solutions. It is dosed in phenytoin equivalents (PEs), and it can be infused up to 150 mg PE/min. Although it has fewer cardiovascular side effects than phenytoin, clinicians should continuously monitor blood pressure, ECG, and heart rate. **Paresthesias**, especially around the lips and groin, are common, but typically resolve within a few minutes and should not necessitate stopping the infusion. If a postload serum level is desired, it should be obtained 2 hours after an IV load; if subtherapeutic, an LD is indicated.

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Valproate Sodium Valproate sodium has been successfully used IV in various types of SE including generalized tonic-clonic, myoclonic, and NCSE.[20] It is particularly useful in patients with cardiorespiratory compromise and/or those allergic to phenytoin and phenobarbital.[21]

Phenobarbital If phenytoin or valproate sodium fails to prevent seizure recurrence, phenobarbital can be considered. However, emerging evidence suggests that phenobarbital may not be effective if SE persists despite benzodiazepines and phenytoin. This may be due to progressive resistance of the $GABA_A$ receptor, where barbiturates also act.[22] Adverse reactions of phenobarbital include sedation, hypotension, and respiratory depression; therefore, patients receiving a rapid IV LD of phenobarbital should have hemodynamic monitoring and be mechanically ventilated if at high risk of respiratory compromise. Its long half-life makes it a popular agent for both acute treatment and chronic maintenance therapy or as adjunct therapy to prevent withdrawal seizures when weaning refractory SE patients off pentobarbital infusions.

LO 7

Treatment of Refractory Status Epilepticus

KEY CONCEPT Seizure activity unresponsive to emergent and urgent therapy is considered RSE.[23] Refractory SE can occur in up to 30% of patients with SE and has a mortality rate approaching 50%. Patients in RSE are unlikely to regain independent function, even if seizures are controlled. Clinical signs may become subtle and an EEG may be required to detect ongoing seizure activity. KEY CONCEPT Even SE patients without clinical signs of seizing are at risk for brain damage or death.

LO 8

Optimal therapy for RSE is undetermined.[24] Clinicians must aggressively investigate and treat possible causes including infection, tumors, drugs or toxins, metabolic disorders, liver failure, or fever. In general, patients with RSE are managed in an ICU with hemodynamic and respiratory support and frequent monitoring. Continuous EEG monitoring is essential and should not be delayed. Any anticonvulsants initiated before treatment for RSE should be continued, and their serum levels optimized to prevent breakthrough or withdrawal seizures. KEY CONCEPT Treatment of RSE consists of intensive monitoring, supportive care, and a continuous intravenous infusion of midazolam, propofol, or pentobarbital to suppress clinical and EEG evidence

LO 6

Table 32–1

Medications Used in Adult Status Epilepticus

Drug Name (Brand Name)	Loading Dose and RSE Maintenance Dose (If Applicable)	Administration Rate	Therapeutic Level	Side Effects	Comments
Diazepam (Valium)	0.15 mg/kg (up to 10 mg per dose); may repeat in 5 minutes	5 mg/min (IVP)	N/A	Hypotension, respiratory depression	Rapid redistribution rate; can be given rectally
Lorazepam (Ativan)	0.1 mg/kg (up to 4 mg per dose); repeat in 5–10 minutes	2 mg/min (IVP)	N/A	Hypotension, respiratory depression	May be longer acting than diazepam
Midazolam (Versed)	0.2 mg/kg IM up to 10 mg per dose RSE: 0.2 mg/kg (2 mg/min) IV then 0.05–2 mg/kg/hour		N/A	Sedation, respiratory depression	Can also be given buccally, intranasally
Phenytoin (Dilantin)	20 mg/kg	Up to 50 mg/min	Total phenytoin level: 10–20 mcg/mL (mg/L; 40–79 µmol/L) Free phenytoin level: 1–2 mcg/mL (mg/L; 4–8 µmol/L)	Arrhythmias, hypotension	Hypotension, especially in older adults
Fosphenytoin (Cerebyx)	20 mg PE/kg	Up to 150 mg PE/min	Total phenytoin level: 10–20 mcg/mL (mg/L; 40–79 µmol/L) Free phenytoin level: 1–2 mcg/mL (mg/L; 4–8 µmol/L)	Paresthesias, hypotension	Less CV adverse effects than phenytoin
Phenobarbital (Luminal)	20 mg/kg	50–100 mg/min	15–40 mcg/mL (mg/L; 65–172 µmol/L)	Hypotension, sedation, respiratory depression	Long-acting
Valproate sodium (Depacon)	20–40 mg/kg	3–6 mg/kg/min	50–150 mcg/mL (mg/L; 347–1040 µmol/L)		Less CV adverse effects than phenytoin
Levetiracetam (Keppra)	1000–3000 mg IV or 60 mg/kg (max 4500 mg)	2–5 mg/kg/min			Minimal drug interactions
Lacosamide (Vimpat)	200–400 mg IV	Over 15 minutes		PR prolongation, hypotension	
Topiramate (Topamax)	200–400 mg NG/PO every 6 hours		2–20 mcg/mL (mg/L; 6–59 µmol/L)	Metabolic acidosis	
Propofol (Diprivan)	Bolus: 1–2 mg/kg RSE: 30–250 mcg/kg/min	Approximately 40 mg every 10 seconds	N/A (typically titrated to EEG)	Hypotension, respiratory depression, PRIS	Requires mechanical intubation; high lipid load (increased calories)
Pentobarbital (Nembutal)	Bolus: 10–15 mg/kg RSE: 0.5–4 mg/kg/hour	Up to 50 mg/min	10–20 mcg/mL (mg/L; 44–89 µmol/L) (typically titrated to EEG)	Hypotension, respiratory depression, cardiac depression, infection, ileus	Requires mechanical intubation, vasopressors, hemodynamic monitoring
Ketamine (Ketalar)	RSE: 0.5–4.5 mg/kg IV bolus, then infusion up to 5 mg/kg/hour		N/A	Hypertension, arrhythmias	Associated cerebral atrophy

CV, cardiovascular; EEG, electroencephalogram; IM, intramuscular; IV, intravenous; IVP, intravenous push; N/A, not applicable; NG, nasogastric; PE, phenytoin equivalents; PO, by mouth; PR, per rectum; PRIS, propofol-related infusion syndrome; RSE, refractory status epilepticus.

LO 8

of seizures (Tables 32–1 and 32–2).[25] These agents are typically titrated to achieve **burst suppression** on the EEG, although this practice lacks strong evidence. Patients should be intubated and mechanically ventilated before initiating treatment for RSE. Seizure control per EEG should be maintained for 24 to 48 hours before considering tapering therapy. Consultation with neurologists or epileptologists is highly recommended.

▶ *Midazolam*

Midazolam infusions must be adjusted, especially in patients with renal impairment, as the active metabolite can accumulate.[26] Breakthrough seizures are common with midazolam infusions and usually respond to boluses and a 20% increase in infusion rate. Despite this, tachyphylaxis can occur, and patients should be switched to another agent if seizures continue.

Table 32–2

Algorithm for Treatment of Status Epilepticus in Adult

Time (minutes)	Assessment/Monitoring	Treatment
0	Vital signs (HR, RR, BP, T) Assess airway Monitor cardiac function (ECG) Pulse oximeter Check blood glucose Check laboratory tests: complete blood count, serum chemistries, liver function tests, arterial blood gas, blood cultures, serum anticonvulsant levels, urine drug/alcohol screen	Stabilize airway (intubate if necessary) Administer oxygen Secure IV access and start fluids Give IV thiamine (100 mg), then IV dextrose (50 mL of 50% solution) if hypoglycemic
0–10	Vital signs Physical examination Patient history including medications (prescription, OTC, and herbals)	Lorazepam 0.1 mg/kg (maximum 4 mg) IVP at 2 mg/min (may repeat in 5–10 minutes to maximum of 8 mg if no response) If no IV access, can give: diazepam 10 mg PR (may repeat in 10 minutes if no response); midazolam 0.2 mg/kg IM (maximum 10 mg; may repeat in 10 minutes if no response) Anticonvulsant may not be necessary if underlying cause is corrected and seizures have ceased
10–20	Vital signs Review laboratory results and correct any underlying abnormalities CT scan (if seizures controlled)	Phenytoin 15–20 mg/kg IV at a maximum rate of 50 mg/min (or fosphenytoin 15–20 mg PE/kg IV at a maximum rate of 150 mg PE/min) In patients allergic to phenytoin, give valproate sodium 20 mg/kg IV at a maximum rate of 6 mg/kg/min Treat for possible infection
20–30	Vital signs Consult neurologist/epileptologist Consider admission to ICU Consider EEG	If seizures continue: additional phenytoin bolus 5–10 mg/kg (or fosphenytoin 5–10 mg PE/kg) **OR** start phenobarbital at 20 mg/kg IV at a maximum rate of 100 mg/min **OR** start valproate sodium 20 mg/kg IV at a maximum rate of 6 mg/kg/min in patients who are not intubated
> 30–60 *refractory status epilepticus*	Vital signs Transfer to ICU Obtain EEG Consider MRI when controlled	Midazolam 0.2 mg/kg IV bolus followed by 0.05–2 mg/kg/hour CI **OR** propofol 1 mg/kg bolus followed by 30–250 mcg/kg/min CI **OR** pentobarbital 10–15 mg/kg bolus over 1–2 hours followed by 0.5–4 mg/kg/hour Consider intubation and/or vasopressor support if needed Optimize anticonvulsant levels: repeat boluses of phenobarbital 10 mg/kg **OR** valproate sodium 20 mg/kg at 6 mg/kg/min max
> 24 hours *super refractory status epilepticus*	Vital signs Continuous EEG	Optimize anticonvulsant therapy Consider ketamine infusion, immunomodulation (eg, steroids, IV immunoglobulin), inhaled anesthetics, ketogenic diet

BP, blood pressure; CI, continuous infusion; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalograph; HR, heart rate; ICU, intensive care unit; IM, intramuscular; IV, intravenous; IVP, intravenous push; MRI, magnetic resonance imaging; OTC, over the counter; PE, phenytoin equivalents; PR, per rectum; RR, respiratory rate; T, temperature.

Patient Encounter 2, Part 2

Over the next hour, he is treated with your recommendations for emergent and urgent treatment of SE as above. His jerky movements stopped, but he remains comatose.

VS: BP 95/62 mm Hg, HR 120 beats/min, RR 14 breaths/min, T 37.1°C (98.8°F)

A continuous EEG is started and reveals the patient is in SE.

What is your assessment of the patient's current condition?

What do you recommend for further nonpharmacologic and pharmacologic therapy?

How would you optimize his outcomes?

▶ *Propofol*

LDs of the anesthetic propofol can be given every 3 to 5 minutes until clinical response, after which an infusion can be initiated. Propofol causes hypotension, especially with LDs; therefore, some clinicians avoid LDs and quickly titrate with a continuous infusion. Long-term, high-dose (> 80 mcg/kg/min) propofol infusions are associated with rhabdomyolysis, acidosis, and cardiac arrhythmias (propofol-related infusion syndrome), especially in children.[27] It has a very short serum half-life and should be tapered off slowly to avoid withdrawal seizures. Propofol infusions are a source of calories (1 kcal/mL [4.2 kJ/mL]), so nutritional support must be adjusted accordingly.

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▶ *Pentobarbital*

Barbiturate infusions are reported to be highly effective in treating RSE[28] and decreasing elevated ICP, but they cause significant hypotension, myocardial and respiratory depression,

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ileus, and infections. Therefore, patients require mechanical ventilation and invasive hemodynamic monitoring. Patients often require IV vasopressor therapy and total parenteral nutrition.

LO 6 A meta-analysis reported a lower incidence of treatment failure with pentobarbital (3%) compared to midazolam (21%) or propofol (20%), although the risk of hypotension requiring vasopressor therapy was higher with pentobarbital.[28] This relative efficacy for pentobarbital must be considered together with its complications when determining which agent to use. Patients who fail midazolam and/or propofol should be switched to pentobarbital.

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▶ *Levetiracetam*

LO 6 Levetiracetam does not have the cardiopulmonary, hepatic, and sedative side effects seen with the other agents; nor does it have potentially harmful drug interactions. Both IV[29] and oral[30] formulations have been used in RSE patients as add-on therapy with some success, although it is unclear if levetiracetam would be effective as monotherapy.[31] LDs up to 2000 mg over 15 to 30 minutes in the critically ill have been given with very little toxicity.[32]

▶ *Other Agents*

Ketamine,[33] topiramate, and inhaled anesthetics have also been used for RSE. Ketamine is an NMDA receptor antagonist that has been given orally[34] and intravenously[35] for pediatric RSE. Topiramate is an oral anticonvulsant with multiple mechanisms of action in RSE. The oral dose in adults ranges from 300 to 1600 mg/day.[36] Children have also been administered topiramate at a starting dose of 2 to 3 mg/kg/day and titrated to a maintenance dose of 5 to 6 mg/kg/day.[16] Topiramate can induce metabolic acidosis, requiring careful monitoring. The inhaled anesthetics, desflurane and isoflurane,[37] require special equipment for administration in an ICU. Lacosamide, an enhancer of slow inhibition of sodium channels, has limited drug interactions.[38] It has been used orally[39] and intravenously[40] in the setting of refractory partial SE.

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Special Populations

Certain patients require special considerations due to their altered metabolism, unique volume of distribution, or increased risk for side effects.[41] Although many of these patients are excluded from clinical trials in SE, the standard algorithm for SE still applies in terms of immediate care, assessment, and drugs (see Table 32–2).

▶ *Pediatrics*

The treatment approach for SE in children is similar to that in adults with a few exceptions (see Table 32–3). The doses are also weight-based but are typically higher than those used in adults due to faster hepatic clearance. Timely IV access in children may be difficult, so alternate routes of administration have been used, including intranasal, buccal, rectal, and IM. Early administration of benzodiazepines and reduced time to hospital admission are important in decreasing prolonged seizures.[42]

▶ *Geriatrics*

Older adults are often vulnerable because of multiple disease states and polypharmacy. Seizures in older adults often arise from metabolic disorders, drug interactions, or incorrect dosing of medications in patients with impaired renal and hepatic function and decreased protein binding. Clinicians treating older adult patients with SE should investigate drug- and disease state–induced causes, since treating these etiologies alone may terminate seizures. Acute treatment with benzodiazepines and anticonvulsants is no different in older adults, but they may experience more profound sedative and cardiorespiratory side effects. Phenytoin/fosphenytoin LDs should be carefully calculated in older adults whose weights may be overestimated, and who may not tolerate high doses. They should also be infused more slowly to minimize hypotension and arrhythmias. Phenobarbital may cause respiratory depression earlier in older adults, especially after benzodiazepines. Clinicians should consider using smaller doses and evaluate for renal and hepatic insufficiency if repeated doses are to be given.

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Table 32–3

Medications Used in Pediatric Status Epilepticus

Drug	Dose	Comments
Diazepam (Valium injection, Diastat rectal gel)	IV: 0.2–0.3 mg/kg over 2–5 minutes	Maximum dose in children < 5 years: 5 mg Maximum dose in children > 5 years: 15 mg
	PR: 2–5 years: 0.5 mg/kg 6–11 years: 0.3 mg/kg > 12 years: 0.2 mg/kg	A second rectal dose can be given 4–12 hours after the first dose if necessary
Lorazepam (Ativan)	0.05–0.1 mg/kg IV over 2–4 minutes	May redose twice in 10–15 minutes if necessary
Midazolam (Versed)	0.2 mg/kg IV bolus followed by 0.05–0.6 mg/kg/hour continuous infusion	Bolus dose may also be given intranasally, buccally, or intramuscularly
Phenytoin (Dilantin)	15–20 mg/kg IV at 1–3 mg/kg/min *max*	
Fosphenytoin (Cerebyx)	15–20 mg PE/kg IV at 3 mg PE/kg/min *max*	
Phenobarbital (Luminal)	15–20 mg/kg IV at 100 mg/min *max*	
Levetiracetam (Keppra)	20–60 mg/kg IV at 2 mg/kg/min	Few drug interactions
Valproate sodium (Depacon)	15–20 mg/kg IV at 1.5–3 mg/kg/min	May have fewer cardiovascular side effects than other agents
Propofol (Diprivan)		Not recommended due to adverse events (eg, propofol-related infusion syndrome)
Pentobarbital (Nembutal)	10–15 mg/kg IV over 1–2 hours followed by continuous infusion at 1 mg/kg/hour	Titrated to EEG

EEG, electroencephalograph; IV, intravenous; PE phenytoin equivalent; PR, per rectum.

Patient Care Process

Collect Information:

- Review time of onset of seizure activity and past medical/surgical history.
- Obtain vital signs and relevant laboratory testing.
- Perform a medication history of prescription and nonprescription medications and identify medication allergies.
- Obtain patient weight.

Assess the Information:

- Determine airway patency, breathing status, and circulatory status.
- Determine precipitating factors or etiology of SE.
- Identify drug interactions.
- Assess efficacy of and adherence to anticonvulsants if appropriate.
- Review laboratory results for electrolyte and glucose abnormalities and anticonvulsant serum levels.

Develop a Care Plan:

- Correct reversible causes of SE.
- Select initial benzodiazepine agent and dose appropriate for patient based on access and vital signs.
- Select initial anticonvulsant for patient based on access and vital signs.
- If patient is taking anticonvulsants that can be monitored, evaluate for subtherapeutic serum levels and calculate appropriate LDs.

Implement the Care Plan:

- Administer therapeutic doses within the appropriate time frame (see Tables 32–1 and 32–2). Provide maintenance dosing of anticonvulsants when indicated.
- Identify potential drug interactions and adjust as needed.
- Obtain expertise of neurologist or epileptologist when appropriate.

Follow-up: Monitor and Evaluate:

- Determine if physical seizures have stopped and the patient regains consciousness. If not, consider continuous EEG monitoring for at least 24 to 48 hours to identify possible nonconvulsive SE.
- Obtain trough serum anticonvulsant levels at steady state, or sooner if seizures continue. Adjust anticonvulsants based on levels, maximizing seizure control and minimizing adverse effects.

▶ *Pregnancy*

The main concern in the treatment of pregnant females in SE is the safety of the fetus which is at risk of hypoxia during periods of prolonged seizures. Although many drugs used in SE are teratogenic, clinicians should still use them acutely to stop seizures, but consider alternative agents for maintenance therapy.[43] The volume of distribution and clearance of many drugs are increased during pregnancy, and this must be considered when calculating doses.

OUTCOME EVALUATION

Start pharmacologic treatment as soon as possible.

- First-line (emergent) treatment for SE should halt seizure activity within minutes of administration.
- In patients who are unarousable following treatment, confirm termination of seizures with an EEG.
- Perform a physical examination and evaluate laboratory results to help determine if the cause or complications of seizure activity are being appropriately treated.
- Once seizure activity has ceased and the patient has stabilized, review the patient's therapeutic regimen.
- Evaluate and monitor serum trough concentrations of anticonvulsants with defined target ranges to determine patient-specific therapeutic goals.
- In patients with RSE on multiple anticonvulsants, slowly decrease the dose of one drug at a time while continuing to evaluate the patient for seizure activity.
- Continue to monitor anticonvulsant serum trough concentrations approximately every 3 to 5 days until the anticonvulsants have reached steady-state concentrations.
- Monitor for signs of drug toxicity and seizures until drug concentrations have stabilized.
- Closely evaluate medication profiles, and change drugs or doses to minimize any drug interactions, if possible.

Abbreviations Introduced in This Chapter

ABG	Arterial blood gas
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
ECG	Electrocardiogram
EEG	Electroencephalography
GABA	γ-aminobutyric acid
GCSE	Generalized convulsive status epilepticus
ICP	Intracranial pressure
ICU	Intensive care unit
IM	Intramuscular
IV	Intravenous
LD	Loading dose
MRI	Magnetic resonance imaging
NCSE	Nonconvulsive status epilepticus
NMDA	*N*-methyl-D-aspartate
PE	Phenytoin equivalent
RSE	Refractory status epilepticus
SE	Status epilepticus
WBC	White blood cell

REFERENCES

1. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17:3–23.
2. Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care. 2014;20: 476–483.
3. Penberthy LT, Towne A, Garnett LK, Perlin JB, DeLorenzo RJ. Estimating the economic burden of status epilepticus to the health care system. Seizure. 2005;14:46–51.
4. Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med. 1998;338:970–976.
5. Wu YW, Shek DW, Garcia PA, Zhao S, Johnston SC. Incidence and mortality of generalized convulsive status epilepticus in California. Neurology. 2002;58:1070–1076.
6. Chen JW, Naylor DE, Wasterlain CG. Advances in the pathophysiology of status epilepticus. Acta Neurol Scand Suppl. 2007;186:7–15.
7. Huff JS, Fountain NB. Pathophysiology and definitions of seizures and status epilepticus. Emerg Med Clin North Am. 2011;29:1–13.
8. Legriel S, Azoulay E, Resche-Rigon M, et al. Functional outcome after convulsive status epilepticus. Crit Care Med. 2010;38:2295–2303.
9. Hirsch LJ, Gaspard N. Status epilepticus. Continuum (Minneap Minn). 2013;19:767–794.
10. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339:792–798.
11. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345:631–637.
12. Fitzgerald BJ, Okos AJ, Miller JW. Treatment of out-of-hospital status epilepticus with diazepam rectal gel. Seizure. 2003;12:52–55.
13. Cock HR, Schapira AH. A comparison of lorazepam and diazepam as initial therapy in convulsive status epilepticus. QJM. 2002;95:225–231.
14. Towne AR, DeLorenzo RJ. Use of intramuscular midazolam for status epilepticus. J Emerg Med. 1999;17:323–328.
15. Scott RC, Besag FM, Boyd SG, Berry D, Neville BG. Buccal absorption of midazolam: pharmacokinetics and EEG pharmacodynamics. Epilepsia. 1998;39:290–294.
16. Kahriman M, Minecan D, Kutluay E, Selwa L, Beydoun A. Efficacy of topiramate in children with refractory status epilepticus. Epilepsia. 2003;44:1353–1356.
17. Knoester PD, Jonker DM, Van Der Hoeven RT, et al. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. Br J Clin Pharmacol. 2002;53:501–507.
18. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012;366:591–600.
19. Abernethy DR, Greenblatt DJ. Phenytoin disposition in obesity. Determination of loading dose. Arch Neurol. 1985;42(5): 468–471.
20. Limdi NA, Shimpi AV, Faught E, Gomez CR, Burneo JG. Efficacy of rapid IV administration of valproic acid for status epilepticus. Neurology. 2005;64:353–355.
21. Alvarez V, Januel JM, Burnand B, Rossetti AO. Second-line status epilepticus treatment: comparison of phenytoin, valproate, and levetiracetam. Epilepsia. 2011;52:1292–1296.
22. Mazarati AM, Baldwin RA, Sankar R, Wasterlain CG. Time-dependent decrease in the effectiveness of antiepileptic drugs during the course of self-sustaining status epilepticus. Brain Res. 1998;814:179–185.
23. Hocker S, Wijdicks EF, Rabinstein AA. Refractory status epilepticus: new insights in presentation, treatment, and outcome. Neurol Res. 2013;35:163–168.
24. Holtkamp M. Treatment strategies for refractory status epilepticus. Curr Opin Crit Care. 2011;17:94–100.
25. Shorvon S. Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation. Epilepsia. 2011;52 (suppl 8):53–56.
26. Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. Neurology. 2000;54:1366–1368.
27. Iyer VN, Hoel R, Rabinstein AA. Propofol infusion syndrome in patients with refractory status epilepticus: an 11-year clinical experience. Crit Care Med. 2009;37:3024–3030.
28. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. Epilepsia. 2002;43:146–153.
29. Moddel G, Bunten S, Dobis C, et al. Intravenous levetiracetam: a new treatment alternative for refractory status epilepticus. J Neurol Neurosurg Psychiatry. 2009;80:689–692.
30. Patel NC, Landan IR, Levin J, Szaflarski J, Wilner AN. The use of levetiracetam in refractory status epilepticus. Seizure. 2006;15:137–141.
31. Knake S, Gruener J, Hattemer K, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. J Neurol Neurosurg Psychiatry. 2008;79:588–589.
32. Ruegg S, Naegelin Y, Hardmeier M, Winkler DT, Marsch S, Fuhr P. Intravenous levetiracetam: treatment experience with the first 50 critically ill patients. Epilepsy Behav. 2008;12:477–480.
33. Zeiler FA, Teitelbaum J, Gillman LM, West M. NMDA antagonists for refractory seizures. Neurocrit Care. 2014;20:502–513.
34. Mewasingh LD, Sekhara T, Aeby A, Christiaens FJ, Dan B. Oral ketamine in paediatric non-convulsive status epilepticus. Seizure. 2003;12:483–489.
35. Sheth RD, Gidal BE. Refractory status epilepticus: response to ketamine. Neurology. 1998;51:1765–1766.
36. Towne AR, Garnett LK, Waterhouse EJ, Morton LD, DeLorenzo RJ. The use of topiramate in refractory status epilepticus. Neurology. 2003;60:332–334.
37. Mirsattari SM, Sharpe MD, Young GB. Treatment of refractory status epilepticus with inhalational anesthetic agents isoflurane and desflurane. Arch Neurol. 2004;61:1254–1259.
38. Kellinghaus C, Berning S, Immisch I, et al. Intravenous lacosamide for treatment of status epilepticus. Acta Neurol Scand. 2011;123:137–141.
39. Tilz C, Resch R, Hofer T, Eggers C. Successful treatment for refractory convulsive status epilepticus by non-parenteral lacosamide. Epilepsia. 2010;51:316–317.
40. Goodwin H, Hinson HE, Shermock KM, Karanjia N, Lewin JJ 3rd. The use of lacosamide in refractory status epilepticus. Neurocrit Care. 2011;14:348–353.
41. Leppik IE. Treatment of epilepsy in 3 specialized populations. Am J Manag Care. 2001;7:S221–S226.
42. Chin RF, Neville BG, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. Lancet Neurol. 2008;7:696–703.
43. Molgaard-Nielsen D, Hviid A. Newer-generation antiepileptic drugs and the risk of major birth defects. JAMA. 2011;305:1996–2002.

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33 Parkinson Disease

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LEARNING OBJECTIVES

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

LO

1. Describe the pathophysiology of Parkinson disease (PD) related to neurotransmitter involvement and targets for drug therapy.
2. Recognize the cardinal motor symptoms of PD and determine a patient's clinical status and disease progression based on the Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS UPDRS).
3. For a patient initiating therapy for PD, recommend appropriate drug therapy and construct patient-specific treatment goals.
4. Recognize and recommend appropriate treatment for nonmotor symptoms.
5. Formulate a plan to minimize patient "off-time" and maximize "on-time" including timing, dosage, and frequency of medications.
6. Recognize and treat various motor complications in PD.
7. Construct appropriate patient counseling regarding medications and lifestyle modifications for PD.
8. Develop a monitoring plan to assess effectiveness and adverse effects of treatment.

INTRODUCTION

LO1 KEY CONCEPT Parkinson disease (PD) is a slow, progressive neurodegenerative disease of the extrapyramidal motor system. Dopamine neurons in the **substantia nigra** are primarily affected, and degeneration of these neurons causes a disruption in smooth motor control. Cardinal features of PD include tremor at rest, rigidity, **akinesia**/bradykinesia, and postural instability. There is no cure, and treatment aims at controlling symptoms and maintaining quality of life (QOL) or functioning.

LO2

EPIDEMIOLOGY AND ETIOLOGY

PD affects approximately 1 million Americans, and a lifetime risk of developing the disease is 1.5%. Median age of the onset is 60 years, but about 10% of people with PD are younger than 45 years. The average time span from diagnosis to death is about 15 years. Approximately 15% of patients with PD have a first-degree relative with the disease.[1,2]

The etiology of neuron degeneration in PD remains unknown, but aging is a primary risk factor. Thus, as the fraction of the population that is elderly continues to increase, this disease may see a subsequent increase in prevalence. Cell death may be caused by oxidative stress, mitochondrial dysfunction, increased excitotoxic amino acids and inflammatory cytokines, immune system disorders, signal-mediated **apoptosis**, and environmental toxins. Oxidative stress may result from increased monoamine oxidase-B (MAO-B) metabolism or decreased glutathione clearance of free radicals.[2–5]

Genetic mutations such as those in *LRRK2* have been linked to PD, and particular mutations may predict early versus late onset of the disease.[2,3] Most likely, a combination of inducers of cell death and genetic mutations are involved in PD.[2] Pigmented cells in the substantia nigra that make and store dopamine are lost. At the time of diagnosis, 50% to 60% of dopamine neurons located here may be dysfunctional. Neurons have lost about 80% of their activity in the striatum at the onset of PD. Cortical **Lewy bodies** along with Lewy neurites in the central nervous system (CNS) and the gastrointestinal (GI) system may explain some of the nonmotor symptoms (e.g., psychiatric, autonomic symptoms) of PD.[2,4,5]

Interestingly, patients with a history of smoking or who drink coffee or tea have demonstrated decreased risk of PD through unknown mechanisms.[2]

PATHOPHYSIOLOGY

The extrapyramidal motor system controls muscle movement through pathways and nerve tracts that connect the cerebral cortex, **basal ganglia**, thalamus, cerebellum, reticular formation, and spinal neurons. The substantia nigra, where dopamine neurons in PD are lost, sends nerve fibers to the corpus striatum. The corpus striatum is composed of the caudate nucleus and the lentiform nuclei that consist of the pallidum (globus pallidus) and putamen (**Figure 33–1**). As dopamine neurons die, dopamine-relayed messages cannot communicate to other motor centers of the brain, and patients develop motor symptoms. A variety of other neurotransmitters active in the basal ganglia lose concentration as well. These deficits possibly explain specific nonmotor symptoms seen in PD as loss of dopamine and norepinephrine in the limbic system correlates with depression and anxiety, while losses of neurotransmitters, acetylcholine and serotonin in the limbic system are associated with cognitive impairment.[2,3,5,6]

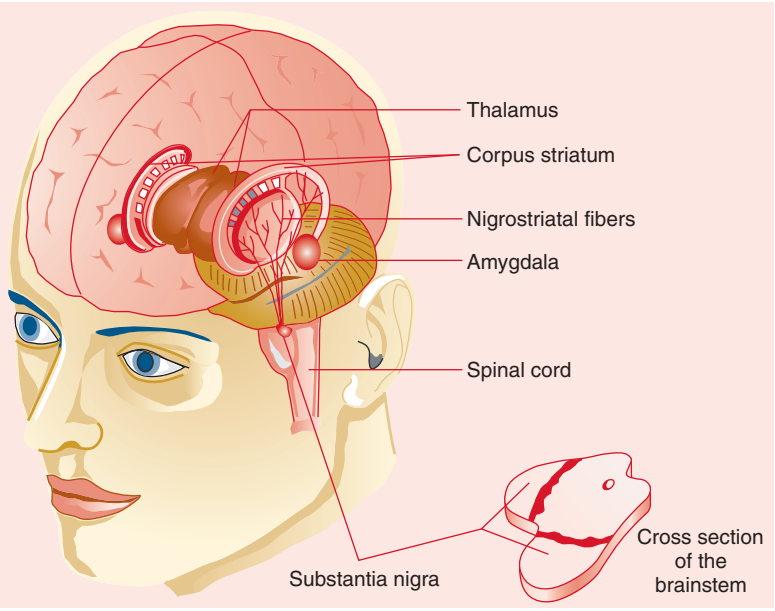

FIGURE 33–1. Anatomy of the extrapyramidal system. The extrapyramidal motor system controls muscle movement through a system of pathways and nerve tracts that connect the cerebral cortex, basal ganglia, thalamus, cerebellum, reticular formation, and spinal neurons. Patients with PD have a loss of dopamine neurons in the substantia nigra in the brainstem that leads to depletion of dopamine in the corpus striatum. The corpus striatum is made up of the caudate nucleus and the lentiform nuclei that are made up of the putamen and the globus pallidus.

Theorized to begin in the autonomic system, olfactory system, or vagus nerve in the lower brainstem, the disease may then spread to the upper brainstem and cerebral hemisphere affecting dopamine pathways later.[2] It is essential to rule out drug-induced pseudoparkinsonism due to dopamine antagonists such as antipsychotics, metoclopramide, and antiemetics (prochlorperazine) before diagnosis. Removing the offending agent generally resolves symptoms.[1,7]

Clinical Presentation of PD

Motor Symptoms (TRAP)

T = Tremor at rest ("pill rolling")

R = Rigidity (stiffness and cogwheel rigidity)

A = Akinesia or bradykinesia

P = Postural instability and gait abnormalities

Nonmotor Symptoms (SOAP)

S = Sleep disturbances (insomnia, REM sleep behavioral disorder, [RLS])

O = Other miscellaneous symptoms (nausea, fatigue, speech, pain, dysesthesias, vision problems, seborrhea)

A = Autonomic symptoms (drooling, constipation, sexual dysfunction, urinary problems, sweating, orthostatic hypotension, dysphagia)

P = Psychological symptoms (anxiety, psychosis, cognitive impairment, depression)

Response Fluctuations (MAD)

M = Motor fluctuations (delayed peak, wearing off, random off, freezing)

A = Akathisia

D = Dyskinesias (eg, chorea, dystonia, diphasic dyskinesia)

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of PD is based substantially on signs and symptoms rather than diagnostic tests or imaging; however, this can be difficult as other illnesses have characteristics similar to PD and patients' presentations vary initially and through time. DaTscan, a radiopharmaceutical contrast agent, may help differentiate PD from other disorders such as essential tremor, but not from similar Parkinson-plus syndromes.[8] Therefore, a thorough patient history and detailed description of symptoms are essential.

Patient Encounter Part 1: Initial Visit—Medical History

A 63-year-old woman presents to the movement disorder clinic on suspicion of new-onset PD. She complained to her physician that "for the past few months, I've had a tremor in my left arm most of the time and have noticed that my muscles in my arms seem to be stiff. I must have a problem with cramping." She reports nothing that worsens symptoms or any acute changes in severity recently. She cares for her 1-year-old granddaughter three times per week but has found that her symptoms disrupt her ability to fully care for the child as she has trouble picking her up and feeding her. She reports that her tremor somewhat affects her ability to feed the child when she uses a spoon. Other complaints include worsening of eyesight, feeling more tired than usual, constipation, decreased libido, and sadness.

What test could be ordered to aid in the diagnosis of PD?

What assessments should be completed at this time?

Identify this patient's motor and nonmotor symptoms of PD.

What additional information would you collect before creating this patient's treatment plan?

Motor Symptoms

KEY CONCEPT PD is a slow, progressive neurodegenerative disease of the extrapyramidal motor system with classic motor symptoms of tremor, rigidity, akinesia/bradykinesia, and postural/gait instability (TRAP).

The onset of PD is gradual, and movement impairment may initially go unnoticed. Tremor occurs during rest and disappears with purposeful movement. Hand tremor may mimic a patient rolling a pill between his or her fingers. Rigidity manifests as stiffness with uniform muscle resistance on examination. Examiners may notice cogwheel rigidity on extension or flexion of extremities and feel rhythmical jerking as if hitting a series of teeth on the rim of a wheel. Bradykinesia manifests as hesitancy in movement initiation, slowness in movement, or rapid fatiguing. Decreased automatic activity (e.g., eye blinking, **hypomimia**, minimal arm swing while walking) is common. Rigidity and bradykinesia may make handwriting difficult as **micrographia** is common. Loss of reflexes to maintain balance as well as stooped posture causes postural instability and unsteadiness. This, combined with gait abnormalities such as slow shuffling, leg dragging, **festination**, or **freezing**, increases the risk of falls.[2,9–13]

Nonmotor Symptoms

Nonmotor symptoms in PD may precede the onset of motor symptoms by many years and result from PD itself or medications. Sleep disturbances, autonomic impairment, psychological disturbances, and sensory disturbances (**anosmia**) are common.[2,6,9,14-17]

Speech problems manifest as **hypophonia**, slurring, monotone speech, rapid speech, or stammering. When ocular muscles are impaired, difficulty reading, double vision, decreased blinking, and burning or itchy eyes are possible.[2,6,9–13]

Autonomic nervous system disruption may produce orthostatic hypotension as well as GI, urinary, sexual, and dermatologic symptoms. Orthostatic hypotension may cause dizziness, lightheadedness, fainting, or falls. Constipation is very common and **dysphagia** may lead to weight loss, **sialorrhea**, and aspiration.[14,15] Genitourinary symptoms include incontinence, urgency, and frequency causing nocturia. Sexual dysfunction includes libido or inability to achieve orgasm and erectile or ejaculatory dysfunction. Dermatologic symptoms include sweating and intolerance to temperature changes.[2,6,9,14,15]

Psychological symptoms of psychosis, dementia, impaired cognitive function, depression, and anxiety may result from PD, during symptom exacerbation, or from medications. Psychosis occurs in nearly 60% of PD patients. Depression is common, but decreased facial expression and bradykinesia may give a false appearance of depression in the PD patient; thus a proper assessment of mood is necessary. Often comorbid with depression, anxiety has been noted in over half of patients with motor fluctuations.[2,6,14,16–18]

Sleep disorders may be due to PD itself or medication adverse effects. Excessive daytime sleepiness, insomnia, and abnormal sleep events, such as rapid eye movement sleep behavior disorder (REM SBD), may occur.[6,9,14]

Motor Complications

Motor complications appear with either disease progression or as a complication of treatment, particularly with levodopa. Motor complications include **delayed peak response**, early and unpredictable "wearing off," freezing, and **dyskinesias**—namely **chorea** and **dystonia**. Risk factors for developing motor complications include younger age at diagnosis, high dosage of levodopa, and longer duration and severity of disease. Wearing off occurs when the therapeutic window of levodopa—the minimum effective concentration required to control PD symptoms ("on" without dyskinesia) through the maximum concentration before experiencing side effects from excessive levodopa ("on" with dyskinesia)—narrows over time. Although the plasma half-life of levodopa is 1.5 to 2 hours, the therapeutic effect in early PD lasts about 5 hours, and the patient experiences no dyskinesias. This is due to supplemental dopamine production in the CNS. As PD progresses, this endogenous supply is lost, the therapeutic window narrows, and each dose of levodopa acts less functionally, with the effect decreasing to only 2 to 3 hours. Additionally, dyskinesias occur more frequently during the on state, particularly as the dose of levodopa is increased.[5,19,20]

KEY CONCEPT The Unified Parkinson Disease Rating Scale (MDS UPDRS) describes total symptom burden, tracks disease progression, and assesses treatment efficacy. This clinician and patient-rated scale has four parts, which allow for evaluation of nonmotor symptoms, activities of daily living (ADL), motor symptoms, and complications of therapy. Each symptom is given a numerical score from 0 to 4 (none to severe) to describe severity.[21]

TREATMENT

Desired Outcomes

KEY CONCEPT The goals of treatment include:

- maintaining patient independence, ADL, and QOL
- minimizing the development of response fluctuations
- limiting medication-related adverse effects

General Approach to Treatment

KEY CONCEPT Treatment of PD is categorized into three types: (1) lifestyle changes, nutrition, and exercise; (2) pharmacologic intervention; and (3) surgical treatments after pharmacologic interventions fail.

LO 3

Initial treatment depends on the patient's age, risk of adverse effects, degree of physical impairment, and readiness to initiate therapy (Figure 33–2).[22,24]

The 2002 American Academy of Neurology (AAN) guidelines suggest that pharmacologic treatment be delayed until the patient experiences functional disability.[23] However, 2017 guidelines by the National Institute for Health and Care Excellence (NICE) differ and recommend dopamine agonists, levodopa, or MAO-B inhibitors be offered to patients even before QOL is affected.[24] While some data do suggest that earlier treatment may delay the progression of disease, many studies examining this have design flaws and inconsistent results.[12,14,25] One must weigh the pros and cons of delaying pharmacotherapy or starting medications early on an individual patient basis.[23,26,27]

Nonpharmacologic Therapy

▶ *Lifestyle Modifications*

Nonpharmacologic therapy and patient education is ideally implemented early and continued throughout treatment for PD. The most common interventions include maintaining

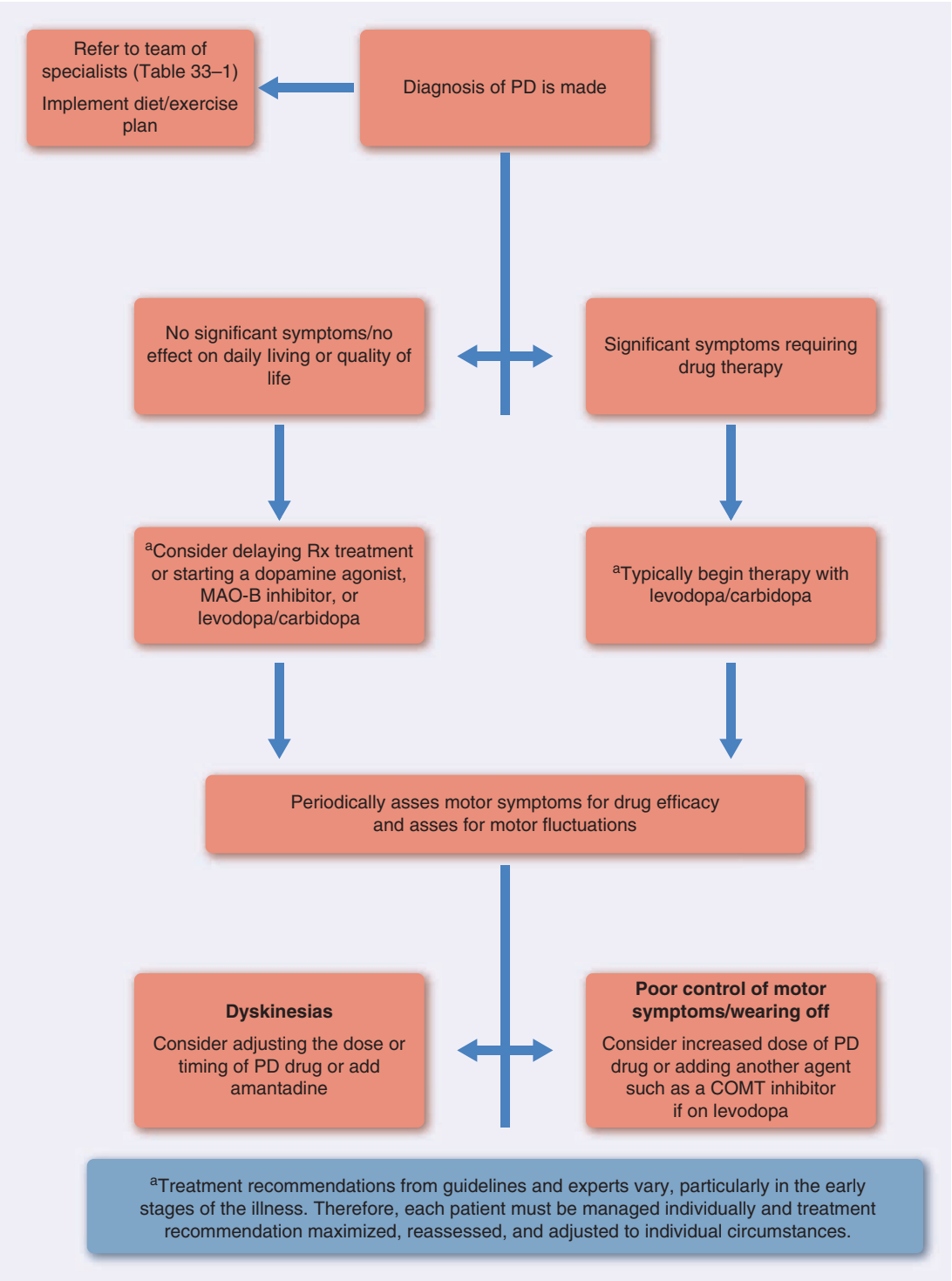

FIGURE 33–2. Algorithm for diagnosis and management of Parkinson disease.[1,19,24]

good nutrition, physical condition, and social interactions.[1,10] These treatments may improve ADLs, gait, balance, and mental health. Coordinated care with multiple health care professionals maximizes patient outcomes as each specialist plays a necessary role in the treatment team (Table 33–1).

Surgery

Consider surgery with deep brain stimulation (DBS) when inadequate control of motor symptoms develop despite pharmacotherapy. This procedure electrically stimulates the subthalamic nucleus (STN) or globus pallidus interna. DBS may significantly reduce motor symptoms and complications and improve QOL compared to medication management. Targeting the STN is preferred when a decrease in PD medication use is desired while targeting the globus pallidus may better treat dyskinesias.[28,29] Thalamic stimulation is available for those with severe tremor who are unsuitable for STN stimulation. These surgeries carry risks and are generally utilized after suboptimal response to drug therapy.[24]

Patient Encounter Part 2: Initial Visit—Physical Examination and Diagnostic Tests

Chief Complaint: New onset unilateral tremor and upper body muscle stiffness; decreased sleep quality

PMH: Constipation for greater than 10 years, osteoporosis, cataracts, mild anemia

SH: Retired. Lives alone but provides childcare for her granddaughter. Denies alcohol use. Smoked 0.5 PPD in her 20s and 30s but has since quit.

Meds: Alendronate 70 mg orally once weekly, ferrous sulfate 325 mg orally twice daily

ROS: (–) Psychosis or agitation; reports depression; denies nausea, vomiting, diarrhea, HA, dizziness, or pain

PE:

Gen: Flat affect, looks older than stated age, speaks softly and often difficult to hear, handwriting when completing the intake forms is difficult to read

VS: BP: sitting 115/75, P 63 beats/min, RR 18/min, Wt 59 kg (130 lb), Ht 165 cm (65 in)

HEENT: Decreased eye blinking and facial expression, CN II-XII intact, PERRLA, TMs intact

CV: RRR, normal S1, S2; no murmurs, rubs, gallop

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly

Skin: Some dryness on the back of her neck, otherwise normal

Exts: Mild to moderate tremor in her left arm most noticeable at rest. Mild cogwheel rigidity bilateral elbows

Neuro: Slow, sensory function intact, normal muscle strength, normal reflexes, alert, mental status examination normal

Rating Scales: Patient Health Questionnaire (PHQ-9) = 10; Mini Mental State Exam (MMSE) = 29/30; UPDRS = 58 at current visit; no prior history to compare to

Labs: Normal metabolic profile and CBC

Given this additional information, what is your assessment of the patient's condition?

Identify treatment goals for the patient.

Describe nonpharmacologic treatments that should be started for the patient.

List options for initial pharmacologic treatments that are available for the patient and differentiate between their appropriateness.

Table 33–1

Specialist Care for Patients with PD

Provider	Reason for Referral
Dentist	PD medications may decrease saliva flow and increase the risk of dental caries
Dietician	Recommend appropriate caloric intake, meal selection, and protein consumption which may: • improve constipation and nausea • decrease weight loss and aspiration • minimize erratic drug absorption
Speech therapist	Improved swallowing, articulation, and force of speech
Physical therapy	Improve strength, activity, sleep quality, and reduce fall risk May provide neuroprotection
Occupational therapist	Educate on adaptive environment of home, specialized clothing, and personal training to evaluate and maximize: • Independence • Safety • ADLs • Handwriting • Driving ability
Social worker	Arrange for community assistance programs and family counseling Increase engagement in family activities

Nutt JG, Wooten GF. Diagnosis and initial management of Parkinson's disease. N Engl J Med. 2005;353:1021–1027.[1]

Anonymous. Drugs for Parkinson's disease. Treat Guidel Med Lett. 2011;9(101):1–6.[27]

Pharmacologic Therapy of Motor Symptoms

KEY CONCEPT Drug therapy aims to enhance dopaminergic activity in the substantia nigra. When to initiate dopaminergic therapy is controversial and patient specific. Medications minimize motor symptoms and improve QOL and ADLs but are not curative (Table 33–2).[1,2,30] Even with pharmacotherapy, PD patients have greater mortality and morbidity than the general population.[1] KEY CONCEPT Choice of pharmacologic agent should be individualized based on patient-specific parameters, and dose regimens based on individual response to maximize "on time" and minimize "off time."

Pharmacologic options for PD include anticholinergics (Ach), amantadine, MAO-B inhibitors, dopamine agonists, levodopa/carbidopa, and catechol-*O*-methyltransferase (COMT) inhibitors. Most pharmacologic treatments in PD aim to avoid degeneration of the dopaminergic nigrostriatal pathway and increase dopamine concentrations (Figure 33–3). The AAN and the Movement Disorder Society recommend most patients initiate treatment with either levodopa/carbidopa or a dopamine agonist.[10–14] The 2017 NICE guidelines slightly differ and recommend levodopa/carbidopa for patients once motor symptoms begin to affect QOL.[24]

Choice between drugs varies based on clinical experience and patient preference. Starting with a dopamine agonist may delay the onset of dyskinesias and response fluctuations seen with long-term levodopa use; however, less motor benefit and greater risk of hallucinations or somnolence may occur. Levodopa causes the greatest motor improvement and should be used as initial therapy in the elderly, but may increase the risk of motor fluctuations over time.[26] Data are insufficient to recommend initiating treatment with combined drug classes. Initiating treatment with anticholinergic medications, amantadine, or MAO-B inhibitors is recommended only for patients who have mild symptoms because they are not as effective as dopamine agonists or levodopa.[1,2,10–14,30]

Table 33–2

Dosing of Medications Used to Treat PD[1,2,32,34]

Generic Name (Trade Name)	Initial Dose	Titration and Maintenance Dose	Available Formulations	Hepatic or Renal Adjustments
Levodopa Formulations				
Levodopa with carbidopa (Sinemet)	Half tablet (100 mg LD, 25 mg CD) twice daily for 1 week, then half tablet three times daily	Increase by half tablet daily every week; usual MD is 300–2000 mg daily; because the duration of LD is 2–3 hours, patients may require doses every 2 hours.	Stalevo—CD/LD/Entacapone tablet	
Sinemet CR	One tablet (100 mg LD, 25 mg CD) two to three times daily	Increase to 200 mg LD tablet two to four times daily; usual MD is 200–2200 mg daily.	Sustained-release tablet	
Rytary (extended-release levodopa with carbidopa)	In levodopa naïve patients: 23.75 mg/95 mg taken orally three times a day for the first 3 days	On the fourth day of treatment, the dosage may be increased to 36.25 mg/145 mg taken three times a day. Individual doses may be increased and doses may be given up to five times a day based on individual response; patients previously on immediate release levodopa should follow recommended conversions.	Extended-release capsule	
Duodopa (intestinal infusion of LD/CD)	Convert patients to Sinemet and calculate a total daily dose.	Dose consists of a morning dose, a continuous infusion, and additional doses. One extra dose per 2 hours is maximum. Maximum dose is 2000 mg of LD over 16 hours.	Intestinal suspension	
Dopamine Agonists				
Apomorphine (Apokyn)	Start trimethobenzamide 300 mg for 3 days; then give apomorphine 2 mg SC injection (1 mg if outpatient) while monitoring blood pressure.	Continue trimethobanzamide as necessary (generally no longer than 2 months). Increase apomorphine by 1–2 mg every ≥ 2 hours; usual MD is 2–6 mg three to five times daily for off periods.	Subcutaneous solution	Reduce initial dose to 1 mg in mild to moderate renal failure.
Bromocriptine (Parlodel)	1.25 mg twice daily	Increase by 2.5 mg daily every 14 to 28 days.	Capsule, tablet	Dosing adjustments may be necessary with hepatic impairment.
Pramipexole (Mirapex)	0.125 mg three times daily	Increase about weekly by 0.375– 0.75 mg/day to a MD of 0.5–1.5 mg three times daily.	Tablet	Dosage reduction needed in creatinine clearance < 50 mL/min (0.83 mL/s).
Mirapex ER	0.375 mg once daily	Increase up to 0.75 mg/day after a minimum of 5 days. Dose may then be increased in increments of 0.75 mg/day no more frequently than every 5–7 days.	Extended-release tablet	
Ropinirole (Requip)	0.25 mg three times daily	Increase about weekly by 0.75–1.5 mg daily to a MD dose of 3–9 mg three times daily. Then may increase by 3 mg/day on a weekly basis to a maximum of 24 mg/day.	Tablet	
Requip XL	2 mg once daily for 1–2 weeks	Increase by 2 mg/day in 1-week intervals; maximum dose is 24 mg/day.	Extended-release tablet	
Rotigotine (Neupro)	2 mg patch once daily for early-stage PD; 4 mg patch for advanced-stage PD	Increase by 2 mg/24 hours on a weekly basis.	Patch	
MAOIs				
Selegiline (Eldepryl)	5 mg in the morning	If symptoms continue, add 5 mg at noon; 5 mg daily may be as clinically effective as 10 mg daily with fewer side effects.	Tablet, capsule	Use is not recommended for creatinine clearance < 30 mL/min (0.50 mL/s) or severe hepatic impairment.

(*Continued*)

Table 33–2

Dosing of Medications Used to Treat PD[1,2,32,34] (*Continued*)

Generic Name (Trade Name)	Initial Dose	Titration and Maintenance Dose	Available Formulations	Hepatic or Renal Adjustments
Selegiline ODT (Zelapar)	1.25 mg once daily	If symptoms continue after 6 weeks, increase dose to 2.5 mg every morning. Avoid food or liquid for 5 minutes before or after the dose.	Dispersable tablet	
Rasagiline (Azilect)	If used with levodopa, 0.5 mg daily	If symptoms continue, increase to 1 mg daily.	Tablet Tablet	Use 0.5 mg/day in mild hepatic impairment. Do not use in moderate to severe impairment.
Safinamide (Xadago)	50 mg once daily	May increase after 2 weeks to 100 mg once daily.		Maximum dose is 50 mg once daily in moderate hepatic impairment and use is contraindicated in severe impairment.
COMT Inhibitors				
Tolcapone (Tasmar)	100 mg with first Sinemet dose once daily	If symptoms continue, increase to 2 and then 3 times daily, then to 200 mg each dose; usual MD is 100–200 mg three times daily.	Tablet	Do not use in patients with active liver disease or SGPT/ALT or SGOT/AST > the upper limit of normal.
Entacapone (Comtan)	200 mg tab with each Sinemet dose	Usual MD is 200 mg three to four times daily (up to eight tablets per day).	Tablet	Decrease dose by 50% with hepatic impairment.
Others				
Amantadine (Symmetrel) Gocovri (amantadine XR)	100 mg daily at breakfast 137 mg once daily at bedtime	After 1 week, add 100 mg daily; usual MD is 200–300 mg daily with last dose in afternoons. After 1 week, increase to 274 mg once daily.	Capsule, tablet, oral syrup Extended-release capsule	Decrease dose for creatinine clearance < 80 mL/min (1.33 mL/s). Start with 68.5 mg once daily in moderate renal impairment and use a maximum dose of 137 mg. In severe renal impairment, use 68.5 mg once daily. Do not use in end-stage renal disease.
Benztropine (Cogentin)	0.5 to 1 mg at bedtime	Assess if dose is adequate and titrate by 0.5 mg increments at 5- to 6-day intervals to a maximum of 6 mg if necessary.	Tablet, solution for injection	

Ach, acetylcholine; CD, carbidopa; COMT, catechol-*O*-methyltransferase; CR, controlled-release; DA, dopamine; LD, levodopa; MAO, monoamine oxidase; MD, maintenance dose; NMDA, *N*-methyl-D-aspartate; ODT, orally disintegrating tablet; PD, Parkinson disease; XR, extended-release.

Regardless of the drug initially chosen, the initial dose is low and increased gradually based on symptoms (see Table 33–2). Dose timing and frequency is then adjusted based on the patient's report of "on time" duration and wearing off symptoms. Dyskinesias may develop with the use of PD drugs and generally relate to dopamine concentrations. Decreasing the dose, frequency, or number of dopaminergic medications may be beneficial. If a PD medication is discontinued, gradual withdrawal is recommended with monitoring of worsening motor symptoms.

▶ *Anticholinergics*

Ach block acetylcholine, decreasing the acetylcholine to dopamine concentration ratio. They minimize resting tremor and drooling, but are not as effective as other agents for rigidity, bradykinesia, and gait problems. Because of their side effects including cognitive impairment, Ach are typically avoided in older patients.[1,2,9,27] Additionally, gastric motility may be compromised delaying gastric emptying and leading to erratic and decreased levodopa absorption. Lastly, they may worsen urinary retention or constipation.[31]

▶ *Amantadine*

Amantadine is an *N*-methyl-D-aspartate (NMDA)-receptor antagonist that blocks glutamate transmission, promotes dopamine release, and blocks acetylcholine. It is likely effective as monotherapy and adjunct therapy for off time and dyskinesia.[20,32,33] An extended release version was approved specifically for dyskinesias in PD making it the only FDA (Food and Drug Administration)-approved option for this complication.[34,35] Side effects include nausea, dizziness, livedo reticularis, peripheral

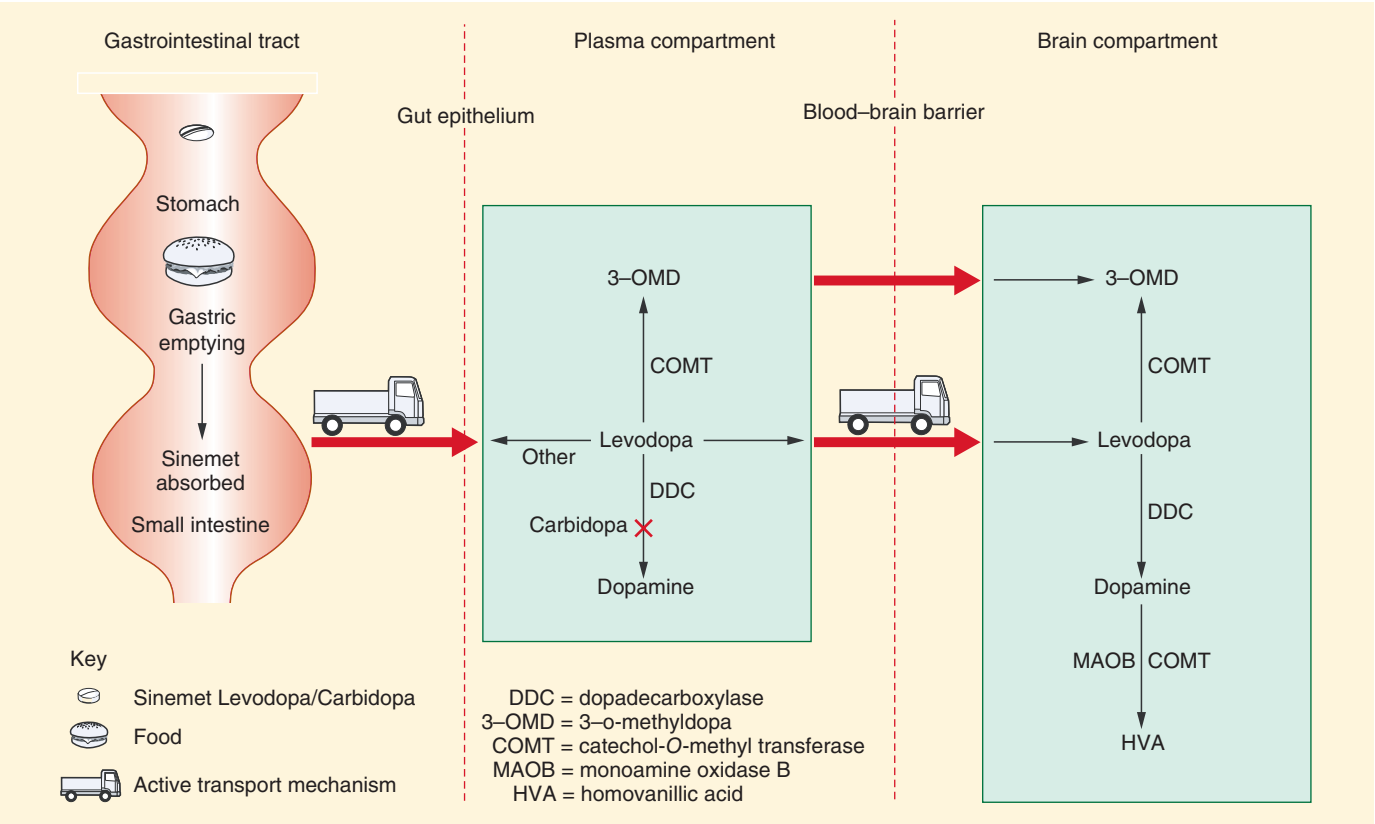

FIGURE 33–3. Levodopa absorption and metabolism. Levodopa is absorbed in the small intestine and distributed into the plasma and brain compartments by an active transport mechanism. Levodopa is metabolized by dopa decarboxylase, monoamine oxidase, and catechol-*O*-methyltransferase. Carbidopa does not cross the blood–brain barrier. Large neutral amino acids in food compete with levodopa for intestinal absorption (transport across gut endothelium to plasma). They also compete for transport into the brain (plasma compartment to brain compartment). Food and anticholinergics delay gastric emptying resulting in levodopa degradation in the stomach and a decreased amount of levodopa absorbed. If the interaction becomes a problem, administer levodopa 30 minutes before or 60 minutes after meals.

edema, orthostatic hypotension, hallucinations, restlessness, anticholinergic effects, and insomnia. Insomnia is minimized by taking the ER (extended-release) formulation at bedtime and the immediate release formulation earlier in the day. It should be avoided in the elderly who cannot tolerate its anticholinergic effects.[7,29,39]

▶ *MAO-B Inhibitors*

Safinamide, selegiline, and rasagiline work through selective blockade of dopamine metabolism through MAO-B. Selegiline and rasagiline provide a mild symptomatic benefit for patients who choose to delay dopaminergic medications and use MAO-B inhibitors as initial therapy. Combining selegiline or rasagiline with levodopa in early treatment may delay motor complications.[20,25,32] For patients with motor fluctuations, they reduce off time when added to levodopa therapy.[9–12,34]

Both rasagiline and selegiline may be neuroprotective and thus may be selected early in therapy, but there is no conclusive evidence to validate this.[36]

Selegiline is generally well tolerated. Adverse effects include nausea, confusion, hallucinations, jitteriness, insomnia, and orthostatic hypotension. Selegiline is available in an orally disintegrating tablet designed to avoid first-pass metabolism. This improves bioavailability and decreases serum concentrations of its amphetamine-like metabolite which may cause insomnia. Daily doses are limited to 10 mg because MAO-B selectivity may be lost at higher doses increasing the risk of drug and food interactions.[25]

Rasagiline has a similar adverse effect profile but is less likely to cause insomnia compared to selegiline. In contrast to nonselective MAOIs, restriction of tyramine-containing foods is not required at recommended dosages, but high tyramine-containing food or exceeding recommend dosing of rasagiline may increase the risk of hypertensive crisis.[32,34]

Safinamide, an MAO-B inhibitor, is the first unique compound approved in recent years for PD. It is indicated specifically in conjunction with levodopa/carbidopa after patients begin to experience off episodes; however, it will likely be used in similar situations as the other MAO-B antagonists.[3,32]

Risk of dyskinesias is minimized by decreasing the levodopa dose when adding any of these agents. Serotonin syndrome and hypertensive crisis may occur in patients using these medications with opioid analgesics, antidepressants, and other serotonergic agents, or sympathomimetic amines (cold and weight loss products) (see Chapter 38).[7,25]

▶ *Dopamine Agonists*

Dopamine agonists bind to postsynaptic dopamine receptors and are reasonable as initial therapy. Their advantages include

delay of levodopa therapy and smaller risk of developing motor fluctuations during the first 4 to 5 years of treatment. Eventually, they inadequately control the patient's symptoms, and levodopa is necessary. In advanced disease, they can be added to levodopa to minimize response fluctuations, decrease off time, improve wearing-off symptoms, allow a reduction in levodopa dose, and improve ADLs.[1,2,10,12,30,37]

Dopamine agonists include the ergot derivatives (bromocriptine) and the nonergot derivatives (rotigotine, pramipexole, ropinirole, and apomorphine). Generally, the nonergot agents are preferred due to a more favorable adverse effect profile and stronger efficacy evidence.[38] Rotigotine is available as a once-daily skin patch which minimizes pulsatile dopaminergic stimulation.[1,7,27,32]

Common side effects with all dopamine agonists include nausea (most common initial symptom), vomiting, sedation (greatest with apomorphine), pedal edema, orthostatic hypotension (greatest with pramipexole), and psychiatric effects that are greater than with levodopa (nightmares, confusion, and hallucinations). Uncommon ergot side effects include painful reddish discoloration of the skin over the shins and pleuropulmonary, retroperitoneal, and cardiac fibrosis.[1,7,27,32] Patients should be given instructions regarding the potential of the dopamine dysregulation syndrome (DDS). This includes drug seeking, complex stereotyped behavior (punding), and impulse control disorders (ICDs) such as gambling or compulsive shopping. Reducing or eliminating the agonist typically resolves DDS.[39] If symptoms continue, zonisamide, topiramate, valproic acid, amantadine, and quetiapine may be trialed to treat these effects.[32]

Dopamine agonists may cause excessive daytime sleepiness in 50% of PD patients. Sudden sleep attacks are potentially dangerous during driving. Modafinil and other agents to promote wakefulness may be used for daytime sleepiness, but use for sleep attacks remains controversial.[32,40]

All dopamine agonists are metabolized by the liver except pramipexole, which is eliminated unchanged in the urine. Ropinirole is metabolized by CYP1A2 and thus subject to drug–drug interactions including tobacco.[7,27]

Apomorphine is subcutaneously injected for acute off episodes in advanced PD when rapid rescue therapy is needed. It requires premedication with an antiemetic due to nausea and vomiting.[7,27,32]

► *Levodopa/Carbidopa*

Although levodopa, a dopamine precursor, is the most effective agent for PD, when to initiate therapy remains controversial. Patients experience a 40% to 50% improvement in motor function with levodopa versus 30% with dopamine agonists.[1,2,26] However, some argue delaying levodopa because approximately 70% of patients experience motor complications within 6 years. Others advocate earlier therapy because, historically, before levodopa availability, patients developed dyskinesias earlier than modern-era patients. Delaying levodopa therapy in early disease may not offer short- or long-term benefits.[1,7,19,22,27]

Levodopa usually peaks in the plasma in 30 to 120 minutes but the concentration is sensitive to GI variables. Excess stomach acid, food, or anticholinergic medications delay gastric emptying and decrease the amount of levodopa absorbed. Antacids improve levodopa absorption, while iron products bind levodopa and reduce bioavailability. Levodopa absorption requires active transport by a large neutral amino acid transporter protein (see Figure 33–3). Amino acids in food compete for this transport mechanism. Thus, in advanced disease, avoidance of protein-rich meals in relationship to levodopa doses may be helpful.[1,7,27]

Controlled-release (CR) formulations act longer than immediate-release tablets but are absorbed slower. This results in a delayed onset (45–60 minutes) compared with the standard formulation (15–30 minutes); thus patients may also require immediate-release (IR) tablets or even a liquid formulation when they want a quicker onset of effect. CR preparations are not directly interchangeable with IR but can be added to IR to extend the duration of action. Generally, the total daily dose of CR preparations should be increased by 30%. An ER formulation of levodopa (Rytary) is also approved, but its ideal place in therapy is yet to be determined.[1,26,27]

Converting patients from oral formulations to enteral or duodenal levodopa administration improves motor fluctuations and UPDRS scores. The levodopa/carbidopa combination can be administered directly to the duodenum via a small tube. This formulation (Duopa) is reserved for advanced PD with severe motor fluctuations.[41]

Levodopa is usually administered as a combination product with carbidopa, a dopa-decarboxylase inhibitor, which decreases the peripheral conversion of levodopa to dopamine. This allows for lower levodopa doses and minimizes levodopa peripheral side effects (nausea, vomiting, anorexia, and hypotension). Carbidopa does not cross the blood–brain barrier and does not interfere with levodopa conversion in the brain. Generally, 75 to 100 mg daily of carbidopa is required to adequately block peripheral dopa-decarboxylase. Higher doses of carbidopa may reduce nausea when initiating levodopa.[1,7]

Initial levodopa side effects include orthostatic hypotension, dizziness, anorexia, nausea, vomiting, and discoloration of urine/sweat. Most of these effects can be minimized by taking levodopa with food and by slowly titrating the dose. Side effects that develop later in therapy include dyskinesias, sleep attacks, ICDs, and psychiatric effects (confusion, hallucinations, nightmares, and altered behavior). Dyskinesias caused by adding other PD drugs to levodopa may be improved by decreasing the levodopa dose.[1,7,26,27]

Because levodopa is short acting, it has a risk of end-of-dose wearing off that requires medication adjustments. Patients with severe dyskinesias and off periods may achieve more constant blood concentrations with a liquid formulation of levodopa/carbidopa compounded from tablets. This may allow for more precise dosing and improvements in motor symptoms and complications.[7,26,27,41]

► *Catechol–O–Methyltransferase (COMT) Inhibitors*

Inhibitors of COMT, an enzyme that catalyzes levodopa to 3–o-methyldopa, are added to levodopa/carbidopa to increase levodopa concentrations, extend its half-life, and decrease wearing off time. Using the COMT inhibitors, entacapone or tolcapone, may allow for a decrease in daily levodopa dose while increasing on time by 1 to 2 hours. Side effects include diarrhea (worse with tolcapone), nausea, vomiting, anorexia, dyskinesias, urine discoloration, daytime sleepiness, sleep attacks, orthostatic hypotension, and hallucinations. Dyskinesias should improve with a decrease in the levodopa dose.[7,26,27]

Tolcapone should be used only in patients who do not tolerate or respond to entacapone due to its hepatic safety profile. Serum liver function tests should be monitored at baseline and throughout therapy.[7,26,30]

▶ *Herbs and Supplements*

There is very little support for using creatine, gingko, ginseng, green tea, ginger, yohimbine, or St John's wort in patients with PD. Patients should eat a balanced diet and consider a multivitamin with minerals, but specific vitamin supplementation is generally unceccesary.[8] Because of osteoporosis and fall risk, consider providing a vitamin D supplement in patients with low concentrations.[24]

Treatment of Nonmotor Symptoms

KEY CONCEPT Treatment of nonmotor symptoms should be based on whether they are exacerbated by an off state or might be related to other neurotransmitter dysfunction.

LO 4

The treatment of nonmotor symptoms, such as psychological conditions, sleep disorders, and autonomic dysfunction, should include both pharmacologic and nonpharmacologic approaches. Patients should be supported to maintain ADLs, a positive self-image, family communication, and a safe environment.

Psychological Symptoms

Psychological symptoms and psychosis are common complaints in PD. When these are present, infections, metabolic changes, electrolyte disturbances, or toxic exposures should first be examined.

▶ *Depression*

Depression is extremely common in patients with PD, affecting 40% or more of patients, and it often precedes the disease. Although evidence supports efficacy of tricyclic antidepressants, their adverse effects are limiting. Alternatively, selective serotonin reuptake inhibitors may be considered because of their increased tolerability. Pramipexole may also improve depression.[19] Antidepressants are also useful for the treatment of anxiety disorders. Because off periods can both precipitate anxiety and worsen depression, therapy should be adjusted to maximize on periods.[2,14,18]

▶ *Dementia*

Dementia occurs in approximately 80% of patients with PD 20 years after diagnosis. Cholinesterase inhibitors may be effective while the efficacy of memantine is unclear.[2,14,16,17,32]

Psychosis

Treating psychosis in PD can be difficult as most antipsychotics act as dopamine antagonists, machanistically opposing most PD drugs, and may worsen motor symptoms. Additionally, all antipsychotics carry a black box warning of increased risk of death when used in patients with dementia. Therefore, first treat any underlying medical causes for psychosis; then gradually decrease and stop low-efficacy PD medications. If these strategies fail, antipsychotics may be considered. Clozapine is more effective, but traditionally, low-dose quetiapine has been preferred because clozapine requires monitoring for neutropenia (see Chapter 37). Neither is approved in PD.[2,14-17,42] Although, pimavanserin, another antipsychotic, is specifically approved for PD psychosis and has the lowest risk of worsening motor symptoms, it is expensive, needs to be dispensed through a specialty pharmacy, interacts with CYP3A4 drugs and can prolong QT interval.[34,42]

Sleep Problems

Sleep problems and fatigue are common in PD and may be due to medications, uncontrolled symptoms, or other causes such as nocturia, sleep attacks during the day, depression, SBD, or restless legs syndrome (RLS). Amantadine and selegiline may worsen insomnia, selegiline and tricyclic antidepressants may worsen REM sleep, and some antidepressants and antipsychotics may worsen RLS; therefore, careful evaluation of drug regimens is necessary in patients with sleep complaints.

Reducing RLS and nighttime leg movement may be achieved through PD medications. Levodopa reduces periodic leg movements while a nighttime dose of a COMT inhibitor may benefit RLS. Furthermore, the rotigotine patch may both improve overall sleep quality as well as morning motor symptoms.[43] Iron supplementation for RLS may decrease levodopa absorption in addition to worsening constipation.[2,14] Generally, improving nighttime motor symptoms, maximizing sleep hygiene, or implementing cognitive behavioral therapy may help.[14,18]

Autonomic and Other Problems

Drooling may accompany speech problems and dysphagia. Ach, botulinum toxin injections, and sublingual atropine can decrease drooling. Nausea improves if PD medications are taken with meals or antiemetic therapy (eg, domperidone or trimethobenzamide).

Sexual dysfunction may respond increased on time, removal of drugs that decrease sexual response, and pharmacologic therapy (eg, sildenafil). Studies of sexual dysfunction in women with PD are lacking.[6,14]

Patients with urinary frequency may find a bedside urinal and decreased evening fluid intake helpful. Improvement in PD symptoms can decrease urinary frequency, but symptoms may require catheterization or pharmacologic measures (eg, oxybutynin, tolterodine, propantheline, imipramine, hyoscyamine, or nocturnal intranasal desmopressin).

Constipation may improve with increased fluid intake, a fiber-rich diet, probiotics, and physical activity. Stool softeners, osmotic or bulk-forming laxatives, glycerin suppositories, or enemas may help; cathartic laxatives should be avoided.[6,14]

Dyskinesia-related sweating may respond to PD therapy adjustment or β-blockers.

Treating orthostasis includes the removal of offending drugs (eg, tricyclic antidepressants, PD medications, alcohol, and antihypertensives) increasing carbidopa doses, increased salt or fluids to the diet, and adding compression stockings, fludrocortisone, indomethacin, or midodrine. Droxidopa, a norepinephrine synthetic precursor is approved for treating orthostatic hypotension associated with PD. It can cause supine hypertension and requires monitoring of blood pressure with treatment. Elevating the head of the bed lessens the risk of supine hypertension and if the blood pressure cannot be managed, reduce or discontinue droxidopa.[32,34]

Seborrhea usually responds to over-the-counter dandruff shampoos or topical steroids.[2,9,15]

Treatment of Response Fluctuations

KEY CONCEPT As the disease progresses, most patients develop response fluctuations. Treatment is based on capitalizing on the pharmacokinetic and pharmacodynamic properties of PD medications.

LO 5

Treatment includes adjusting or adding medications to maximize the patient's on time, minimizing the time with dyskinesia, and minimizing off time (Table 33–3). Levodopa doses and intervals should be adjusted to minimize suboptimal or delayed peak levodopa concentrations. Longer acting formulations minimize wearing-off periods. Adding or adjusting

Table 33–3

Management of Motor Complications in Advanced PD[2,11,12,20,35]

I. Motor Fluctuations

Nonpharmacologic Approaches	Drugs to Alter Formulation or Dose	Drugs to Add
A. Suboptimal or delayed peak response		
Take Sinemet on an empty stomach Decrease dietary protein and fat around the delayed dose Minimize constipation Assess for *Helicobacter pylori* infection	Crush Sinemet, or make liquid Sinemet Substitute standard Sinemet for some of the Sinemet CR Withdraw drugs with anticholinergic properties	Intermittent subcutaneous apomorphine
B. Optimal peak but early wearing off		
	Decrease dose and increase frequency of standard Sinemet Substitute Sinemet CR for some of the standard Sinemet	Dopamine agonist MAO-B inhibitor Amantadine COMT inhibitor
C. Optimal peak but unpredictable offs		
Adjust time of medications with meals and avoid high-protein meals or redistribute the amount of protein in diet Deep brain stimulation procedure	Substitute or add liquid Sinemet Switch to a different dopamine agonist if already on an agent Consider continuous infusion of levodopa or apomorphine	COMT inhibitor Dopamine agonist if not using one
D. Freezing		
Gait modifications (use visual cues such as walkover lines, tapping, rhythmic commands, rocking; use rolling walker) Physical therapy	Difficult to treat—adjust current medications based on other PD symptoms. Guide changes based on: On freezing, reduce dopamine medications, inject botulinum toxin. Off freezing, increase Sinemet dose or add dopamine agonists.	If present, treat anxiety with pharmacologic agents

II. Dyskinesias

Nonpharmacologic Approaches	Drugs to Alter Formulation or Dose	Drugs to Add
A. Chorea		
Deep brain stimulation	Decrease risk of occurrence by lowering Sinemet dose when adding other PD medications Evaluate the value of adjunctive PD medications and discontinue if motor complications outweigh benefit Adjust levodopa formulation, dose, or frequency	Amantadine Propranolol Fluoxetine Buspirone Clozapine
B. Off period dystonia in the early morning (eg, foot cramping)		
No recommendations	Add or change short acting to long acting formulations at bedtime if having nighttime offs Change morning Sinemet CR dose to immediate-release with or without CR.	Lithium Baclofen Selective denervation with botulinum toxin
C. Diphasic dyskinesia		
Deep brain stimulation	Change CR preparations to immediate release; consider liquid Sinemet Increase Sinemet dose and frequency	Dopamine agonist Amantadine COMT inhibitor

III. Akathisia

Nonpharmacologic Approaches	Drugs to Alter Formulation or Dose	Drugs to Add
No recommendations	Evaluate if due to antidepressant or antipsychotic and decrease dose or change drug	Benzodiazepine Propranolol Dopamine agonist Gabapentin

LO 6

medications to combat unpredicted off periods and providing treatments that decrease freezing episodes may be necessary. Treatment plans also involve adjusting or adding medications to decrease chorea, dystonia, **diphasic dyskinesias**, or **akathisia**. When away from home, an extra dose of medication is advisable for wearing off.[2,11,13,18,20]

OUTCOME EVALUATION

LO 8

KEY CONCEPT Patient monitoring involves a regular systematic evaluation of efficacy and adverse events, referral to appropriate specialists, and patient education. Evaluate the clinical outcomes of treatment over time by assessing the change in the UPDRS from baseline.

Patient Encounter Part 3: Follow-up Visit 3 Years Later

Three years have passed since the patient was started on a drug regimen for her PD symptoms. Levodopa/carbidopa 100/25 mg by mouth three times daily (8 AM, 3 PM, and 10 PM) was initiated for her motor symptoms. She was instructed in sleep hygiene and referred to physical and occupational therapy as well as an eye specialist for vision complaints. With her initial therapy, she reported a decrease in her tremor and an overall improvement in muscle stiffness for most of the day which continued unchanged until the past few weeks. Now, she says her symptoms tend to return in the evening and are also severe in the early morning upon wakening. This continues to cause problems when caring for her granddaughter. Her sleep has not improved despite sleep hygiene techniques. Additionally, she still complains of constipation frequently despite increasing fluids and using a stool softener. She was placed on sertraline 50 mg by mouth daily which has improved her mood.

Create a problem list and provide an assessment of each problem.

Considering the goals of therapy, treatment options, and your assessment of each of the problems, create a care plan for each problem.

Patient Care Process

Collect Information:

- Review the physical examination and note the specific type of symptoms including their frequency and exacerbating factors.
- Review diagnostic data such as the UPDRS and compare this data to previous encounters.
- Interview the patient to assess PD symptom impact on quality of life (QOL) and ADLs.
- Obtain a complete medication list.

Assess the Information:

- Identify any worsening of motor symptoms or disease progression.
- Determine if on time is maximized and or medications require adjustment.
- Identify drug-indiced dyskinesias and note specific times when these occur.
- Evaluate for appropriate use of each medication including noting drugs which may worsen PD symptoms as well as polypharmacy for PD.
- Assess if nonmotor symptoms are being adequately addressed and treated through pharmacologic or nonpharmcologic therapy.
- Assess the complete PD pharmacologic profile for drug or diet interactions, adverse drug reactions, adherence, and patient understanding of regimens.

Develop a Care Plan:

- Identify other specialists such as physical therapy, occupational therapy, speech, and a palliative care team and develop a plan in conjunction with their recommendations.
- Recommend a therapeutic regimen for motor symptoms that is effective in reducing UPDRS scores but also increases quality of life and daily functioning.
- Adjust dosages and timing of medications to maximize on time and reduce dyskinesia.
- Recommend drug therapy and other options for nonmotor symptoms which will not worsen motor symptoms.
- Develop a detailed medication administration schedule that is simple for the patient to follow, especially if medications with multiple daily dosing schedules are used.

Implement the Care Plan:

- Educate the patient about lifestyle modifications that will improve symptoms and sustain independence.
- Provide instruction on how to use medications including timing of doses with food.
- Educate the patient on how to adjust medications for fluctuations in response.
- Provide information to the patient and family and document about risks with dopaminergic drugs such as impulse control disorders, sudden sleep attacks, and psychosis.
- Refer the patient and family members to further information such as books and websites (http://www.parkinson.org). Provide information concerning local PD support groups when available.

Follow-up: Monitor and Evaluate:

- Instruct the patient to follow up for assessment of symptoms and disease progression.
- Follow up at least every 6 to 12 months and determine when symptoms are controlled, if the patient is experiencing any drug interactions or adverse reactions.
- Provide patient education on changes to medication regimens and nonpharmacologic options.

Instruct patients to record the amount of on and off time daily to guide medication adjustment. Assess fall risk and implement appropriate safety measures to prevent falls. Scales assessing QOL, depression, anxiety, and sleep disorders are useful to track progression.

Abbreviations Introduced in This Chapter

Ach	Anticholinergics
ADL	Activities of daily living
COMT	Catechol-*O*-methyltransferase
CR	Controlled-release
DBS	Deep brain stimulation
DDS	Dopamine dysregulation syndrome
GI	Gastrointestinal
ICD	Impulse control disorder
MAO	Monoamine oxidase
NMDA	*N*-methyl-D-aspartate
PD	Parkinson disease
QOL	Quality of life
REM SBD	Rapid eye movement sleep behavior disorder
RLS	Restless legs syndrome
TRAP	Tremor, rigidity, akinesia/bradykinesia, postural/gait instability
UPDRS	Unified Parkinson Disease Rating Scale

REFERENCES

1. Nutt JG, Wooten GF. Diagnosis and initial management of Parkinson's disease. N Engl J Med. 2005;353:1021–1027.
2. Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet. 2009;373(9680):2055–2066. Review. Erratum in: Lancet. 2009; 374(9691):684.
3. Oertel WH. Recent advances in treating Parkinson's disease. F1000Res. 2017;13(6):260.
4. Suchowersky O, Gronseth G, Perlmutter J, et al.; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: Neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;66:976–982. Erratum in: Neurology. 2006;67(2):299.
5. Goetz CG. Hypokinetic Movement Disorders. In: Textbook of Clinical Neurology, 3rd ed. Philadelphia, PA: Saunders; 2007:Chap.16. Available from: http://www.mdconsult.com. Accessed August 15, 2014.
6. Zesiewicz TA, Sullivan KL, Arnulf I, et al. Practice parameter: treatment of nonmotor symptoms of Parkinson disease. Neurology. 2010;74(11):924–931.
7. Chen JJ, Dashtipour K. Pharmacotherapy, 10th ed. New York: McGraw-Hill Medical, c2017. Chapter 59, Parkinson Disease: 895–908.
8. Fernandez HH. Updates in the medical management of Parkinson disease. Clev Clin J Med. 2012;79(1):28–35.
9. Weiner WJ, Shulman LM, Lang AE. Parkinson's isease: a complete guide for patients and families, 3rd ed. Baltimore, MD: John Hopkins University Press; 2013.
10. Horstink M, Tolosa E, Bonuccelli U, et al.; European Federation of Neurological Societies; Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society-European Section. Part I: Early (uncomplicated) Parkinson's disease. Eur J Neurol. 2006;13(11):1170–1185.
11. Horstink M, Tolosa E, Bonuccelli U, et al.; European Federation of Neurological Societies; Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies (EFNS) and the Movement Disorder Society-European Section (MDS-ES). Part II: Late (complicated) Parkinson's disease. Eur J Neurol. 2006;13(11): 1186–1202.
12. Oertel WH, Berardelli A, Bloem BR. Early (uncomplicated) Parkinson's disease. In: Gilhus NE, Barnes MP, Brainin M, eds. European Handbook of Neurological Management. Vol. 1, 2nd ed. Blackwell, 2011:217–236.
13. Oertel WH, Berardelli A, Bloem BR. Late (uncomplicated) Parkinson's disease. In: Gilhus NE, Barnes MP, Brainin M, eds. European Handbook of Neurological Management. Vol. 1, 2nd ed. Blackwell, 2011:237–267.
14. Zesiewicz TA, Sullivan KL, Arnulf I, et al. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: treatment of nonmotor symptoms of Parkinson disease: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74(11):924–931.
15. Pfeiffer RF. Autonomic dysfunction in Parkinson's disease. Expert Rev Neurother. 2012;12(6):697–706.
16. Bakay S, Bechet S, Barjona A, Delvaux V, Salmon E, Garraux G. Dementia in Parkinson's disease: risk factors, diagnosis and treatment. Rev Med Liege. 2011;66(2):75–81.
17. Burn DJ. The treatment of cognitive impairment associated with Parkinson's disease. Brain Pathol. 2010;20(3):672–678.
18. Blonder LX, Slevin JT. Emotional dysfunction in Parkinson's disease. Behav Neuro. 2011;24(3):201–217.
19. Rizek P, Kumar N, Jog MS. An update on the diagnosis and treatment of Parkinson disease. CMAJ. 2016;188(16):1157–1165.
20. Gottwald MD, Aminoff MJ. Therapies for dopaminergic-induced dyskinesias in Parkinson disease. Ann Neurol. 2011;69(6):919–927.
21. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129–2170.
22. PD Med Collaborative Group. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomized trial. Lancet. 2014;384(9949):1196–1205.
23. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2002;58:11–17.
24. Parkinson's Disease in Adults. NICE guideline [NG71]. National Institute for Health and Care Excellence. Available from: https://www.nice.org.uk/guidance/ng71. Accessed September 11, 2017.
25. Clarke CE, Patel S, Ives N, Rick C, Wheatley K, Gray R. Should treatment for Parkinson's disease start immediately on diagnosis or delayed until functional disability develops? Mov Disord. 2011;26(7):1187–1193.
26. Dietrichs E, Odin P. Algorithms for the treatment of motor problems in Parkinson's disease. Acta Neurol Scand. 2017 Jan 30. [Epub ahead of print.]
27. Anonymous. Drugs for Parkinson's disease. Treat Guidel Med Lett. 2011;9(101):1–6.
28. Williams NR, Okun MS. Deep Brain Simulation (DBS) at the interface of neurology and psychiatry. J Clin Invest. 2013;123(11): 4546–4556.
29. Gazewood JD, Richards DR, Clebak, K. Parkinson disease: an update. Am Fam Physician. 2013;87(4):267–273.

30. Diagnosis and Pharmacological Management of Parkinson's Disease. A National Clinical Guideline. Scottish Intercollegiate Guidelines Network (SIGN). Available from: www.sign.ac.uk/sign113.pdf. Accessed September 1, 2017.
31. Heetun ZS, Quigley E. Gastroparesis and Parkinson's disease: a systematic review. Parkinsonism Relat Disord. 2012;18:443–440.
32. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. JAMA. 2014;311(16):1670–1683.
33. Product information. Symmetrel (amantadine). Chadds Ford, PA. Endo Pharmaceuticals, January 2009.
34. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; January 29, 2017 (last accessed September 1, 2017).
35. Oertel W, Eggert K, Pahwa R, et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3). Mov Disord. 2017 Aug 21. [Epub ahead of print.]
36. Ahlskog JE, Uitti RJ. Rasagiline, Parkinson neuroprotection, and delayed-start trials: Still no satisfaction? Neurology. 2010;74(14):1143–1148.
37. Hauser RA. Early pharmacologic treatment in Parkinson's disease. Am J Manag Care. 2010;(16 Suppl Implications):S100–S107.
38. Perez-Lloret S, Rascol O. Dopamine receptor agonists for the treatment of early or advanced Parkinson's disease. CNS Drugs. 2012;24(11):941–968.
39. Voon V, Gao J, Brezing C, et al. Dopamine agonists and risk: Impulse control disorders in Parkinson's disease. Brain. 2011;134(5):1438–1446.
40. Knie B, Mitra MT, Logishetty K, Chaudhuri KR. Excessive daytime sleepiness in patients with Parkinson's disease. CNS Drugs. 2011;25(3):203–212.
41. Antonini A, Chaudhuri KR, Martinez-Martin P, Odin P. Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson's disease. CNS Drugs. 2010;24(2):119–129.
42. Combs BL and Cox AG. Update on the treatment of Parkinson's disease psychosis: role of pimavanserin. Neuropsychiatr Dis Treat. 2017;13:737–744.
43. Trenkwalder C, Kies B, Rudzinska M, et al.; Recover Study Group. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: a double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord. 2011;26(1):90–99.

34 Pain Management

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LEARNING OBJECTIVES

LO

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

1. Identify characteristics of the types of pain: nociceptive, inflammatory, neuropathic, and functional.
2. Explain the mechanisms involved in pain transmission.
3. Select an appropriate method of pain assessment.
4. Recommend an appropriate choice of analgesic, dose, and monitoring plan for a patient based on type and severity of pain and other patient-specific parameters.
5. Perform calculations involving equianalgesic doses, conversion of one opioid to another, rescue doses, and conversion to a continuous infusion.
6. Educate patients and caregivers about effective pain management, dealing with chronic pain, and the use of nonpharmacologic measures.

INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] KEY CONCEPT Pain is an unpleasant subjective experience that is the net effect of a complex interaction of the ascending and descending neurons involving biochemical, physiologic, and psychological processes. Pain can affect all areas of a person's life including sleep, thought, emotion, and activities of daily living. There are no reliable objective markers for pain, thus the patient is the only person who can describe the intensity and quality of their pain.

EPIDEMIOLOGY AND ETIOLOGY

Prevalence of Pain

Most people experience pain at some time in their lives, and pain is a symptom of a variety of diseases. Thus identifying the exact prevalence of pain is a difficult task. Prevalence rates for a variety of different types of pain have been described (Table 34–1). Patients 65 years and older bear a significant burden of pain. The prevalence of pain in people older than 60 years is twice that in those younger than 60 years.[8] Studies suggest that 25% to 50% of community-dwelling elderly suffer pain. Pain is quite common among nursing home residents. It is estimated that 45% to 80% of nursing home patients and 25% of those with daily pain received neither analgesic medication nor nonpharmacologic treatment for their pain, contributing to functional impairment and a decreased quality of life.[8]

The financial impact of pain is considered to be significant. The total cost of pain in the United States has been estimated at $560–$635 billion annually, about half of this cost is due to direct costs of health care while the other half is due to lost productivity.[9]

Challenges in Pain Management

Despite the growing emphasis on pain management, pain often remains undertreated and continues to be a problem in hospitals, long-term care facilities, and the community. In one series of reports, 50% of seriously ill hospitalized patients reported pain; however, 15% were dissatisfied with pain control, and some remained in pain after hospitalization.[10]

Barriers to adequate pain management may be due to fear of becoming addicted to opioids or cultural beliefs. Elderly patients might not report pain for a variety of reasons including belief that pain is something they must live with, fear of consequences (eg, hospitalization, loss of independence), fear that the pain might be forecasting impending illness, inability to understand terminology used by health care providers, or a belief that showing pain is unacceptable behavior.

Concerns about adequate pain management must be balanced with concerns about opioid misuse, abuse, and diversion to achieve optimal pain management. Opioid use, abuse, and adverse effects have risen to epidemic proportions since the 1990s. While the United States has 4.6% of the global population, the country used 69% of the world's opioid supply.[11] Over the last 15 years, there has been an increase in deaths related to prescription opioids and increase in overdoses due to illicit opioids.[12] Several recent guidelines have been published by the Centers for Disease Control and Prevention (CDC) and American Society of Interventional Pain Physicians (ASIPP) to provide guidance for the use of opioids to ensure patients have access to safer, more effective chronic pain treatment while reducing the number of people who misuse, abuse, or overdose from these drugs.[13,14]

Table 34–1

Prevalence of Selected Pain Diagnoses[2–7]

Pain Diagnoses	Prevalence (%)
Back pain	74.7
Cancer	14–100
Chronic pain	10.4
Complex regional pain syndrome	1.2
Degenerative spine disease	63.6
Fibromyalgia	2
Limb pain	50
Migraine	12
Neuritis/radiculitis	52.8
Neuropathic pain	9.8

PATHOPHYSIOLOGY

Types of Pain

LO 1 Several distinct types of pain have been described, for example, nociceptive, inflammatory, neuropathic, and functional.[15] Nociceptive pain is a transient pain in response to a noxious stimulus at **nociceptors** that are located in cutaneous tissue, bone, muscle, connective tissue, vessels, and viscera. Nociceptors are classified as thermal, chemical, or mechanical. The nociceptive system extends from the receptors in the periphery to the spinal cord, brainstem, and the cerebral cortex where pain sensation is perceived. This system is a key physiologic function that prevents further tissue damage due to the body's autonomic withdrawal reflex. When tissue damage occurs despite the LO 2 nociceptive defense system, inflammatory pain ensues. The body now changes focus from protecting against painful stimuli to protecting the injured tissue. The inflammatory response contributes to pain hypersensitivity that serves to prevent contact or movement of the injured part until healing is complete, thus reducing further damage.

LO 1 Neuropathic pain is defined as spontaneous pain and hypersensitivity to pain associated with damage to or pathologic changes in the peripheral or central nervous system (CNS). Functional pain, a relatively newer concept, is pain sensitivity due to an abnormal processing or functioning of the CNS in response to normal stimuli. Several conditions considered to have this abnormal sensitivity or hyperresponsiveness include fibromyalgia and irritable bowel syndrome.

Mechanisms of Pain

▶ *Pain Transmission*

LO 2 The mechanisms of nociceptive pain are well defined and provide a foundation for the understanding of other types of pain.[16] Following nociceptor stimulation, tissue injury causes the release of substances (bradykinin, serotonin, potassium, histamine, prostaglandins, and substance P) that might further sensitize and/or activate nociceptors. Nociceptor activation produces action potentials (transduction) that are transmitted along myelinated Aδ-fibers and unmyelinated C-fibers to the spinal cord. The Aδ-fibers are responsible for first, fast, sharp pain, and release excitatory amino acids that activate α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in the dorsal horn. The C-fibers produce second pain, which is described as dull, aching, burning, and diffuse. These nerve fibers synapse in the dorsal horn of the spinal cord, where several neurotransmitters are released including glutamate, substance P, and calcitonin gene-related peptide. Transmission of pain signals continues along the spinal cord to the thalamus, which serves as the pain relay center, and eventually to the cortical regions of the brain where pain is perceived.

▶ *Pain Modulation*

Modulation of pain (inhibition of nociceptive impulses) can occur by a number of processes. Based on the gate-control theory, pain modulation might occur at the level of the dorsal horn.[17] Because the brain can process only a limited number of signals at one time, other sensory stimuli at nociceptors might alter pain perception. This theory supports the effectiveness of counterirritants and transcutaneous electrical nerve stimulation (TENS) in pain management. Pain modulation can occur through several other complex processes. The endogenous opiate system consists of endorphins (enkephalins, dynorphins, and β-endorphins) that interact with μ-, δ-, and κ-receptors throughout the CNS to inhibit pain impulses and alter perception. The CNS also includes inhibitory descending pathways from the brain that can attenuate pain transmission in the dorsal horn. Neurotransmitters involved in this descending system include endogenous opioids, serotonin, norepinephrine, γ-aminobutyric acid (GABA), and neurotensin. The perception of pain involves not only nociceptive stimulation but also physiologic and emotional input. Consequently, cognitive behavioral treatments such as distraction, relaxation, and guided imagery can reduce pain perception by altering pain processing in the cortex.

▶ *Peripheral Sensitization, Central Sensitization, and Windup*

Under normal conditions, a balance generally exists between excitatory and inhibitory neurotransmission. Changes in this balance can occur both peripherally and centrally, resulting in exaggerated responses and sensitization, such as that observed in inflammatory, neuropathic, or functional chronic pain. Pain in these settings might occur spontaneously without any stimulus or might be evoked by a stimulus. Evoked pain might arise from a stimulus that normally does not cause pain (**allodynia**) such as a light touch in neuropathic pain. **Hyperalgesia**, an exaggerated and/or prolonged pain response to a stimulus that normally causes pain, can also occur as a result of increased sensitivity in the CNS.

During normal pain transmission, the AMPA receptors are activated, but the *N*-methyl-D-aspartate (NMDA) receptor is blocked by magnesium.[16] Repeated nerve depolarization causes release of the magnesium block, allowing the influx of calcium and sodium, and results in excessive excitability and amplification of signals. Continued input from C-fibers and subsequent increases in substance P and glutamate causes the activation of the NMDA receptor, a process referred to as windup. Windup increases the number and responsiveness of neurons in the dorsal horn irrespective of the input from the periphery. Recruitment of neurons not normally involved in pain transmission or spread occurs, leading to allodynia, hyperalgesia, and spread to uninjured tissues.[18] The windup phenomenon supports the observation that untreated acute pain can lead to chronic pain and the belief that pain processes are plastic and not static.

CLINICAL PRESENTATION AND DIAGNOSIS

Classification of Pain

Pain has always been described as a symptom. However, recent advances in the understanding of neural mechanisms have

demonstrated that unrelieved pain might lead to changes in the nervous system known as neural plasticity. Because these changes reflect a process that influences a physiologic response, pain, particularly chronic pain, might be considered a disease unto itself.

Pain can be divided into two broad categories: acute and chronic pain. Acute pain is also referred to as adaptive pain because it serves to protect the individual from further injury or promote healing.[17] However, chronic pain has been called maladaptive, a pathologic function of the nervous system or pain as a disease.

▶ *Acute Pain*

Acute pain is pain that occurs as a result of injury or surgery and is usually self-limited, subsiding when the injury heals. Untreated acute pain can produce physiologic symptoms including tachypnea, tachycardia, and increased sympathetic nervous system activity, such as pallor, diaphoresis, and pupil dilation. Furthermore, poorly treated pain can cause psychological stress and compromise the immune system due to the release of endogenous corticosteroids. Somatic acute pain arises from injury to skin, bone, joint, muscle, and connective tissue, and it is generally localized to the site of injury. Visceral pain involves injury to nerves on internal organs (eg, intestines, liver) and can present as diffuse, poorly differentiated, and often referred pain. Acute pain should be treated aggressively, even before the diagnosis is established, except in conditions of head or abdominal injury where pain might assist in the differential diagnosis.

▶ *Chronic Pain*

Chronic pain persists beyond the expected normal time for healing and serves no useful physiologic purpose. Chronic pain might be nociceptive, inflammatory, neuropathic, or functional in origin; however, all forms share some common characteristics. Chronic pain can be intermittent or persistent, or both. Physiologic responses observed in acute pain are often absent in chronic pain; however, other symptoms might predominate. The four main effects of chronic pain include (a) effects on the physical function, (b) psychological changes, (c) social consequences, and (d) societal consequences. Effects of chronic pain on physical function include impaired activities of daily living and sleep disturbances. Psychological components of chronic pain might include depression, anxiety, anger, and loss of self-esteem. As a result of physical and psychological changes, social consequences might ensue, such as changes in relationships with friends and family, intimacy, and isolation. Management of chronic pain should be multimodal and might involve cognitive interventions, physical manipulations, pharmacologic agents, surgical intervention, and regional or spinal anesthesia.

Chronic Malignant Pain Chronic malignant pain is associated with a progressive disease that is usually life threatening such as cancer, AIDS, progressive neurologic diseases, end-stage organ failure, and dementia.[19] The goal is pain alleviation and prevention, often through a systematic and stepwise approach. Tolerance, dependence, and addiction are often not a concern due to the terminal nature of the illness.

Chronic Nonmalignant Pain Pain not associated with a life-threatening disease and lasting more than 6 months beyond the healing period is referred to as chronic nonmalignant pain. Pain associated with low back pain, osteoarthritis, previous bone fractures, peripheral vascular disease, genitourinary infection, rheumatoid arthritis, and coronary heart disease is considered nonmalignant. The numerous causes of this type of chronic pain make treatment complex and involves a multidisciplinary approach. Treatment is initially conservative but might involve the use of more potent analgesics including opiates in psychologically healthy patients.[20]

Neuropathic Pain Neuropathic pain is considered to be a type of chronic nonmalignant pain involving disease of the central and peripheral nervous systems. Neuropathic pain might be broadly categorized as peripheral or central in nature. Examples of neuropathic pain include postherpetic neuralgia (PHN), which is pain associated with acute herpetic neuralgia or an acute shingles outbreak. Peripheral or polyneuropathic pain is associated with the distal polyneuropathies of diabetes, human immunodeficiency virus (HIV), and chemotherapeutic agents. Types of **central pain** include central stroke pain, trigeminal neuralgia, and a complex of syndromes known as complex regional pain syndrome (CRPS). CRPS includes both reflex sympathetic dystrophy and **causalgia**, both of which are neuropathic pain associated with abnormal functioning of the autonomic nervous system.

The symptoms of neuropathic pain are characterized as tingling, burning, shooting, stabbing, electric shock–like quality, or radiating pain. The patient might describe either a constant dull throbbing or burning pain, or an intermittent pain that is stabbing or shooting. Damage to the peripheral nerves might frequently be referred to the body region innervated by those nerves.

Clinical Presentation and Diagnosis of Pain

General

Patients may be in acute distress (acute pain) or have no signs or symptoms of suffering (chronic pain).

Symptoms

Pain is described based on the following characteristics: onset, duration, location, quality, severity, and intensity. Other symptoms may include anxiety, depression, fatigue, anger, fear, and insomnia.

Signs

Acute pain may cause hypertension, tachycardia, diaphoresis, mydriasis, and pallor.

Diagnosis

The patient is the only person who can describe the intensity and quality of their pain. There are no laboratory tests that can diagnose pain.

Pain Assessment

Effective pain management begins with a thorough and accurate assessment of the patient. Even though pain is a common presenting complaint, lack of regular assessment and reassessment of pain remains a problem and contributes to the mismanagement of pain.[21]

KEY CONCEPT Following initial assessment of pain, reassessment should be done as needed based on medication choice and the clinical situation.

▶ *Methods of Pain Assessment*

A patient-oriented approach to pain is essential, and methods do not differ greatly from those used in other medical conditions. A comprehensive history (medical, family, and psychological) and physical are necessary to evaluate underlying disease processes for the source of pain and other factors contributing to the pain.[18] A thorough assessment of the characteristics of the pain should be completed, including questions about the pain (onset, duration, location, quality, severity, and intensity), pain relief efforts, and efficacy and side effects of current and past treatments for pain. A common mnemonic for pain assessment is PQRST (Palliative/precipitating, Quality, Radiation, Severity, and Time).[22] Some clinicians have suggested the addition of U ("you") to this mnemonic.[23] During the pain interview, the impact of pain on the patient's functional status, behavior, and psychological status should also be assessed. Evaluation of psychological status is especially important in patients with chronic pain because depression and other affective disorders might be common comorbid conditions. A history of drug and alcohol use should be elicited due to the potential for addiction in patients who take opiates or other pain medications with a potential for abuse. Other conditions, such as renal or hepatic dysfunction, diabetes, and conditions that affect bowel function, can influence therapy choices and goals. A discussion of the patient's expectations and goals with respect to pain management (level of pain relief, functional status, and quality of life) should also be part of any pain interview.

▶ *Pain Assessment Tools*

LO 3

Pain, particularly acute pain, might be accompanied by physiologic signs and symptoms, but there are no reliable objective markers for pain. Many tools have been designed for assessing the severity of pain including rating scales and multidimensional pain assessment tools.

Rating scales provide a simple way to classify the intensity of pain, and they should be selected based on the patient's ability to communicate (Figure 34–1).[24] Numeric scales are widely used and ask patients to rate their pain on a scale of 0 to 10, with 0 indicating no pain and 10 being the worst pain possible. Using this type of scale, 1 to 3 is considered mild pain, 4 to 6 is moderate pain, and 7 to 10 is severe pain. The visual analog scale (VAS) is similar to the numerical scale in that it requires patients to place a mark on a 10-cm line where one end is no pain, and the worst possible pain is on the other end. For patients who have difficulty assigning a number to their pain, a categorical scale might be an option to communicate the intensity of the pain experience. Examples of this include a simple descriptive list of words and the Wong–Baker FACES of Pain Rating Scale.[25]

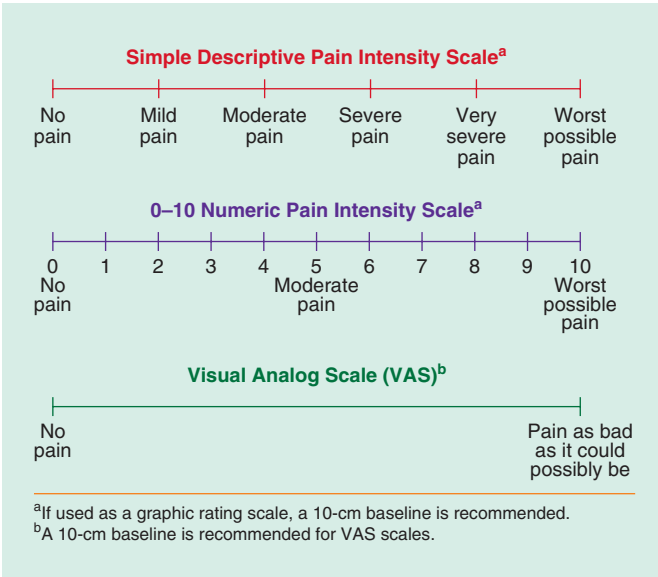

FIGURE 34–1. Pain rating scales. (From U.S. Department of Health and Human Services, Agency for Health Care Policy and Research. Clinical practice guideline, cancer pain management. Rockville, MD: AHCPR; 1994 [cited 2014 Nov 6]. http://www.ncbi.nlm.nih.gov/books/bookres.fcgi/hstat6/f37_capcf4.gif.)

Multidimensional assessment tools obtain information about the pain and impact on quality of life, but they are often more time consuming to complete. Examples of these types of tools include the Initial Pain Assessment Tool, Brief Pain Inventory, McGill Pain Questionnaire, the Neuropathic Pain Scale, and the Oswestry Disability Index.[26–30] The pain intensity, enjoyment of life, general activity (PEG) assessment tool is an ultra-brief pain assessment tool derived from the Brief Pain Inventory and is recommended by the CDC.[31] The PEG score is the average of three individual scores.

▶ *Pain Assessment in Challenging Populations*

Children Pain interviews can be conducted with children as young as 3 or 4 years of age; however, communication might be limited by vocabulary.[32] Terms familiar to children such as *hurt, owie*, or *boo* boo might be used to describe pain. The VAS is best used with children older than 7 years. Other scales based on numbers of objects (eg, pokers chips), increasing color intensity, or faces of pain might be helpful for children between 4 and 7 years of age. In children younger than 3 to 4 years, behavioral or physiologic measures, such as pulse or respiratory rate, might be more appropriate. Pain assessment in newborns and infants relies on behavioral observation for such clues as vocalizations (crying and fussing), facial expressions, body movements (flailing of limbs and pulling legs in), withdrawal, and change in eating and sleeping habits.[32] Preschool children experiencing pain might become clingy, lose motor and verbal skills, and start to deny pain because treatment might be linked to discomfort or punishment.

Patient Encounter Part 1

HPI: A 78-year-old man who is to undergo a left above the knee amputation due to a limb abscess

PMH: Peripheral artery disease for 18 years; cardiomyopathy, benign prostatic hypertrophy for 13 years

FH: Mother had osteoporosis; father had diabetes

SH: Lives with wife; has two grown children

Meds: aspirin 81mg daily; atorvastatin 80 mg at bedtime; multivitamin 1 daily; pantoprazole 40 mg daily; tamsulosin 0.4 mg daily

Pain Assessment: Patient rates pain as 8 on a scale of 0 to 10

Based on the type of injury, what type of pain is this patient likely to experience?

What type of pain management regimen would you recommend in the postoperative period?

Explain your answer.

School-age children might exhibit aggressiveness, nightmares, anxiety, and withdrawal when in pain; adolescents might respond to pain with oppositional behavior and depression.

Elderly Most of the previously discussed pain scales can be used in older persons who are cognitively intact or with mild dementia. The pain thermometer and FACES of pain have been studied in older persons. In persons with moderate to severe dementia or those who are nonverbal, observation of pain behaviors, such as guarding or grimacing, provides an alternative for pain assessment. The Pain Assessment in Advanced Dementia (PAINAD) tool might be used to quantify signs of pain and involves observing the older adult for 15 minutes for breathing, negative vocalizations, facial expression, body language, and consolability.[33] Regardless of which pain assessment tool is used, the practitioner should first determine if the patient understands the concept of the scale to ensure reliability of the instrument.

TREATMENT

Desired Outcomes

Prevention, reduction, and/or elimination of pain are important goals for the treatment of acute pain. With chronic pain, elimination of pain might not be possible, and goals might focus on improvement or maintenance of functional capacity and quality of life.

General Approach to Treatment

KEY CONCEPT Effective treatment involves an evaluation of the cause, duration, and intensity of the pain, and selection of an appropriate treatment modality for the pain situation. Depending on the type of pain, treatment might involve pharmacologic and nonpharmacologic therapy or both. General principles for the pharmacologic management of pain are listed in the section "Patient Care Process." Two common approaches to the selection of treatment are based on severity of pain and the mechanism responsible for the pain (Figure 34–2). Clinical practice guidelines for pain management are available from the American Pain Society (APS), the Agency for Healthcare Research and Quality (AHRQ), the American Geriatrics Society (AGS), and the American Society of Anesthesiologists (ASA).

▶ *Selection of Agent Based on Severity of Pain*

KEY CONCEPT Whenever possible, the least potent oral analgesic should be selected. Guidelines for the selection of therapeutic agents based on pain intensity are derived from the World Health Organization (WHO) analgesic ladder for the management of cancer pain (Table 34–2).[34] Mild to moderate pain is generally treated with nonopioid analgesics. Combinations of medium-potency opioids and acetaminophen (APAP) or nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for moderate pain. Potent opioids are recommended for severe pain. Throughout this progression, adjuvant medications are added, as needed, to manage side effects and to augment analgesia. While these guidelines can be useful for initial therapy, the clinical situation (type of pain), cost, pharmacokinetic profile of available drugs, and patient-specific factors (age, concomitant illnesses, previous response, and other medications) must also be considered. Pain medications might also be used in the absence of pain in anticipation of a painful event such as surgery to minimize peripheral and central sensitization.

LO 4

▶ *Mechanistic Approach to Therapy*

Current analgesic therapy is aimed at controlling or blunting pain symptoms. However, diverse mechanisms contributing to the various types of pain continue to be further elucidated.

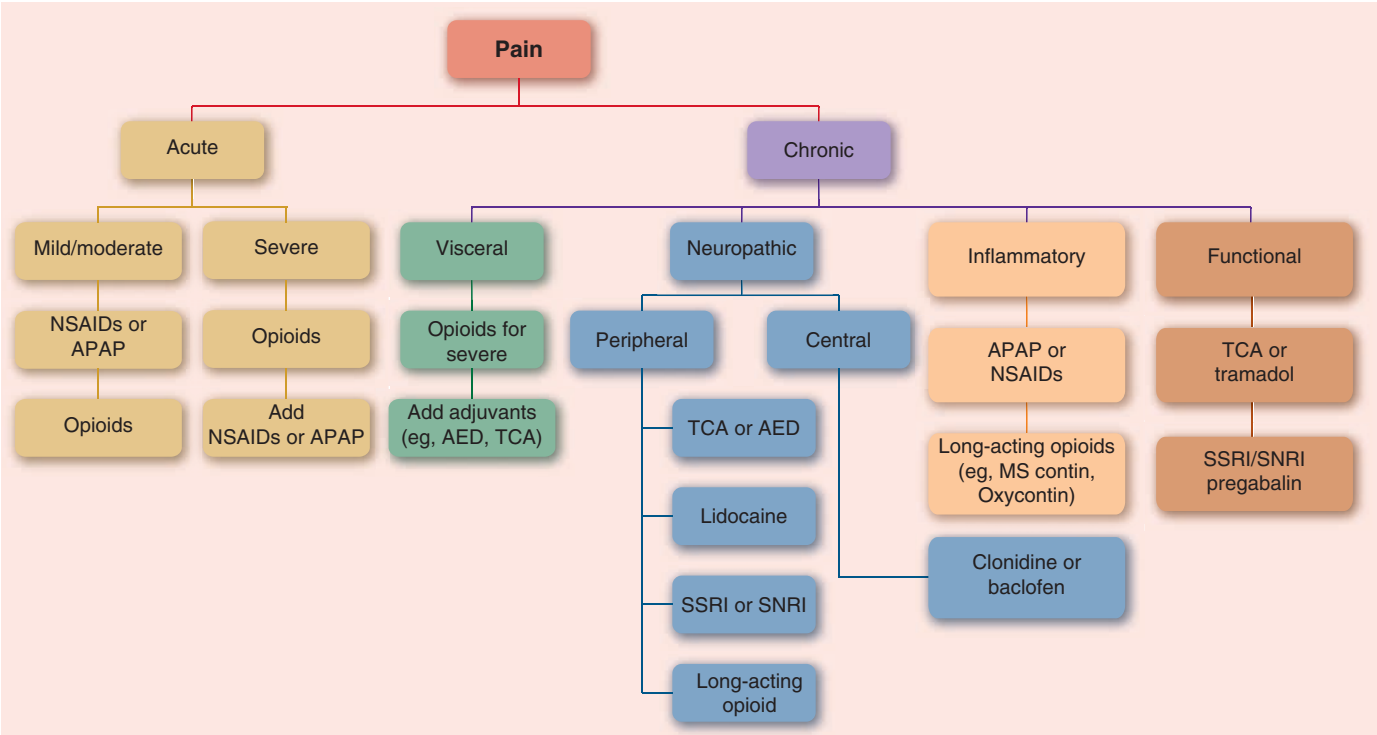

FIGURE 34–2. Pain algorithm. (AED, antiepileptic drugs; APAP, acetaminophen; MS, morphine sulfate; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.)

Table 34–2

Selection of Analgesics Based on Intensity of Pain[34,35,38]

Pain Intensity	Corresponding Numerical Rating	WHO Therapeutic Recommendations	Examples of Initial Therapy	Comments
Mild	1–3/10	Nonopioid analgesic; regular scheduled dosing	Acetaminophen 1000 mg every 6 hours; ibuprofen 600 mg every 6 hours	Consider adding an adjunct or using an alternate regimen if pain is not reduced in 1–2 days
Moderate	4–6/10	Add an opioid to the nonopioid for moderate pain; regular scheduled dosing	Acetaminophen 325 mg + codeine 60 mg every 4 hours; acetaminophen 325 mg + oxycodone 5 mg every 4 hours	Consider step-up therapy if pain is not relieved by two or more different drugs
Severe	7–10/10	Switch to a high-potency opioid; regular scheduled dosing	Morphine 10 mg every 4 hours; or hydromorphone 4 mg every 4 hours	

An understanding of these new mechanisms of pain transmission might lead to improvement in pain management as pharmacologic management of pain becomes more mechanism specific. Use of NSAIDs for inflammatory types of pain is an example of a mechanistic approach. Because several mechanisms of pain often coexist, a multimodal approach seems rational to target each mechanism.

Nonpharmacologic Therapy

LO 6 Nonpharmacologic therapies (psychological interventions and physical therapy) might be used in both acute and chronic pain. Psychological interventions can reduce pain as well as the anxiety, depression, fear, and anger associated with pain. Psychological interventions helpful in management of acute pain are imagery (picturing oneself in a safe, peaceful place) and distraction (listening to music or focusing on breathing). Chronic pain patients might benefit from relaxation, biofeedback, cognitive behavioral therapy, psychotherapy, support groups, and spiritual counseling.

Physical therapy is an essential part of many types of pain situations. Treatment modalities include heat, cold, water, ultrasound therapy, TENS, massage, and therapeutic exercise. Heat and cold therapy are utilized in a variety of musculoskeletal conditions (muscle spasms, low back pain, fibromyalgia, sprains, and strains).

Pharmacologic Therapy

▶ *Nonopioid Analgesics*

LO 4 **Acetaminophen** APAP, an analgesic and antipyretic, is often selected as initial therapy for mild to moderate pain and is considered first line in several pain situations such as low back pain and osteoarthritis.[35] Mechanistically, APAP is believed to inhibit prostaglandin synthesis in the CNS and block pain impulses in the periphery. APAP is well tolerated at usual doses and has few clinically significant drug interactions except causing increased hypoprothrombinemic response to warfarin in patients receiving APAP doses of more than 2000 mg/day.[36] The maximum recommended dose for patients with normal renal and hepatic function is 4000 mg/day. Hepatotoxicity has been reported with excessive use and overdose, and the risk of this adverse effect increases in those with hepatitis or chronic alcohol use, as well as those who binge drink or are in a fasting state. Due to concerns of unintentional overuse and hepatoxicity, the FDA requires warning labels on OTC APAP products and limited the APAP component of narcotic analgesic combination to 325 mg per dosing unit. For these reasons, the maximum dose should be reduced by 50% to 75% in patients with renal dysfunction or hepatic disease and in those who engage in excessive alcohol use.

Aspirin and Other Salicylates Aspirin, nonacetylated salicylates, and other NSAIDs have analgesic, antipyretic, and anti-inflammatory actions. These agents inhibit cyclooxygenase (COX-1 and COX-2) enzymes, thereby preventing prostaglandin synthesis, which results in reduced nociceptor sensitization and an increased pain threshold.

Aspirin is effective for mild to moderate pain; however, the risk of gastrointestinal (GI) irritation and bleeding limits frequent use of this drug for pain management. Direct effects of aspirin on the GI mucosa and irreversible platelet inhibition contribute to this risk, which can occur even at low doses. Hypersensitivity reactions are also possible and might occur in 25% of patients with coexisting asthma, nasal polyps, or chronic urticaria. Of additional concern is the potential for cross-sensitivity of other NSAIDs in this group of patients. Nonacetylated salicylates (choline magnesium salicylate and sodium salicylate) have a reduced risk of GI effects and platelet inhibition and might be used in aspirin-sensitive patients.

LO 4 **Nonsteroidal Anti-inflammatory Drugs** NSAIDs are the preferred agents for mild to moderate pain in conditions that are mediated by prostaglandins (rheumatoid arthritis, menstrual cramps, and postsurgical pain) and in the management of pain from bony metastasis, but they are of minimal use in neuropathic pain. NSAIDs provide analgesia equal to or better than that of aspirin or APAP combined with codeine, and they are very effective for inflammatory pain and pain associated with bone metastasis.[16] These agents are classified by their chemical structures (fenamates, acetic acids, propionic acids, pyranocarboxylic acids, pyrrolizine carboxylic acids, and COX-2 inhibitors). Although only some members of this class have approval for treatment of pain, it is likely that all of them have similar analgesic effects. All members of this class appear to be equally effective, but there is great intrapatient variability in response. After an adequate trial of 2 to 3 weeks with a particular oral agent, it is reasonable to switch to another member of the class. Ketorolac and ibuprofen are available in parenteral and oral

dosage forms; unlike other NSAIDs, ketorolac's duration of use is limited to 5 days due to risk of serious GI side effects. NSAIDs demonstrate a flat-dose response curve, with higher doses producing no greater efficacy than moderate doses but resulting in an increased incidence of adverse effects (GI irritation, hepatic dysfunction, renal insufficiency, platelet inhibition, sodium retention, and CNS dysfunction).

Patients at increased risk of NSAID-induced GI adverse effects (eg, dyspepsia, peptic ulcer formation, and bleeding) include the elderly, those with peptic ulcer disease, coagulopathy, and patients receiving high doses of concurrent corticosteroids. Nephrotoxicity is more common in the elderly, patients with creatinine clearance values less than 50 mL/min (0.84 mL/s), and those with volume depletion or on diuretic therapy. NSAIDs should be used with caution in patients with reduced cardiac output due to sodium retention and in patients receiving antihypertensives, warfarin, and lithium.

NSAIDs are classified as nonselective (they inhibit COX-1 and COX-2) or selective (inhibit only COX-2) based on degree of COX inhibition. COX-2 inhibition is responsible for anti-inflammatory effects, whereas COX-1 inhibition contributes to increased GI and renal toxicity associated with nonselective agents. Because the antiplatelet effect of nonselective NSAIDs is reversible, concurrent use might reduce the cardioprotective effect of aspirin due to competitive inhibition of COX-1. A boxed warning highlighting the potential for increased risk of cardiovascular events and GI bleeding is now required for all prescription nonselective NSAIDs and celecoxib. Stronger warnings about these adverse events are also required on nonprescription NSAIDs. When an NSAID is needed in a patient with cardiovascular risk, the benefits of therapy must outweigh the risks, and the lowest effective dose of the NSAID is recommended.[37]

▶ *Opioid Analgesics*

LO 4

Opioids are considered the agents of choice for the treatment of severe acute pain and moderate to severe pain associated with cancer.[38] Opioids are classified by their activity at the receptor site, usual pain intensity treated, and duration of action (short acting versus long acting).

Selection and Dosing The opioids exert their analgesic efficacy by stimulating opioid receptors (μ, κ, and δ) in the CNS. There is a wide variety of potencies among the opioids, with some used for moderate pain (codeine, hydrocodone, tramadol, and partial agonists) and others reserved for severe pain (morphine and hydromorphone). Pure agonists (morphine) bind to μ-receptors to produce analgesia that increases with dose without a ceiling effect. Pure agonists are divided into three chemical classes: phenanthrenes or morphine-like, phenyl piperidine or meperidine-like, and diphenyl heptane or methadone-like. Partial agonists/antagonists (butorphanol, pentazocine, and nalbuphine) partially stimulate the μ-receptor and antagonize the κ-receptors. This activity results in reduced analgesic efficacy with a ceiling dose, reduced side effects at the μ-receptor, psychotomimetic side effects due to κ-receptor antagonism, and possible withdrawal symptoms in patients who are dependent on pure agonists.

LO 4

Selection of the agent and route depend on individual patient-related factors including severity of pain, individual perceptions, weight, age, opioid tolerance, and concomitant disease (renal or hepatic dysfunction). Because pure agonists are pharmacologically similar, choice of agent might be also guided by pharmacokinetic parameters and other drug characteristics. Hepatic impairment can decrease the metabolism of most opioids, particularly methadone, meperidine, and pentazocine. Furthermore, the clearance of meperidine and morphine and their metabolites is reduced in renal dysfunction.

Table 34–3

Equianalgesic Doses of Selected Opioids[23,38,41,42]

Opioid (Brand Name)	Dose Equianalgesic to 10 mg of Parenteral Morphine (mg)	
	Parenteral (mg)	Oral (mg)
Mild to Moderate Pain		
Codeine (generic, various)	120	200
Hydrocodone (Vicodin, Lorcet)	N/A	30
Oxycodone (OxyContin, OxyFAST, Oxy IR)	N/A	20
Meperidine (Demerol)	100	400
Moderate to Severe Pain		
Morphine (Roxanol, MS Contin, Kadian, Avinza)	10	30
Hydromorphone (Dilaudid)	1.5	7.5
Oxymorphone (Opana, Opana SR, Numorphan)	1	N/A
Levorphanol (Levo-Dromoran)	2	4
Fentanyl (Duragesic)	0.1–0.2	N/A[a]
Methadone (Dolophine)	10[b]	3–5[b]

[a]Transdermal: 100 mcg/hour = 2–4 mg/hour of IV morphine.

[b]Dosage calculations when converting from morphine to methadone are not linear. The equianalgesic dose of methadone will decrease progressively as the morphine equivalents increase (Table 34–4).

IR, immediate release.

Table 34–3 provides a summary of opiate options, but several drugs warrant further discussion. Normeperidine, the active metabolite of meperidine, can produce tremors, myoclonus, delirium, and seizures. Due to the potential for accumulation of normeperidine, meperidine should not be used in the elderly, those with renal impairment, in patients using patient-controlled analgesia (PCA) devices, or for more than 1 to 2 days of intermittent dosing. Methadone is unique among the opiates because it has several mechanisms (μ-agonist, NMDA-receptor antagonist, and inhibition of reuptake of serotonin and norepinephrine). The long half-life of methadone (30 hours) permits extended dosing intervals; however, the potential for accumulation with repeated dosing often results in challenging dose conversion and concerns for respiratory depression. Another safety concern with methadone involves risk of arrhythmia secondary to QT prolongation. Tramadol is a synthetic opioid with a dual mechanism of action (μ-agonist and inhibition of serotonin and norepinephrine reuptake) and efficacy and safety similar to that of codeine plus APAP. Tramadol has been evaluated in several types of neuropathic pain and might have a role in the treatment of chronic pain. Tramadol is associated with an increased risk of seizures in patients with a seizure disorder, those at risk for seizures, and those taking medications that can lower the seizure threshold. The use of tramadol with other serotonergic drugs (eg, selective serotonin reuptake inhibitors [SSRIs]) might precipitate serotonin syndrome. Although originally thought not to be habit forming, dependence can occur with tramadol.

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About 70% of individuals will experience significant analgesia from 10 mg/70 kg of body weight of intravenous (IV) morphine or its equivalent.[16] For severe pain in opiate-naive patients, a usual starting dose is 5 to 10 mg of IV morphine every 4 hours.

In the initial stages of severe pain, medication should be given around the clock. Rescue doses should be made available for breakthrough pain in doses equivalent to 10% to 20% of the total daily opioid requirement and administered every 2 to 6 hours if needed. Alternatively, one-sixth of the total daily dose or one-third of the 12-hourly dose might be used. Scheduled doses should be titrated based on the degree of pain. One method involves adjustment of the maintenance dose based on the total 24-hour rescue dose requirement. Alternatively, utilizing dose escalation, doses could be increased by 50% to 100% or 30% to 50% of the current dose, for those in severe and moderate pain, respectively. Once pain relief is achieved, and if treatment is necessary for more than a few days for cancer-related pain, conversion to a controlled-release or long-acting opioid may be made with an equal amount of agent. Several sustained-release products are available containing morphine, oxycodone, and fentanyl. Some clinicians will reduce the total daily dose of the long-acting dosage form by 25% when initiating a sustained-release product to reduce the likelihood of oversedation. The dose of a pure agonist is limited only by tolerability to side effects. Tolerance might develop to analgesic effects, necessitating increasing doses to achieve the same level of pain relief. Physical dependence will occur with the long-term use of opioids. However, addiction or psychological dependence is unlikely in legitimate pain patients unless there are predisposing risk factors. Several opioid risk assessment screening tools have been proposed and may be helpful as part of a more comprehensive assessment to screen patients prior to opioid use.[39]

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Opioids are not first-line therapy for chronic pain. In response to the increase in opioid use and adverse events associated with such use, guidelines for the use of opioids in chronic pain have been recommended by the CDC.[14] The guidelines are not intended for patients receiving opioids for cancer treatment, palliative care, or in end-of-life. Table 34–4 provides a summary of these guidelines. In addition to these guidelines, the use of informed consent for chronic opioid therapy, medication management agreements, or pain contracts might be appropriate to monitor the use (prescribing and dispensing) of controlled substances.

Opioids are administered by a variety of routes, including oral (tablet and liquid), sublingual, rectal, transdermal, transmucosal, IV, subcutaneous, and intraspinal. Although the oral and transdermal routes are most common, the method of administration is based on patient needs (severity of pain) and characteristics (swallowing difficulty and preference). Oral opioids have an onset of effect of 45 minutes, so IV or subcutaneous administration might be preferred if more rapid relief is desired. Intramuscular (IM) injections are not recommended because of pain at the injection site and wide fluctuations in drug absorption and peak plasma concentrations achieved. More invasive routes of administration such as PCA and intraspinal (epidural and intrathecal) are primarily used postoperatively but might also be used in refractory chronic pain situations. PCA delivers a self-administered dose via an infusion pump with a preprogrammed dose, minimum dosing interval, and a maximum hourly dose. Morphine, fentanyl, and

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Table 34–4

CDC Guidelines for Prescribing Opioids for Chronic Pain[14]

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.
4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when considering increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
7. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed.
8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.

PDMP, prescription drug monitoring program.

hydromorphone are commonly administered via PCA pumps by the IV route but less frequently by the subcutaneous or epidural route.

Epidural analgesia is frequently used for lower extremity procedures and pain (eg, knee surgery, labor pain, and some abdominal procedures). Intermittent bolus or continuous infusion of preservative-free opioids (morphine, hydromorphone, or fentanyl) and local anesthetics (bupivacaine) might be used for epidural analgesia. Opiates given by this route might cause pruritus that is relieved by naloxone. Adverse effects including respiratory depression, hypotension, and urinary retention might occur. When epidural routes are used in narcotic-dependent patients, systemic analgesics must also be used to prevent withdrawal because the opioid is not absorbed and remains in the epidural space. Doses of opioids used in epidural analgesia are 10 times less than IV doses, and intrathecal doses are 10 times less than epidural doses (ie, 10 mg of IV morphine is equivalent to 1 mg epidural morphine and 0.1 mg of intrathecally administered morphine).[37]

Combination Analgesics Combinations of opioids and nonopioids often result in enhanced analgesia and lower dose of each. Combination analgesics are frequently used in moderate pain. However, in severe pain, the nonopioid component reaches maximum dosage, and thus the usefulness of nonopioids in this situation is limited. Additionally, the combination products are short acting and often not suitable for chronic therapy. Single agents offer greater dosing flexibility than combination products.

Opioid Allergy True narcotic allergies are rare and should not be confused with pruritus associated with opiate use. Cross-sensitivity between morphine-like, meperidine-like, and methadone-like agents is unlikely. Therefore, when an individual is allergic to one drug in a chemical class of opioids, it is reasonable to select an agent in another chemical class. For the purpose of drug selection in patients with allergies, mixed agonists/antagonists should be treated as morphine-like agents.

Tapering of Opioids Tapering of opioids should be considered in the following siutations: painful situation has resolved; in those with prolonged opioid use; upon requests for dosage reduction; lack of clinically meaningful improvement in pain and function (eg, at least 30% improvement on the 3-item PEG scale) dosages ≥ 50 morphine milligram equivalents (MME)/day without benefit or opioids are combined with benzodiazepines; signs of substance use disorder (eg, work or family, problems related to opioid use, difficulty controlling use); overdose or other serious adverse event; or shows early warning signs for overdose risk such as confusion, sedation, or slurred speech. In these situations, the dose should be reduced by 10% per week to avoid withdrawal symptoms.

Managing Opioid Side Effects and Drug Interactions Side effects common to all opioids include sedation, hallucinations, constipation, nausea and vomiting, urinary retention, myoclonus, and respiratory depression. Table 34–5 shows management strategies for side effects. The most frequent side effects are sedation, nausea, and constipation. Sedation and nausea are common when initiating therapy and when increasing doses. Tolerance to respiratory depression develops rapidly with repeated doses, and respiratory depression is rarely a clinically significant problem in pain patients even those with respiratory impairment. Constipation is a significant adverse effect to which tolerance does not develop, and prophylaxis with stimulant laxatives (eg, senna or bisacodyl) and stool softeners such as docusate is recommended.

Table 34–5

Managing Opioid Side Effects[24,38,41]

Adverse Effects	Drug Treatment/Management
Excessive sedation	Reduce dose by 25% or increase dosing interval
Constipation	Casanthranol-docusate one capsule at bedtime or twice daily; senna one to two tablets at bedtime or twice daily; bisacodyl 5–10 mg daily plus docusate 100 mg twice daily; polyethylene glycol 3350 17 grams daily; methylnaltrexone 0.15 mg/kg SQ every other day; naloxegol 12.5–25 mg daily
Nausea and vomiting	Prevention: Hydroxyzine 25–100 mg (po/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (po/IM) every 6 hours as needed; ondansetron 4 mg IV or 16 mg po Treatment: Prochlorperazine 5–10 mg (po/IM) every 3–4 hours as needed or 25 mg PR twice daily; ondansetron 4–8 mg IV every 8 hours as needed
Gastroparesis	Metoclopramide 10 mg (po/IV) every 6–8 hours (Caution: duration < 3 months)
Vertigo	Meclizine 12.5–25 mg po every 6 hours as needed
Urticaria/itching	Hydroxyzine 25–100 mg (po/IM) every 4–6 hours as needed; diphenhydramine 25–50 mg (po/IM) every 6 hours as needed
Respiratory depression	Mild: Reduce dose by 25% Moderate to severe: Naloxone 0.4–2 mg IV every 2–3 minutes (up to 10 mg) for complete reversal; 0.1–0.2 mg IV every 2–3 minutes until desired reversal for partial reversal; may need to repeat in 1–2 hours depending on narcotic half-life
CNS irritability	Discontinue opioid; treat with benzodiazepine

IM, intramuscular; IV, intravenous; po, orally; PR, per rectum; SQ, subcutaneous.

Codeine, hydrocodone, morphine, methadone, and oxycodone are substrates of the cytochrome P450 (CYP) enzyme: CYP2D6.[40] Inhibition of CYP2D6 results in decreased analgesia of codeine and hydrocodone due to decreased conversion to the active metabolites (eg, morphine and hydromorphone, respectively) and increased effects of morphine, methadone, and oxycodone. Methadone is a substrate of CYP3A4 and its metabolism is increased by phenytoin and decreased by cimetidine. CNS depressants might potentiate the sedative effects of opiates.

Patients with CYP450 pharmacogenetic variations may respond differently to opioids, ranging from drug unresponsiveness to toxicity with elevated serum levels.

Opioid Rotation Opioid rotation is the switch from one opioid to another to achieve a better balance between analgesia and treatment-limiting adverse effects. This practice is often used when escalating doses (> 1 g morphine/day) become ineffective. In some settings, opioid rotation is used routinely to prevent the development of analgesic tolerance.[41]

Equianalgesic Dosing of Opioid Analgesics Conversion from one dosage form to another or from one opioid to another might be necessary in situations such as ineffective pain control, emergence of side effects, change in patient status, and in formulary restrictions. KEY CONCEPT Equianalgesic doses should be used when converting from one opioid to another. Clinicians should be familiar with the equianalgesic dosing and conversion strategies to avoid analgesic failure. Opioid potency is compared using a reference standard of 10 mg parenteral morphine. Switching from one dosage form to another of the same opioid (ie, IV to oral) is relatively simple. The current total daily dose is calculated and the total of the new dosage form is determined using a ratio of the equianalgesic doses. This result is then adjusted based on the usual dosing frequency of the new form. When converting to a sustained-release form of the same opioid, the oral dosage may be reduced by 25% to avoid initial sedation; however, the specific product literature should also be consulted.

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The first step in an opioid conversion is to calculate the patient's total daily dose of opioid based on the regularly scheduled dose and the total amount of rescue dose needed in 24 hours. This total is then converted to morphine-dosing equivalents using equianalgesic doses (see Table 34–3). The total daily morphine dose is then used to calculate the daily dose of the new opioid using dosing equivalents from an equianalgesic table. Because cross-tolerance may not be complete between opioids, some references suggest that the calculated equianalgesic dose be reduced by 25% to 50%.[38] If the opioid switch is due to uncontrolled pain, a dosage reduction may not be needed. The calculated equianalgesic dose may need to be reduced more in the medically frail and when converting to methadone.[42,43] Methadone appears to be much more potent than once believed, and morphine-to-methadone ratios vary according to the total dose of morphine taken at the time of making the conversion to methadone (Table 34–6).[44,45] Conversion to methadone is a complex process, and several different strategies have been proposed including a switch of the entire dose in 1 day or a gradual conversion over 3 days.

Patient Encounter Part 2

Following surgery, he was placed on morphine patient-controlled analgesia (PCA). He has been using 55 mg of morphine/24 hours with adequate pain control; however, he has developed redness and itching on his neck that is believed to be due to the morphine.

Current Meds: Morphine PCA; aspirin 81 mg daily; atorvastatin 80 mg at bedtime; multivitamin 1 daily; gabapentin 100 mg three times daily; pantoprazole 40 mg daily, tamsulosin 0.4 mg daily; heparin 5000 units twice daily until discharged home. He will be discharged to a skilled nursing facility for rehabilitation therapy.

The physician would like to convert him to a combination preparation of hydrocodone and APAP.

What dosing regimen would you suggest?

Recommend a monitoring plan for this patient.

How would you assess pain response?

The patient is concerned about the redness and itching she developed while on morphine. What other interventions or education may be necessary at this time?

Table 34–6

Methadone Dose Conversions

Total Daily Dose of Oral Morphine	Morphine:Methadone Factor
< 100 mg	3:1 3 mg morphine:1 mg methadone
101–300 mg	5:1
301–600 mg	10:1
601–800 mg	12:1
801–1000 mg	15:1
> 1000 mg	20:1

Data from Gazelle G, Fine PG. Fast fact and concepts #75. Methadone for the treatment of pain. End-of-life Physician Education Resource Center [Internet], [cited 2017 Aug 31]. http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_075.htm, with permission.

▶ *Adjuvant Agents for Chronic Pain*

The role of NSAIDs and opioids in chronic nonmalignant pain has been discussed; however, a review of adjuvant agents for chronic pain, particularly neuropathic pain, is warranted. Adjuvant analgesics are drugs that have indications other than pain but are useful as monotherapy or in combination with nonopioids and opioids. Common adjuvants include antiepileptic drugs (AEDs), antidepressants, antiarrhythmic drugs, local anesthetics, topical agents (eg, capsaicin), and a variety of other drugs (eg, NMDA antagonists, clonidine, and muscle relaxants).

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Published guidelines have been suggested for the general management of neuropathic pain.[46] Suggestions for first-line therapy include gabapentin or pregabalin, transdermal lidocaine, or tricyclic antidepressants (TCAs) (Table 34–7).[46–49] Newer antidepressants, such as the SSRIs, have fewer side effects but appear to be less effective than the TCAs for neuropathic pain. However, serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine and venlafaxine) have been used successfully for painful diabetic peripheral neuropathy (DPN). A stepwise approach is suggested for managing the patient with neuropathic pain beginning with the least invasive, effective therapeutic choice and proceeding to the rational use of multiple drug regimens (see Figure 34–2). Choice of agent might also depend on dosing frequency and comorbidities. Data

Patient Encounter Part 3

He was discharged to a skilled nursing facility and is receiving physical therapy and occupational therapy 6 days each week.

Current Meds: Aspirin 81 mg daily, atorvastatin 80 mg at bedtime, multivitamin 1 daily, gabapentin 100 mg three times daily, pantoprazole 40 mg daily, tamsulosin 0.4 mg daily, heparin 5000 units twice daily until discharged home, hydrocodone/acetaminophen 5/325 mg every 6 hours as needed for pain.

Pain Assessment: Patient reports pain of 7 out of 10; worse with movement.

Physical therapy notes indicate patient is unable to complete therapy goals due to complaints of pain.

Based on this information, what would you recommend to optimize pain control?

Table 34–7

Selected Adjuvant Analgesics and Suggested Dosing[46–49]

Agent	Dosing Guidelines	FDA-Approved Indication
Amitriptyline (Elavil)	10–25 mg at bedtime with weekly increments to a target dose of 25–150 mg of amitriptyline or an equivalent dose of another TCA	
Duloxetine (Cymbalta)	DPN: 60 mg daily Fibromyalgia: 30 mg daily, may be increased to a target dose of 60 mg/day	DPN, fibromyalgia
Gabapentin (Neurontin)	Initially, 300 mg three times a day up to a maximum of 3600 mg daily, in divided doses[a]	PHN
Pregabalin (Lyrica)	DPN: Initially, 50 mg three times a day; may be increased to 100 mg three times a day within 1 week based on efficacy and tolerability[a] PHN: Initially 75 mg twice a day or 50 mg three times a day; may be increased to 100 mg three times a day within 1 week based on efficacy and tolerability[a] Fibromyalgia: Initially 75 mg twice a day, increase after 1 week to 300 mg to 450 mg/day (in divided doses every 12 hours)	DPN, PHN, and fibromyalgia
Lidocaine 5% (Lidoderm patch)	Up to three patches may be applied directly over the painful site once daily; patches are applied using a regimen of 12 hours on and 12 hours off	PHN

[a]Dosing for creatinine clearance of ≥ 60 mL/min (1.0 mL/s).

DPN, diabetic peripheral neuropathy; PHN, postherpetic neuralgia; TCA, tricyclic antidepressant.

on combination therapy are lacking, and the use of combined treatment is empirical based on the additive therapeutic benefit. Scheduled medication regimens instead of "as-needed" dosing should be used when treating chronic pain, and the effectiveness of therapy should be reassessed regularly. If patients are managed on a multiple drug regimen and changes are indicated, changing only one drug at a time is suggested. Topical agents (eg, capsaicin) might be added to a regimen to reduce the oral medication load, particularly if adverse effects are a problem or if pain is not relieved.

Patient Encounter Part 4

The patient has been at the skilled nursing facility for 4 weeks and is making progress toward rehabilitation goals; however, he complains that his leg is throbbing and feels like pins and needles. As a result, he requests to rest several times during his therapy sessions. During unit rounds, his therapist inquires whether his previous pain medication should be reordered.

Pain Assessment: 4 out of 10

Current Meds: Aspirin 81 mg daily, atorvastatin 80 mg at bedtime, multivitamin 1 daily, gabapentin 100 mg thrice daily, pantoprazole 40 mg daily, tamsulosin 0.4 mg daily, heparin 5000 units twice daily until discharged

What additional recommendations would you have at this time regarding pain management?

Are there any other therapeutic issues that should be addressed?

▶ *Complementary and Alternative Medicine*

Complementary and alternative medicine (CAM) is a term used to encompass a variety of therapies (eg, acupuncture, chiropractic, botanical and nonbotanical dietary supplements, and homeopathy). Painful conditions are among the most common reasons individuals seek relief from CAM. A variety of dietary supplements have been suggested for painful conditions such as S-adenosylmethionine (SAM-e), ginger, fish oil, feverfew, γ-linoleic acid, glucosamine, and chondroitin. Of these, glucosamine and chondroitin are the most popular and have the most evidence supporting their efficacy. Glucosamine in doses of 1500 mg/day has been shown to be effective in reducing the pain of osteoarthritis by fostering repair of cartilage, and it is recommended by the Osteoarthritis Research Society International (OARSI).[35]

Patient Care Process

Collect Information:

- Identify the source of pain.
- Assess the level of pain using a pain intensity scale.
- Review the medical and medication history.
- Determine if patient has insurance coverage for prescription medications.

Assess the Information:

- Determine if the patient is a candidate for pharmacotherapy.
- If patient is already receiving drug therapy, assess efficacy, side effects, adherence, and drug interactions.

Develop a Care Plan:

- Base the initial choice of analgesic on the severity and type of pain, as well as on the patient's medical condition and concurrent medications.
- Select the least potent oral analgesic that provides adequate pain relief and causes the fewest side effects.
- Avoid excessive sedation.

(*Continued*)

Patient Care Process (*Continued*)

- Adjust the route of administration if the patient is unable to take oral medications.
- Use equianalgesic doses as a guide when switching opioids.
- Use a dosing schedule versus as-needed dosing.

Implement the Care Plan:

- Communicate the recommendations to the prescriber and members of the team.
- Communicate expectations of the therapy to the patient.

Follow-up: Monitor and Evaluate:

- Assess the patient for analgesic effectiveness and for side effects at each visit or more frequently, depending on the acuity of the patient's condition.
- Titrate the dose to one that achieves an adequate level of pain control.

OUTCOME EVALUATION

Routine pain assessment is essential for evaluating outcomes of therapy. For example, pain goals for acute pain might include "pain scale less than 3" or 30% reduction in PEG scale. Functional goals such as "be able to play a game with grandchildren," or "be able to knit again" may be appropriate for chronic pain. Assess patients periodically, depending on the method of analgesia and pain condition, for achievement of pain goals. Evaluate the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.

Abbreviations Introduced in This Chapter

AED	Antiepileptic drug
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research and Quality
ASIPP	American Society of Interventional Pain Physicians
AIDS	Acquired immunodeficiency syndrome
AMPA	α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid
APAP	Acetaminophen
APS	American Pain Society
ASA	American Society of Anesthesiologists
CAM	Complementary and alternative medicine
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
COX	Cyclooxygenase
CRPS	Complex regional pain syndrome
CYP	Cytochrome P450 enzyme
DPN	diabetic peripheral neuropathy
GABA	γ-Aminobutyric acid
GI	Gastrointestinal
HIV	Human immunodeficiency virus
IASP	International Association for the Study of Pain
IM	Intramuscular
IV	Intravenous
MME	Morphine milligram equivalents
NMDA	*N*-methyl-D-aspartate
NSAID	Nonsteroidal anti-inflammatory drug
OARSI	Osteoarthritis Research Society International
PAINAD	Pain Assessment in Advanced Dementia (tool)
PEG	Pain intensity, Enjoyment of life, General activity Assessment Tool
PCA	Patient-controlled analgesia
PHN	Postherpetic neuralgia
PQRST	Palliative/precipitating, Quality, Radiation, Severity, and Time
SAM-e	*S*-adenosylmethionine
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analog scale
WHO	World Health Organization

REFERENCES

1. IASP Taxonomy. International Association for the Study of Pain. Available from: https://www.iasppain.org/Taxonomy?navItemNumber=576. Accessed August 31, 2017.
2. Murphy KR, Han JL, Yang S, et al. Prevalence of specific types of pain diagnoses in a sample of United States adults. Pain Physician. 2017;20:E257–E268.
3. Lipton RB, Bigal ME, Diamond M, et al. American Migraine Prevalence and Prevention (AMPP) Advisory Group. Migraine prevalence, disease burden, and the need for preventative therapy. Neurology. 2007;68(5):343–349.
4. Fibromyalgia Fact Sheet. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/arthritis/basics/fibromyalgia.htm. Accessed August 31, 2017.
5. Christo PJ, Mazloomdoost D. Cancer pain and analgesia. Ann N Y Acad Sci. 2008;1138:278–298.
6. Yawn BP, Wollan PC, Weingarten TN, et al. The prevalence of neuropathic pain: clinical evaluation compared with screening tools in a community population. Pain Med. 200910(3):586–593.
7. Sadosky A, McDermott AM, Brandenburg NA, Strauss M. A review of the epidemiology of painful diabetic peripheral neuropathy, postherpetic neuralgia, and less commonly studied neuropathic pain conditions. Pain Pract. 2008;8:45–56.
8. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57:1331–1346.
9. Gaskin DJ, Richard P. The economic costs of pain in the United States. The J Pain. 2012;13:715–724.
10. Gianni RA, Madaio L, DiCioccio F, et al. Prevalence of pain in elderly hospitalized patients. Arch Gerontol Geriatr. 2010;51:273–276.
11. Annual Reports, Tables of Reported Statistics. Part Four: Statistical Information on Narcotic Drugs. International Narcotics Control Board. Available from: www.incb.org/documents/Narcotic-Drugs/Technical-Publications/2011/Part_FOUR_Complete_Englich-NARReport-2011.pdf. Accessed August 31, 2017.
12. Rudd RA, Aleshire N, Zibbel JE, et al. Increases in drug and opioid overdose deaths-United States, 2000–2014. MMWR Morb Mortal Wkly Rep. 2016;64:1378–1382.
13. Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic, noncancer pain: American Society Interventional Pain Physicians (ASIPB Guidelines). Pain Physician. 2017;20:S3–S92.
14. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opiods for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65:1–49.

15. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med. 2004;140:441–451.
16. Kral LA, Ghafoor VL. Pain and its management. In: Allredge BK, Corelli RL, Ernst ME, et al., eds. Applied Therapeutics: The Clinical Use of Drugs, 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012:112–147.
17. Renn CL, Doresy SG. The physiology and processing of pain. A review. AACN Clin Issues. 2005;16:277–290.
18. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. Brain Res Rev. 2009;60:214–225.
19. Ashburn MA, Lipman AG. Pain in society. In: Lipman AG, ed. Pain Management for Primary Care Clinicians. Bethesda, MD: American Society of Health-System Pharmacists; 2004:1–12.
20. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database of Syst Rev. 2010:(1):CD006605.
21. Curtiss CP, McKee AL. Assessment of the person with pain. In: Lipman AG, ed. Pain Management for Primary Care Clinicians. Bethesda, MD: American Society of Health-System Pharmacists; 2004:27–42.
22. Twycross RG. Pain and analgesics. Curr Med Res Opin. 1978;5:497–505.
23. Gammaitoni AR, Fine P, Alvarez N, et al. Clinical application of opioid equianalgesic data. Clin J Pain. 2003;19:286–297.
24. Clinical Practice Guideline, Cancer Pain Management. U.S. Department of Health and Human Services, Agency for Health Care Policy and Research. Available from: http://www.ncbi.nlm.nih.gov/books/bookres.fcgi/hstat6/f37_capcf4.gif. Accessed August 31, 2017.
25. Wong D, Baker C. Pain in children: comparison of assessment scales. Pediatr Nurs. 1988;14:9–17.
26. Brief Pain Inventory. Available from: http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/bpilong.pdf. Accessed August 31, 2017.
27. Initial Pain Assessment Tool. Available from: http://www.partnersagainstpain.com/printouts/A7012AF4.pdf. Accessed August 31, 2017.
28. Melzack R. The McGill Pain Questionnaire. From description to measurement. Anesthesiology. 2005;103:199–202.
29. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. Neurology. 1997;48:332–338.
30. Oswestry Disability Index. Available from: http://thepainsource.com/wp-content/uploads/2010/12/Oswestry-Disability-Questionnaire.pdf. Accessed August 31, 2017.
31. Krebs EE, Lorenz KA, Blair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. J Gen Intern Med. 2009;24:733–738.
32. Chiaretti A, Pierri F, Valentini P, et al. Current practice and recent advances in pediatric pain management. Eur Rev Med Pharmacol Sci. 2013;17(suppl 1):112–126.
33. Warden V, Hurley AC, Volicer L. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J Am Med Dir Assoc. 2003;4:9–15.
34. WHO's Cancer Pain Ladder for Adults. World Health Organization. Available from: http://www.who.int/cancer/palliative/painladder/en/. Accessed August 31, 2017.
35. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008;16:137–162.
36. Lopes RD, Horowitz JD, Garcia DA, et al. Warfarin and acetaminophen interaction: a summary of the evidence and biologic plausibility. Blood. 2011;118:6269–6273.
37. Moore RA, Derry S, McQuay HJ. Cyclo-oxygenase 2-selective inhibitors and nonsteroidal anti-inflammatory drugs: balancing gastrointestinal and cardiovascular risk. BMC Musculoskelet Disord. 2007;8:73.
38. American Pain Society. Principles of Analgesic Use 7th ed. Glenview, IL: American Pain Society; 2016.
39. Jamison RN, Serraillier J, Michna E. Assessment and treatment of abuse risk in opioid prescribing for chronic pain. Pain Res Treat. 2011;2011:941808.
40. Armstrong SC, Wynn GH, Sandson NB. Pharmacokinetic drug interactions of synthetic opiate analgesics. Psychosomatics. 2009;50:169–176.
41. Cleary JF. The pharmacologic management of cancer pain. J Palliat Med. 2007;10:1369–1394.
42. Ripamonti C, Groff L, Brunelli C, et al. Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol. 1998;16:3216–3221.
43. Mancini I, Lossignol D, Body JJ. Opioid switch to oral methadone in cancer pain. Curr Opin Oncol. 2000;12:308–313.
44. Ripamonti C, Bianchi M. The use of methadone for cancer pain. Hematol Oncol Clin North Am. 2002;16:543–555.
45. Gazelle G, Fine PG. Fast Fact and Concepts #75. Methadone for the Treatment of Pain. End-of-life Physician Education Resource Center. Available from: http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_075.htm. Accessed August 31, 2017.
46. Hurley RW, Adams MCB, Benzon HT. Neuropathic pain: Treatment guidelines and updates. Curr Opin Anesthesiol. 2013;26:580–587.
47. Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. BMJ. 2009;339:b3002.
48. Zin CS, Nissen LM, Smith MT, et al. An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. CNS Drugs. 2008;22:417–442.
49. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc. 2010;85(3 suppl):S3–S14.

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35 Headache

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LEARNING OBJECTIVES

LO

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

1. Differentiate types of headache syndromes based on clinical features.
2. Recommend nonpharmacologic measures for headache treatment and prevention.
3. Determine when the pharmacologic treatment of headache is indicated.
4. Construct individualized treatment regimens for the acute and chronic management of headache syndromes.
5. Monitor headache treatment to ensure its safety, tolerability, and efficacy.

INTRODUCTION

Headache is a common medical complaint with approximately 50% of the adult population experiencing at least one headache per year.[1] KEY CONCEPT Even when persistent or recurrent, headaches are usually a benign primary condition; secondary headaches are caused by an underlying medical disorder and may be medical emergencies. Primary headache syndromes are the focus of this chapter. Patients may seek headache care from multiple providers. All clinicians should be familiar with the various types of headache, clinical indicators suggesting the need for urgent medical attention or specialist referral, and nonpharmacologic and pharmacologic options for treatment. KEY CONCEPT The International Headache Society (IHS) classifies primary headaches as migraine, tension-type, or cluster and other trigeminal autonomic cephalalgias.[2]

EPIDEMIOLOGY OF HEADACHE DISORDERS

Migraine Headache

Migraine is a primary headache disorder with an estimated 3-month prevalence rate in the United States of 14.2% in adults over 18. Prevalence is higher in females at 19.1% compared to 9%. Highest prevalence was in females 18 to 44 years of age at 23.5%.[3] In pediatric patients, there is also a higher incidence in females after the age of 10.[4] The difference in gender distribution is thought to be due to hormonal differences.

Tension-Type Headache

KEY CONCEPT Tension-Type Headache (TTH) is the most common primary headache disorder and can be further divided into episodic or chronic.[2] The term *TTH* is used to describe all headache syndromes in which sensitization to pericranial **nociception**, noxious stimuli, is the most significant factor in the pathogenesis of pain.[5] Overall reported prevalence of TTH is approximately 86%, and incidence is more common in women than men. Episodic TTH is the most common type followed by frequent episodic TTH, and chronic TTH. Incidence of TTH increases until approximately age 40, then incidence begins to slowly decline.[6] Environmental factors, as opposed to genetic predisposition, play a central role in the development of TTH. The mean frequency of attacks is 3 days per month in episodic disorders; chronic TTH is defined as 15 or more attacks in a 1-month period.[2]

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache disorders are uncommon and severe primary headache syndromes.[2] The lifetime prevalence is estimated to be 124 per 100,000.[7] Unlike migraine and TTH, cluster headaches are more frequently found in men. Onset most commonly occurs between 20 and 40 years.[2] A genetic predisposition is apparent, although affected individuals often provide the additional history of tobacco use, caffeine intake, and alcohol abuse.[7] Attacks consist of debilitating, unilateral head pains that occur in series lasting up to months at a time but may abate for extended periods, resulting in months or years between occurrences. In rare instances, cluster headache can be a chronic disorder without remission.[2]

ETIOLOGY AND PATHOPHYSIOLOGY OF HEADACHE DISORDERS

Migraine Headache

The exact mechanism by which migraines occur remains obscure, but the belief that only vascular changes are responsible for the pain is no longer accepted.[8] The vascular hypothesis suggested that intracerebral vasoconstriction led to neural ischemia, which was followed by reflex extracranial vasodilation and pain. Negative neuroimaging evidence for such vascular changes and the effectiveness of medications with no vascular properties make this contention untenable.[5] A neuronal etiology has emerged as the leading mechanism for the development of migraine pain.[9] It is believed that depressed neuronal electrical activity spreads across the brain, producing transitory neural dysfunction.[8] Headache pain is likely due to compensatory overactivity in the trigeminovascular system

of the brain. Activation of trigeminal sensory nerves leads to the release of vasoactive neuropeptides (eg, calcitonin gene-related peptide [CGRP], neurokinin A, substance P) that produce a sterile inflammatory response around vascular structures in the brain, provoking the sensation of pain.[9] Continued sensitization of central nervous system (CNS) sensory neurons can potentiate and intensify headache pain as an attack progresses.[8] Bioamine pathways projecting from the brainstem regulate activity within the trigeminovascular system. The pathogenesis of migraine is most likely due to an imbalance in the modulation of nociception and blood vessel tone by serotonergic and noradrenergic neurons.[9]

Tension-Type Headache

The pathophysiologic mechanisms producing TTHs are not clearly understood and are likely multifactorial. However, central sensitization to peripheral nociceptive input arising from the pericranial myofascia is the leading hypothesis. The belief that sustained muscle contraction is solely responsible for generating the pain cannot be supported. Muscle tenderness is prominent in this syndrome, but it only reflects a heightened sensitivity to pain. TTH pain is believed to arise by disturbances in the muscles and tissues of the head being misinterpreted due to disordered CNS pain processing.[10]

Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache is one of a group of disorders referred to as trigeminal autonomic cephalalgias.[11] This autonomic nervous system dysfunction is characterized by sympathetic underactivity coupled with parasympathetic activation. Similar to migraine, the pain of a cluster headache is believed to be the result of vasoactive neuropeptide release and neurogenic inflammation. The exact cause of trigeminal activation in this intermittently manifest syndrome is unclear.[11] One hypothesis is that hypothalamic dysfunction, occasioned by diurnal or seasonal changes in neurohumoral balance, is responsible for headache periodicity.[5] Serotonin affects neuronal activity in the hypothalamus and trigeminal system and may play a role in the pathophysiology of cluster headache. The precipitation of cluster headache by high-altitude exposure also implicates hypoxemia in the pathogenesis of trigeminal autonomic cephalalgias.[8]

CLINICAL PRESENTATION AND DIAGNOSIS OF HEADACHES

Migraine Headache

Migraine presents as a recurrent headache that is severe enough to interfere with daily functioning. KEY CONCEPT Migraine headaches are classified as migraine with **aura** and migraine without aura.[2] Aura is defined as a transient focal neurologic symptom that can occur prior to or during an attack. These typically present as wavy lines or spots, but can also present as a **scotoma**.[2] The IHS outlines diagnostic criteria that differentiate migraine with and without aura. Migraines can be triggered by changes in behavior, environment, diet, and hormone levels. Migraines can additionally be triggered by intake of tyramine, aspartame, monosodium glutamate, and nitrites.[8] Migraines occurring 15 or more days per month for a 3-month period or longer, without the overuse of analgesic medications, are classified as chronic migraines.[2] Severe and debilitating migraine pain lasting more than 72 hours is termed status migrainosus.[2]

LO 1

Clinical Presentation and Diagnosis of Migraine Without Aura

Patients experiencing "migraine without aura" may display the following headache symptoms and characteristics:

Two or more of the following are present:

1. Pain interrupts or worsens with physical activity
2. Unilateral pain
3. Pulsating pain
4. Moderate to severe pain intensity

One or more of the following are present during headache:

1. Nausea/vomiting
2. Photophobia and phonophobia

Duration: 4 to 72 hours (treated or not treated)

Criteria for diagnosis: Five or more attacks fulfilling above criteria are necessary

Laboratory assessments that may be helpful in excluding medical comorbidities: Complete blood count (CBC), complete chemistry panel including liver function tests (LFTs), thyroid function tests (TFTs), erythrocyte sedimentation rate (ESR)

Tension-Type Headache

LO 1

TTH pain differs from migraine pain in that it is usually reported to be mild to moderate in severity, nonpulsating, and bilateral.[6] The pain is described by sufferers as a band-like tightness or pressure around the head. No transient neurologic deficits are noted, and systemic symptoms are rare. TTHs

Clinical Presentation and Diagnosis of Migraine with Aura

Patients experiencing "migraine with aura" may display the following headache symptoms and characteristics:

One or more of the following present with no motor weakness:

1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal

Two or more of the following:

1. At least one aura symptom that spreads gradually over at least 5 minutes
2. Individual aura symptoms last 5 to 60 minutes
3. At least one aura symptom is unilateral
4. The aura is accompanied or followed by a headache within 60 minutes

Criteria for diagnosis: Two or more attacks fulfilling above criteria are necessary

Clinical Presentation and Diagnosis of Tension-Type Headache

Patients experiencing TTH may display the following headache symptoms and characteristics:

Two or more of the following present and are not aggravated by routine physical activity:

1. Bilateral pain
2. Nonpulsating pain
3. Mild or moderate pain intensity

Both of the following:

1. No nausea or vomiting (anorexia possible)
2. Either photophobia or phonophobia (not both)

Duration: 30 minutes to 7 days

Criteria for diagnosis: 10 or more attacks fulfilling above criteria occurring on average less than 1 day per month are necessary

occurring more than 15 days per month for more than 3 months, without evidence medication overuse, would be classified as chronic TTH.[2]

Cluster Headache

LO 1

Pain associated with cluster headache differs from migraine and TTH in that it is severe, intermittent, and short in duration.[5] Headaches typically occur at night, but attacks may occur multiple times per day.[11] The pain is usually unilateral, but, unlike migraine, it is not described as pulsatile.[5] Aura is not a feature, and pain intensity peaks early after onset, although it may persist for hours.[5] The headache is described as explosive, excruciating, and referred to as a "suicide headache." A constellation of features, ascribed to parasympathetic overactivity, can be seen, such as ipsilateral conjunctival injection as well as lacrimation, rhinorrhea, and

Clinical Presentation and Diagnosis of Cluster Headache

Patients experiencing "cluster headache" may display the following headache symptoms and characteristics:

At least one or more of the following symptoms:

1. Lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead or facial sweating/flushing
5. Sensation of fullness in the ear
6. Miosis and/or ptosis

Or a sense of restlessness or agitation

Duration of pain: 15–180 minutes (untreated)

Frequency of attacks: One every other day and/or up to 8 per day for more than half the time the disorder is active (may have long periods when headaches are inactive)

Criteria for diagnosis: Five or more attacks fulfilling the above criteria

Patient Encounter Part 1

A 34-year-old woman who is 24 weeks pregnant and describes having headache pain that is so severe that she has to stay home from work and lie down in a darkened room. She describes her pain as sharp, unilateral, and pulsating. She reports that she can tell when it is about to begin because she can see "floaters" then her peripheral vision begins to fade. She reports using OTC pain relievers to help ease the pain, but she has not had any success thus far.

What type of headache is the patient most likely experiencing?

What characteristics of the headache support this diagnosis?

What are possible causes or triggers of headache in this patient?

What additional information is needed to formulate a treatment plan?

sweating. Cluster headache patients tend to become excited and restless during attacks, rather than seeking quiet and solitude as in migraine.[11]

TREATMENT OF HEADACHE DISORDERS

Desired Outcomes

KEY CONCEPT The short-term treatment goal of migraine is to achieve rapid pain relief to allow the patient to resume normal activities. The long-term goal of therapy is to prevent headache recurrences and to diminish headache severity.[12] Similarly, the goal of TTH care is to lessen headache pain, whereas the long-term goal is to avoid analgesic overuse and dependence.[8,13] The short-term therapeutic goal in cluster headache is to achieve rapid pain relief. Prophylactic therapy may be necessary to obtain the intermediate-term outcome of reducing the frequency and severity of headaches within a periodic cluster series as well as to achieve the long-term goal of delaying or eliminating recurrent periods.[14]

General Approach to Treatment

First-line pharmacologic agents include nonsteroidal and opiate analgesics, and serotonin-receptor agonists (triptans).[12]

LO 3

KEY CONCEPT Pharmacologic treatment of acute headache should be started early to abort the intensification of pain and to improve response to therapy. The long-term management of headache syndromes focuses on lifestyle modification and other nonpharmacologic therapeutic options; if headaches are severe and frequent, then prophylactic pharmacologic therapy is needed.[12] KEY CONCEPT Several clinical markers, so-called red flags, have been identified that warrant urgent physician referral and further diagnostic evaluation (Table 35–1).[15]

Nonpharmacologic Therapy

LO 2

The successful management of headache disorders depends on comprehensive patient education. Recording headache frequency, duration, severity, possible triggers, and medication response in a "headache diary" provides beneficial information for the patient regarding headache precipitants and useful insights for the clinician selecting appropriate management strategies.[12] To prevent future occurrences, exposure to headache triggers (Table 35–2) should be limited.[14] In the acute setting, environmental control

Table 35–1

Headache "Red Flags" Indicating Need for Urgent Medical Evaluation

New-onset sudden and/or severe pain
Stereotyped pain pattern worsens
Systemic signs (eg, fever, weight loss, or accelerated hypertension)
Focal neurologic symptoms (ie, other than typical visual or sensory aura)
Papilledema
Cough-, exertion-, or Valsalva-triggered headache
Pregnancy or postpartum state
Patients with cancer, human immunodeficiency virus (HIV), and other infectious and immunodeficiency disorders
Seizures

Adapted from Refs. 8 and 15.

can lessen the severity of an attack, so patients may benefit from resting in a dark, quiet area. Behavioral interventions, such as biofeedback, relaxation therapy, and cognitive-behavioral training, are effective and can be recommended for headache prevention. Headache sufferers may also benefit from stress management training.[8] Acupuncture has yielded inconsistent benefits in clinical trials.[16] Although the response is variable, headache patients should be advised to moderate alcohol use and curtail tobacco abuse.[14] All such nonpharmacologic therapies may be useful in augmenting pharmacologic response.

Table 35–2

Migraine Triggers

Behavioral
Emotional let down
Fatigue
Menstruation or menopause
Sleep excess or deficit
Stress
Vigorous physical activity

Environmental
Flickering lights
High altitude
Loud noises
Strong smells such as perfumes
Tobacco smoke
Weather changes

Food
Alcohol
Caffeine intake or withdrawal
Chocolate
Citrus fruits, bananas, figs, raisins, avocados
Dairy products
Fermented or pickled products
Missing meals

Food Containing
Monosodium glutamate (MSG): Asian food, seasoned salt
Nitrites: processed meats
Saccharin/aspartame: diet soda or diet food
Sulfites: shrimp
Tyramine: cheese, wine, organ meats
Yeast: breads

Medications
Cimetidine
Estrogen or oral contraceptives
Indomethacin
Nifedipine
Nitrates
Reserpine
Theophylline
Withdrawal due to overuse of analgesics, benzodiazepines, decongestants, or ergotamines

Adapted from Refs. 8 and 44.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Normal childhood illnesses

FH: Father living, age 67 years: HTN, diabetes mellitus; mother living, age 62 years: migraine headaches; two sisters in good health

SH: Medical lab technician; former smoker; 1–2 cups of coffee per day; eliminated alcohol intake since being pregnant

Meds: Acetaminophen 500 mg, one tablet orally every 4 to 6 hours as needed for headache

ROS: Headache, moderate-severe intensity, sensitivity to light; no dizziness; no chest pain or palpitations; no shortness of breath with exertion; no weakness or joint discomfort

PE:

VS: BP 122/81, P 91, RR 18, T 37.0˚C (98.6˚F) oral

HEENT: No papilledema, neck tender without stiffness

CV: RRR, normal S1, S2, S4 gallop, no MR

Chest: CTA

Abd: Benign, bowel sounds positive

Neuro: Nonfocal

Labs: CBC and complete chemistry panel within normal limits

What is your assessment of this patient's condition?

What medical comorbidities or drug therapies may be contributing to her distress?

Identify treatment goals for this patient.

What nonpharmacologic options are needed at present, and what options are appropriate in the long term?

What pharmacologic therapy would you recommend in the acute setting?

Does this patient require long-term pharmacologic prophylaxis against recurrent headaches?

Pharmacologic Therapy

► *Migraine*

LO 3

Analgesics, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and combination products containing caffeine, with or without an opioid, are the initial pharmacologic option for the acute management of migraine headache especially when severity is mild to moderate. If these analgesics prove to be ineffective, and when headaches are severe, then migraine-specific medications, such as triptans, are administered. Early abortive treatment should be the rule. Larger doses of oral medications may be necessary for pain relief, due to the enteric stasis and poor drug absorption accompanying migraine attacks.

Intranasal, parenteral, and rectal administration can circumvent this complication.[12]

Clinical trial evidence supports many NSAID medications in the acute treatment of migraines with and without aura. Acetaminophen alone or in proprietary combinations with aspirin, opioids, caffeine, or butalbital is also effective.[17]

Triptans inhibit neurotransmission in the trigeminal complex and activate serotonin 1B/1D pathways in the brainstem, which modulate nociception. They also decrease the release of vasoactive neuropeptides leading to vascular reactivity and pain.[18] The triptans are available in intranasal, subcutaneous, and oral dosage forms including tablets or orally dissolving tablets. The available agents differ in their dosing and pharmacokinetic properties, but all are effective treatments to abort or diminish migraine headache (Table 35–3).[8,19–28] Patient responses can be variable; if a patient does not respond to one agent, then another is selected before a patient is prematurely labeled as triptan-unresponsive. The initial severity of headache correlates with symptomatic response; thus administration should be prompt. Relief is usually experienced within 2 to 4 hours. Treatment delay may lead to decreased analgesia through the development of refractory central pain sensitization. Efficacy tends to be dose-related, although adverse effects are less so. These medications are well tolerated; the most common side effects are dizziness, a sensation of warmth, chest fullness, nausea, and paresthesia. Rarely, ischemic vascular events may be precipitated by the potential vasoconstrictive nature of these drugs. An initial dose under direct practitioner supervision is indicated for patients at increased cardiovascular risk. Triptans are avoided in patients with migraine associated with neurologic focality, a history of previous stroke, poorly controlled hypertension (HTN), or unstable angina. Triptans are relatively contraindicated for routine use in pregnancy.[29] Triptans should not be used with concurrent ergotamine administration with the wait time at least 24 hours between use depending on the half-life of the triptan.[8]

Ergotamine derivatives produce salutary effects on serotonin receptors similar to triptans. They also impact adrenergic and dopaminergic receptors. Ergotamine tartrate

Table 35–3

Comparison of Serotonin Receptor Agonists (Triptans)

Medication (Brand Name)	Dosage Forms	Strength (mg)	Usual Dosage (mg)	May Repeat (hours)	Hepatic and Renal Dosing Considerations (mg)	Potential Drug Interactions
Almotriptan (Axert)	Oral tablets	6.25 12.5	6.25–12.5	2	HI and severe RI: 6.25 starting dose and ≤ 12.5	Ergot derivatives Substrate: CYP 3A4, CYP 2D6
Eletriptan (Relpax)	Oral tablets	20 40	20–40	2	Severe HI: not recommended	Ergot derivatives Substrate: CYP 3A4, CYP 2D6
Frovatriptan (Frova)	Oral tablets	2.5	2.5	2	Severe HI: use caution	Ergot derivatives Substrate: CYP 1A2
Naratriptan (Amerge)	Oral tablets	1 2.5	2.5	4	Mild-mod RI or HI: do not exceed 2.5; severe RI (< 15 mL/min [0.25 mL/s]): do not administer	Ergot derivatives Substrate: CYP (various)
Rizatriptan (Maxalt and Maxalt MLT)	Oral tablets Disintegrating tablets	5 10	5–10	2	None identified	Ergot derivatives MAO-A inhibitors
Sumatriptan (Imitrex)	Oral tablets Subcutaneous injection Nasal spray	25, 50, 100 4,6 5, 20/spray	50 6 5–20	2 1 2	Mild-mod HI: oral dose not to exceed 50; severe HI: contraindicated	Ergot derivatives MAO-A inhibitors
Sumatriptan (Onzetra Xsail)	Nasal powder	11 mg/spray	22–44	2		
Sumatriptan/ Naproxen sodium (Treximet)	Oral tablets	85/500	85/500	2	RI (CrCl < 30 mL/min [0.50 mL/s]): not recommended; mild to severe HI: contraindicated	Ergot derivatives MAO-A inhibitors
Zolmitriptan (Zomig and Zomig-ZMT)	Oral tablets Disintegrating tablets Nasal spray	2.5, 5 2.5, 5 2.5, 5/spray	2.5 1.25–2.5 2.5	2 2 2	CrCl 5–25 mL/min (0.08–0.42 mL/s): clearance reduced by 25%, use caution; mod-severe HI: not recommended	Ergot derivatives MAO-A inhibitors Substrate: CYP 1A2

CrCl, creatinine clearance; CYP, cytochrome P450 enzyme; HI, hepatic impairment; MAO-A, monoamine oxidase type A; RI, renal impairment.

Adapted from Refs. 8 and 20–28.

and dihydroergotamine (DHE) are the most commonly used agents.[12] Analgesic onset is within 4 hours, although additional dosing is required if an acceptable response is not achieved. When dosed parenterally, these drugs are usually provided with an antiemetic due to their potential to worsen nausea associated with migraine. The outpatient use of subcutaneous ergotamines is limited by the lack of a prefilled syringe form with the exception of intranasal DHE which can be self-administered to abort an attack.[12] The same cautions associated with triptan use are also applicable to ergot use in patients at risk for vascular events.

The choice of initial therapy for acute migraine attacks is a subject of debate among specialists. Some believe that nonspecific analgesics should be used first line, whereas others believe migraine-specific drugs should be the choice for patients with severe pain or a history of significant disability. A stepped-care approach within attacks from less to more specific drugs is usually recommended. Once a history of headache refractory to common analgesics is established, triptans should be used as initial therapy.[12] Selection of initial headache treatment is important in reducing the incidence of medication overuse headache (MOH). This occurs when patients use ergotamines, triptans, opioids, or other combinations for more than 10 days per month. This can also be considered in patients who are using nonspecific analgesics for more than 15 days per month.[13] In patients who present to the hospital with intractable pain, IV metoclopramide supplemented with DHE may be needed. Oral medications in this setting are not used because nausea and vomiting limit their bioavailability.[12] Migraine patients with frequent and severe attacks are candidates for prophylactic treatment.[30]

▶ *Tension-Type Headache*

LO 3 Most individuals who experience episodic TTHs will not seek medical attention.[2] Instead, they will find relief with the use of widely available OTC analgesics. Acetaminophen products and NSAIDs are commonly utilized. An individual patient LO 2 may benefit from topical analgesics (eg, ice packs) or physical manipulation (eg, massage) during an acute attack, but the evidence supporting nonpharmacologic therapies is inconsistent.[5] Relaxation techniques can often reduce headache frequency and severity. When pain is unrelieved, prescription-strength NSAID use is required, or the combination of acetaminophen with an opioid analgesic may be necessary. The frequent use of these more potent analgesics should be limited, so that the development of dependency is prevented. As described above, MOH can occur with frequent use of analgesics for TTH. For patients experiencing frequent TTH, prophylactic treatment should be considered.[13]

▶ *Cluster Headache*

Cluster headache responds to many of the treatment modalities used in acute migraine; however, initial prophylactic therapy is required to limit the frequency of recurrent headaches within LO 3 a periodic series. A therapy specific to cluster headaches is the administration of high-flow-rate oxygen: 100% at 12 to 15 L/min by nonrebreather face mask for approximately 15 minutes.[31] If the pain is not aborted, retreatment is indicated. No long-term side effects are seen with short-term oxygen use. If oxygen therapy is not wholly effective, then drugs are useful adjunctive therapy. Drug therapy is also used when supplemental oxygen LO 3 is not readily available. The triptan class is safe and effective. Intranasal or subcutaneous sumatriptan as well as intranasal zolmitriptan has demonstrated efficacy in decreasing cluster headache pain.[32] Oral triptans are also effective, but their delayed onset of action may limit their applicability in acute cluster headache treatment.[18] Cluster headache is rapid in onset and achieves peak intensity quickly, but it can be of short duration. Oral agents may have utility in limiting the recurrence of cluster attacks. Intranasal, intramuscular, or IV ergotamine agents are alternatives to triptan use.[5] Repeated dosing may break a cluster series. For those patients in whom triptans and ergotamine derivatives are contraindicated due to ischemic vascular disease, octreotide may be helpful to relieve pain.[33] Octreotide is a somatostatin analogue that has a short half-life and may be administered subcutaneously. Unlike the other abortive agents, it has no vasoconstrictive effects; the most prominent treatment emergent adverse effect is gastrointestinal (GI) upset. Glucocorticoids, provided IV and later tapered orally, are effective when cluster headache attacks are not satisfactorily controlled.[12]

Pharmacologic Therapy for Headache Prophylaxis

KEY CONCEPT Prophylaxis for headache disorders is indicated if headaches are frequent or severe, if significant disability occurs, if pain-relieving medications are used frequently, or if adverse events occur with acute therapies.[12,30]

▶ *Migraine Prophylaxis*

LO 4 Migraine headaches that are severe, frequent, or lead to significant disability require long-term medication therapy. Prophylactic therapy is also recommended for migraines associated with neurologic focality because it may prevent permanent disability.[12] Although multiple medication classes have garnered US Food and Drug Administration (FDA) labeling for migraine prevention, there is no consensus on the best initial therapy (Table 35–4).[30]

Table 35–4

Medications for Prophylaxis of Migraines[12,17]

Medication (Brand Name)	Usual Dosage (mg/day)	Main Adverse Effects
Antiepileptics		
Topiramate (Topamax)[a]	25–200	Paresthesias, dizziness, fatigue, nausea
Valproic acid (Depakene)[a]	500–1500	
Divalproex sodium (Depakote)[a]	500–1500	
β-Blockers		
Atenolol (Tenormin)[b]	25–200	
Metoprolol (Lopressor)[a]	50–200	Fatigue, exercise intolerance
Nadolol (Corgard)[b]	20–160	
Propranolol (Inderal)[a]	80–240	
Timolol (Blocadren)[a]	10–30	
Antidepressants		
Amitriptyline (Elavil)[a]	10–150	Weight gain, dry mouth, sedation
Venlafaxine (Effexor)[a]	37.5–150	

[a]Level A: Established efficacy.

[b]Level B: Probably effective.

KEY CONCEPT The choice of pharmacologic agent is individually tailored to patient tolerability and medical comorbidities.

The β-blockers have long been a mainstay in migraine prevention, and many have been proven to be effective in improving patient symptoms. Cautious dosage titration is advised for those patients who do not have other indications for β-blocker use. Comorbid reactive airway disease is a relative contraindication to β-blocker prophylaxis, and patients with cardiac conduction disturbances should be closely monitored.[17] Patients should also be advised to take only 5 mg of rizatriptan (max 15 mg/day) when they are prescribed propranolol.[24] Calcium channel antagonists are often used when patients cannot tolerate β-blockers. None of the calcium channel blockers carry an FDA indication, and their efficacy is considered to be variable. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been evaluated for migraine prevention, but only two, lisinopril and candesartan, have shown possible efficacy.[17]

Low-dose amitriptyline or other tricyclic antidepressants (TCAs) have proven efficacy in migraine prevention.[17] Due to sedation, these medications are commonly administered at night. Later generation TCAs (eg, nortriptyline) or heterocyclic compounds (eg, trazodone) have fewer dose-limiting adverse effects than the TCAs, especially anticholinergic effects (eg, dry mouth, constipation, and urinary retention), but efficacy has been variable with these agents. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have been evaluated for migraine prevention, but thus far, only venlafaxine has demonstrated probable efficacy. The FDA has issued a controversial warning about using serotonergic antidepressants along with triptans due to the rare occurrence of serotonin syndrome.[34]

The antiepileptics valproic acid and topiramate are approved for migraine prophylaxis. In patients whose migraine headaches are believed to be related to trigeminal neuralgia, carbamazepine is used as prevention for both disorders.[17] Divalproex sodium doses are gradually titrated to 1000 mg/day; topiramate is titrated to a maximum of 100 mg twice per day. At these doses, serum drug level monitoring is infrequently needed.[17] Topiramate is especially useful in patients who have metabolic syndrome, diabetes, and dyslipidemia because it is unlikely to cause weight gain often seen with valproic acid. Topiramate does come with the potential for side effects such as paresthesia, fatigue, anorexia, nausea, and cognitive impairment which occurs at a lower frequency than the other mentioned side effects. These side effects can be mitigated by a slow dosage titration and maintaining adequate hydration.[35]

Methysergide is an ergotamine derivative that impacts central serotonin balance. Inflammatory fibrosis is a rare but serious, adverse reaction associated with the prolonged use of methysergide. Retroperitoneal fibrosis, pulmonary fibrosis, or fibrosis in cardiac tissue can occur. These conditions may resolve upon drug withdrawal, but cardiac valvular damage can be irreversible. Some experts believe it is the best choice for refractory migraine with frequent attacks, but due to its significant adverse effect profile, it is not marketed in the United States.[36]

Given that migraines can be triggered by changes in hormonal balance, it is not surprising that some women have migraines around the time of menstruation. Often, these migraines can be prevented by starting NSAIDs prior to the beginning of menstruation. Triptans can be tried in patients unresponsive to NSAIDs. Three triptans have been shown to be effective in preventing menstrual migraines. Frovatriptan, naratriptan, and zolmitriptan can be considered and should be started 2 to 3 days prior to the beginning of menstruation.[30]

OnabotulinumtoxinA has received FDA approval for the treatment of chronic migraine, but the evidence supporting its use is conflicting. In 2008, the American Academy of Neurology conducted an evidence review and concluded that OnabotulinumtoxinA was probably ineffective for the prevention of migraines.[37] In the PREEMPT 1 and PREEMPT 2 trials, there was a statistically significant reduction in the number of headache days per month when compared to placebo, but the absolute difference between the two groups was only 1.8 days.[38,39]

While evidence is limited, some complementary alternative therapies can be considered for migraine prophylaxis. Petasites (butterbur) has been associated with a potential 60% reduction in the number of headaches experienced over a 1-month period when compared to placebo, but the risk of liver toxicity associated primarily with the plant's root and allergic reactions in asthmatics may limit it use. Studies for riboflavin have been mixed, with some older studies supporting its use for migraine prevention, but some newer studies have failed to show efficacy. Finally, MIG-99 (feverfew) has also shown possible efficacy with very limited trial evidence.[40]

► *Tension-Type Headache Prophylaxis*

LO 4 The prevention of chronic TTHs uses the same pharmacologic strategies as for migraine prophylaxis. TCAs are a mainstay of chronic therapy. The efficacy of serotonergic agonists remains in question. Although there is little need for muscle relaxants (eg, methocarbamol) in the treatment of acute TTH, they are often provided as a preventive intervention. Combination prophylactic therapies may be needed to wean patients from daily analgesic abuse. Stress reduction techniques may be particularly effective in this setting.[5]

► *Cluster Headache Prophylaxis*

LO 4 The calcium channel blocker verapamil is the mainstay of cluster attack prevention and chronic prophylaxis.[5] Within an attack period, it is dosed at 240 to 360 mg/day. Higher doses may be necessary to stave off recurrent cluster periods. Beneficial effects may be appreciated after 1 week of treatment, but 4 to 6 weeks is usually needed. Adverse effects include smooth muscle relaxation with the subsequent exacerbation of gastroesophageal reflux and the development of constipation. Caution should be exercised in patients with myocardial disease because verapamil is an inotropic and chronotropic cardiac suppressant.[5] Pharmacokinetic drug–drug interactions must be considered, as verapamil is a moderate inhibitor of oxidative metabolism through cytochrome P450 (CYP) enzyme 3A4. Eletriptan, a CYP 3A4 substrate, should be avoided concurrently with verapamil.[5,21] Lithium is another effective therapy to reduce headache frequency in a cluster series and to limit recurrences.[12] The dose administered should be individualized to achieve a low serum concentration (0.4–0.8 mEq/L [mmol/L]). Dose adjustments in the setting of renal disease or congestive heart failure are required.[5] Lithium is contraindicated in patients concurrently prescribed thiazide diuretics, NSAIDs, ACEIs, or ARBs. Patient persistence with long-term lithium therapy may be hindered by the emergence of tremor, GI distress, and lethargy. Verapamil and lithium doses can be lowered when used in combination with ergotamine. If possible, bedtime dosing is recommended, given the nocturnal predilection of cluster headache attacks.[11]

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for the acute and chronic management of this patient's headache. Your plan should include:

A statement of the drug-related needs and/or problems.

The goals of therapy.

A detailed, patient-specific therapeutic plan.

A monitoring plan to determine whether the goals have been achieved and adverse effects avoided.

SPECIAL POPULATIONS

Migraine Headache in Children and Adolescents

Migraine headaches are common in children, and their prevalence increases in the adolescent years.[4] The diagnosis and evaluation of headaches is especially difficult in children, given their decreased ability to articulate symptoms. Treatment presents another challenge because medications used for headache management in adults have not been fully evaluated for efficacy and safety in children. Consensus panel recommendations identify ibuprofen as effective and acetaminophen as probably effective in the acute treatment of headache in patients older than 6 years.[41] Aspirin use is avoided due to the risk of precipitating Reye syndrome. The use of triptans in children and adolescents has not been shown to be more effective than placebo. Only rizatriptan is FDA approved for children over 6 and almotription for children over 12. The rest are approved for greater than 18 years of age.[20,24,41] Medication prophylaxis for migraines in children and adolescents is understudied with conflicting data.[41,42] Nonpharmacologic interventions and trigger identification and avoidance are advised.

Pregnancy

Headaches are common in pregnancy likely related to hormonal shifts. TTHs predominate; migraine attacks may increase in frequency but more usually frequency decreases during pregnancy.[43] Recommendations for headache care during pregnancy are based on limited evidence and are largely anecdotal. Because headaches are not associated with fetal harm, reflexive pharmacologic therapy should be avoided and drug treatment choices considered carefully. Standard nonpharmacologic therapies are often sufficient. Acetaminophen is safe for the pregnant woman and her fetus.[43] NSAIDs are avoided late in the third trimester to prevent detrimental prostaglandin alterations leading to premature ductus arteriosus closure. Opioids are second-line agents and should not to be used chronically because they can lead to dependence in the mother and to acute withdrawal in the infant after birth.[43] Centrally acting antiemetic agents are safe and may be useful as adjunctive agents. Corticosteroids

Patient Care Process

KEY CONCEPT Individualized treatment regimens for headache disorders are based on: headache type, pattern of occurrence, response to therapy, medication tolerability, and comorbid medical conditions.

Collect Information:

- Obtain a complete medical and social history to identify any potential drug–disease interactions or social factors that may influence treatment choices.
- Obtain a family medical history, focusing on headache or mental health disorders in first-degree relatives.
- Perform medication history including prescription and non-prescription medications along with dietary supplements. Identify medication allergies.
- Complete a review of systems and physical examination to identify causes or complications of headache.
- Review medical records including any laboratory assessments and radiographic findings.

Assess the Information:

- Based on information obtained for reviewing the patient's medical history, patient interview, review of systems, and physical examination, identify the type of headache.
- Determine if there are triggers for the patient's headaches.
- Assess laboratory assessments to determine renal function and liver function as these may affect medication choice.
- Based on patient history and family history, evaluate the patient's cardiovascular health especially if considering a triptan.
- If patient is already receiving pharmacotherapy, assess for appropriateness and efficacy.

Develop a Care Plan:

- Recommend appropriate pharmacologic therapy to abort headache based on type, patient characteristics, current medication profile, and comorbid conditions.
- When selecting new agents for acute management or for prophylaxis, ensure that the medication is financially accessible.
- Consider insurance coverage when selecting therapy.

Implement the Care Plan:

- Educate the patient on the administration, maximum dosage, and anticipated adverse effects of the prescribed medication, and advise the patient when to seek emergency medical attention.
- Instruct the patient to keep a headache diary to assess therapeutic response.
- Educate on the potential for medication overuse headache.

Follow up: Monitor and Evaluate:

- Follow-up should be scheduled within 4 weeks of starting any new medications for headache to assess efficacy.
- As patient becomes more aware of headache symptoms and appropriate agents are on board for prevention and treatment of headache, follow-up can become less frequent (ie, 3–6 months).

may be needed for intractable headache relief. Prednisone and methylprednisone are preferred, as they are metabolized in the placenta and do not expose the fetus. In pregnant women with migraine, vasoconstrictive agents such as triptans are relatively contraindicated, even though maternal registry data reveal little teratogenicity. If triptans are considered for acute migraine treatment, sumatriptan, naratriptan, and rizatriptan have the greatest evidence of safe use during pregnancy.[43] Ergot compounds are strictly avoided because they may precipitate uterine contractions and placental ischemia leading to hypoxemia in the fetus. Migraine prophylaxis is considered cautiously because β-blockers and calcium channel antagonists may lead to maternal hypotension and diminished placental blood flow or fetal bradycardia.[43] Antiepileptic drug use in this setting has not been sufficiently studied to allow definitive recommendations.

Outcome Evaluation

LO 5

LO 5

Monitoring for therapeutic response is an important part of headache management. In acute management, monitor patients for the pain improvement within 2 to 4 hours and for normal functioning within 3 to 4 hours of treatment initiation. If pain control has not been achieved, additional therapy may be needed for a therapeutic effect. With chronic management for headache prevention, monitor overall headache status every several weeks to months for improvement. A slow decrease in headache frequency is anticipated over this time. Encourage patients to track progress in a headache diary to assist in monitoring improvements in frequency and severity of headaches and corresponding disability. Clinicians monitor attack frequency to determine therapeutic response, seeking a 50% or greater reduction over the course of treatment. Monitoring for adverse effects is central to successful treatment. For acute management, monitor for GI effects from analgesics such as NSAIDs or octreotide, vasoconstrictive symptoms from triptans, and nausea and vascular problems from ergotamine derivatives. Monitor those taking beta blockers for reactive airway disease and cardiac conduction disturbances. Monitor those taking TCAs for sedation and anticholinergic effects such as dry mouth, constipation, and urinary retention. Monitor patients taking calcium channel blockers for gastroesophageal reflux symptoms and constipation, and monitor those taking lithium for tremor, GI distress, and lethargy. To ensure optimal headache management, in acute treatment and prophylactic therapy, monitor regimens both for therapeutic outcomes and adverse events, which may impact quality of life and medication adherence.

Abbreviations Introduced in This Chapter

ACEI	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
BP	Blood pressure
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
CTA	Clear to auscultation
CYP	Cytochrome P450 isoenzyme system
DHE	Dihydroergotamine
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GI	Gastrointestinal
HTN	Hypertension
IHS	International Headache Society
MAO-A	Monoamine oxidase type A
MOH	Medication overuse headache
MR	Murmur, rub
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
RR	Respiratory rate
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TTH	Tension-type headache

REFERENCES

1. Fact Sheet: Headache Disorders. World Health Organization. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs277/en/. Accessed May 1, 2018.
2. (IHS) HCC of the IHS. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808.
3. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache. 2015;55(1):21–34.
4. Victor T, Hu X, Campbell J, Buse D, Lipton R. Migraine prevalence by age and sex in the United States: a life-span study. Cephalalgia. 2010;30(9):1065–1072.
5. Silberstein SD, Lipton RB, Goadsby PJ. Headache in Clinical Practice, 2nd ed. Martin Dunitz; 2002:21–33,69–128.
6. Russell MB, Levi N, Šaltyte-Benth J, Fenger K. Tension-type headache in adolescents and adults: a population based study of 33,764 twins. Eur J Epidemiol. 2006;21(2):153–160.
7. Broner SW, Cohen JM. Epidemiology of cluster headache. Curr Pain Headache Rep. 2009;13(2):141–146.
8. Minor DS, Harrell TK. Headache isorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill Education; 2017.
9. Burstein R, Noseda R, Borsook D. Migraine: multiple processes, complex pathophysiology. J Neurosci. 2015;35(17):6619–6629.
10. Goadsby PJ, Raskin NH. Migraine and other primary headache disorders. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 19th ed. New York, NY: McGraw-Hill Education; 2015.
11. Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalgias and hemicrania continua. Drugs. 2003; 63(16):1637–1677.
12. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000;55(6):754–762.
13. Munksgaard SB, Jensen RH. Medication overuse headache. Headache J Head Face Pain. 2014;54(7):1251–1257.
14. Biondi D, Mendes P. Treatment of primary headache: cluster headache. In: Standards of Care for Headache Diagnosis and Treatment. Chicago, IL: National Headache Foundation; 2004:59–72.
15. Lipton RB, Bigal ME, Steiner TJ, Silberstein SD, Olesen J. Classification of primary headaches. Neurology. 2004; 63(3):427–435.
16. Evans RW. A rational approach to the management of chronic migraine. Headache. 2013;53(1):168–176.
17. Silberstein SD. Preventive migraine treatment. Continuum (Minneap Minn). 2015;21(4 Headache):973–989.
18. Bahra A, Gawel MJ, Hardebo JE, Millson D, Breen SA, Goadsby PJ. Oral zolmitriptan is effective in the acute treatment of cluster headache. Neurology. 2000;54(9):1832–1839.

19. Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia. 2002;22(8):633–658.
20. Axert [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2017.
21. Relpax [package insert]. New York, NY: Pfizer; 2013.
22. Frova [package insert]. Malern, PA: Endo Pharmaceuticals; 2013.
23. Amerge [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2016.
24. Maxalt [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2016.
25. Imitrex [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.
26. Onzetra Xsail [package insert]. Aliso Viejo, CA: Avanir Pharmaceuticals, Inc.; 2016.
27. Treximet [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2016.
28. Zomig [package insert]. Haywood, CA: Impax Laboratories, Inc.; 2016.
29. Becker WJ. Acute migraine treatment in adults. Headache. 2015;55(6):778–793.
30. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults report of the quality standards subcommittee of the American academy of neurology and the american headache society. Neurology. 2012;78:1337–1345.
31. Rozen TD. High oxygen flow rates for cluster headache. Neurology. 2004;63(3):593.
32. Weaver-Agostoni J. Cluster headache. Am Fam Physician. 2013;88(2):122–128.
33. Tyagi A, Matharu M. Evidence base for the medical treatments used in cluster headache. Curr Pain Headache Rep. 200913:168–178.
34. Shapiro RE, Tepper SJ. The serotonin syndrome, triptans, and the potential for drug-drug interactions. Headache. 2007;47:266–269.
35. Topamax [package insert]. Titusville, NJ: Janssen Pharmaceuticals; 2017.
36. Silberstein S. Methysergide. Available from: http://journals.sagepub.com/doi/pdf/10.1111/j.1468-2982.1998.1807421.x. Accessed May 8, 2018.
37. Naumann M, So Y, Argoff CE, et al. Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70(19 PART 1):1707–1714.
38. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010;30(7):793–803.
39. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010;30(7):804–814.
40. Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: [RETIRED]. Neurology. 2012;78(17):1346–1353.
41. Lewis DW, Ashwal S, Dahl G, et al. Practice parameter: evaluation of children and adolescents with recurrent headaches: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2002;59(4):490–498.
42. Powers SW, Coffey CS, Chamberlin LA, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. N Engl J Med. 2017;376(2):115–124.
43. MacGregor EA. Headache in pregnancy. Neurol Clin. 2012;30(3):835–866.
44. Snow V, Weiss K, Wall EM, Mottur-Pilson C. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002;137:840–849.

36 Substance-Related Disorders

Chris Paxos and Christian J. Teter

LEARNING OBJECTIVES

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

LO
1. Identify the prevalence of use for alcohol, opioids, central nervous system (CNS) stimulants, cannabinoids, and tobacco in the US population.
2. Explain the commonalities of action of substances of abuse on the reward system in the brain.
3. Determine when a patient meets criteria for substance use disorder.
4. Identify the typical signs and symptoms of intoxication and withdrawal associated with the use of alcohol, opioids, CNS stimulants, cannabinoids, and tobacco.
5. Determine the appropriate treatment measures to produce a desired outcome after episodes of intoxication and withdrawal.
6. Choose specific pharmacotherapeutic options based on patient-specific factors.
7. Recommend a comprehensive medication treatment and monitoring program to help maintain recovery and prevent relapse to substance use.

INTRODUCTION

Substance use disorders (SUDs) are highly prevalent worldwide. In the United States, patterns of substance use and abuse have been cyclical. For example, cocaine was first isolated from coca leaves in 1860. Its use was advocated by many in the medical establishment until the mid-1890s when it became evident chronic use might be addictive in some individuals and could have deleterious physiologic effects. Its use decreased after prescribing and dispensing restrictions in the early 20th century. In the 1980s, a smokeable formulation (ie, crack) became available, and cocaine use again became epidemic. This historically cyclic nature of substance abuse is common to many substances of abuse.

KEY CONCEPT Pharmacotherapy has a role in treatment of some substance-related disorders, including intoxication, withdrawal, and/or long-term relapse prevention. These substances include alcohol, opioids, central nervous system (CNS) stimulants, cannabinoids, and tobacco. This chapter focuses on pharmacotherapy for these common substance-related disorders. Although other substances are misused (eg, prescription sedatives and tranquilizers), they are not the focus of this chapter.

EPIDEMIOLOGY AND ETIOLOGY

LO 1 The National Survey on Drug Use and Health (NSDUH) uses a representative sample of individuals 12 years or older to determine the annual prevalence of licit and illicit substance use.[1] In 2015, more than half (51.7%; 138.3 million) of Americans reported current (ie, past month) alcohol use. In the 30 days prior to the survey, nearly 1 in 4 Americans (24.9%; 66.7 million) reported binge drinking (ie, 5 or more drinks for men and 4 or more drinks for women), and 6.5% (17.3 million) reported heavy drinking (ie, binge drinking on 5 or more occasions). Approximately one-quarter (23.9%; 64.0 million) of Americans were current users of tobacco. Past month cigarette use declined in 2015; however, this may be due in part to electronic cigarettes. Regarding illicit drug use, 1 in 10 Americans (10.1%; 27.1 million) reported current use, with marijuana and prescription pain relievers being most common (Figure 36–1). Americans reporting current CNS stimulant use varied by substance (ie, 0.7% with cocaine, 0.6% with prescription stimulants, and 0.3% with methamphetamine). While uncommon by comparison, past month heroin use was 0.1% (0.3 million).[1] The NSDUH findings indicate that substance use is wide ranging and continues to be a major public health concern.

Reward Pathway

LO 2 KEY CONCEPT Virtually all substances of abuse appear to activate the same brain reward pathway, which is highlighted by dopaminergic neurotransmission arising in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NA) and prefrontal cortex (PFC).

Figure 36–2 depicts the mesocorticolimbic dopamine (DA) pathway. Key components are DA projections from the VTA to the NA and PFC.[2,3] Many studies support mesolimbic DA system involvement in natural rewards and drug reinforcement; however, there is also evidence that reinforcement independent of DA exists.[4,5] The initial pleasurable experiences secondary to drug use appear to be primarily attributable to activation of primary reward circuits in the brain. These same reward circuits operate under normal circumstances to reinforce activities that promote survival, such as food and water consumption, social affiliation, or sexual activity. However, these systems appear to be disrupted, especially after repeated drug use in susceptible individuals.

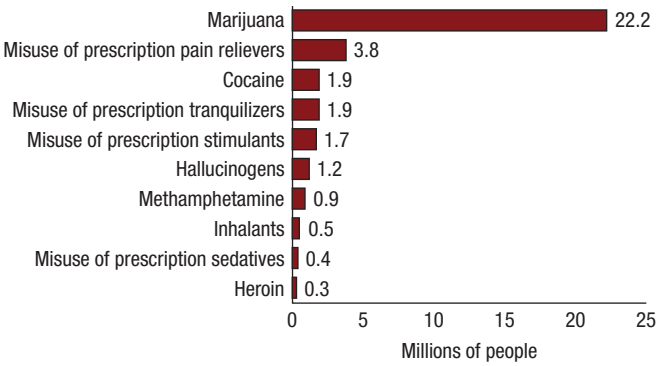

FIGURE 36–1. Past-month illicit drug use in the US among individuals 12 years and older in 2015. (Data and figure in the public domain from Substance Abuse and Mental Health Services Administration, Results from the 2015 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-51, HHS Publication No. (SMA) 16-4984. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2016.)

Although most individuals experience pleasant effects, not everyone abuses these drugs or becomes dependent on them. Why some abuse drugs while most do not relates to complex genetic, environmental, and cultural factors.

PATHOPHYSIOLOGY

Neuronal Adaptation

KEY CONCEPT Although activation of reward pathways explains the pleasurable sensations associated with acute substance use, chronic use (which may result in substance-related disorders) may be related to neuroadaptive effects within the brain.

Addiction is often described as a repeating cycle with three phases: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation.[5] Binge/intoxication refers to the acute rewarding effects of drugs of abuse. In the withdrawal/negative affect phase, chronic use leads to neuroadaptations in the brain, including a generalized decrease in DA neurotransmission and increase in corticotropin-releasing factor (CRF). In phase 3, other neurotransmitters (ie, beyond DA) are postulated to be involved. For example, elevated CRF, norepinephrine (NE), and glutamate may exist in the "extended amygdala" during prolonged abstinence. Perhaps these changes lead to a long-term need to use substances to relieve unpleasant symptoms, such as stress.[5] Multiple factors are associated with an increased risk of relapse, including substance availability, psychological stressors, and triggers such as seeing a white powder or returning to a location where drugs were previously obtained. These factors may trigger residual adaptive changes (eg, elevated glutamatergic activity) that occurred during the period of drug addiction.

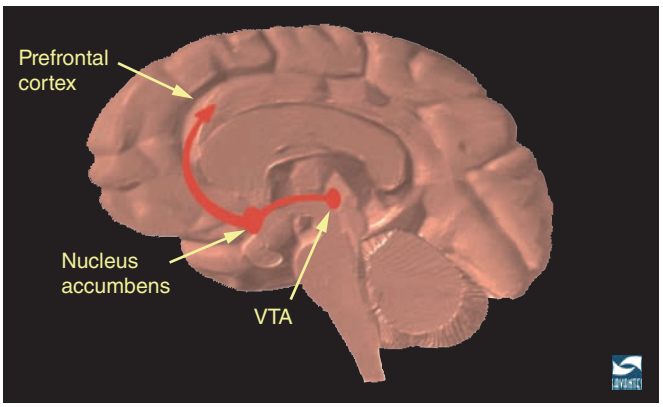

FIGURE 36–2. The mesocorticolimbic dopaminergic (ie, "reward") pathway. (VTA, ventral tegmental area.) (Data available in the public domain from The Neurobiology of Drug Addiction [Internet]. http://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-i-introduction-to-brain.)

Patient Encounter 1

A 66-year-old woman is admitted to the inpatient psychiatry unit secondary to depression. Past medical history includes major depressive disorder and alcohol use disorder. She reports home medications of sertraline and disulfiram but has not filled or taken either medication for nearly 3 months. On examination, the patient is diaphoretic and tremulous when arms are extended. Heart rate is 112 beats per minute. On further questioning, she reports relapsing to drinking approximately 2 months ago. She typically drinks 3 to 4 cases of beer per week and denies any tobacco or illicit substance use. The patient recently stopped drinking "cold turkey" and states she would like to "dump this drinking habit once and for all."

What is the most immediate action to be taken regarding this patient's treatment?

What pharmacotherapy can help her maintain abstinence from alcohol?

CLINICAL PRESENTATION AND DIAGNOSIS

LO 3

KEY CONCEPT Assess individuals with a pattern of chronic use of commonly abused substances to determine if they meet the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*) criteria for substance-related disorders.[6] Most notably, in cases of addiction, there is a loss of control over substance use or use has become compulsive. Diagnostic criteria for SUDs from the *DSM-5* are listed in Table 36–1.[6] Consistent with the *DSM-5*, the remainder of this chapter is organized by pharmacologic class and discusses intoxication, withdrawal, and SUDs for each class (except tobacco use disorders, which do not have *DSM-5* intoxication criteria).

A variety of standardized instruments are available to screen for and assess the various stages of substance use and its consequences, such as withdrawal symptoms and functional impairment (Table 36–2).[7–9] The Addiction Severity Index (ASI) is the gold-standard instrument that assesses seven problem areas associated with substance use, such as medical and psychiatric status, in addition to measures of alcohol and drug use.[7] Many SUD instruments can be freely obtained from the Substance Abuse and Mental Health Services Administration (SAMHSA).

Intoxication Signs and Symptoms

Intoxication caused by most substances is described in the *DSM-5* as clinically significant, problematic behavioral or psychological changes to the individual which are caused by the physiological effects of the substance. These changes are observed during or shortly after use of the substance. Euphoria or experiencing a pleasurable sensation are effects of most drugs of abuse.[10] Other

Table 36–1

***DSM-5* Criteria for Diagnosis of Substance Use Disorders**

A problematic pattern of substance use leading to clinically significant impairment or distress; manifested by ≥ 2 of the following, occurring within a 12-month period:

1. Substance often taken in larger amounts or over longer period than intended.
2. Persistent desire or unsuccessful efforts to cut down or control substance use.
3. Great deal of time spent in activities necessary to obtain substance, use substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent substance use resulting in failure to fulfill major role obligations at work, school, or home.
6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.
7. Important social, occupational, or recreational activities are given up or reduced because of substance use.
8. Recurrent substance use in situations in which it is physically hazardous.
9. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by substance.
10. Tolerance, as defined by either of the following:
    a. Need for markedly increased amounts of substance to achieve intoxication or desired effect.
    b. Markedly diminished effect with continued use of same amount of substance.
11. Withdrawal, as manifested by either of the following:
    a. Characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the *DSM-5* criteria set for substance withdrawal).
    b. Substance (or closely related substance) is taken to relieve or avoid withdrawal symptoms

Specify[a] current severity:
Mild: Presence of 2 to 3 symptoms.
Moderate: Presence of 4 to 5 symptoms.
Severe: Presence of ≥ 6 symptoms.

[a]Additional specifiers (eg, early vs. sustained remission) and substance-specific notes (eg, taking opioid under medical supervision) are included in the *DSM-5*.

Data from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013; with permission.

LO 4 signs and symptoms are specific to the particular drug or drug class involved. Table 36–3 lists the psychological/behavioral and physiologic effects of intoxication from selected substances.[6,11–14]

Withdrawal Signs and Symptoms

Although most drugs of abuse can cause some degree of **physical dependence**, the severity of withdrawal varies considerably among these drugs. LO 4 Table 36–4 lists common withdrawal symptoms that emerge upon abstinence from drug use.[6,11–15] Typically, withdrawal symptoms are opposite of the acute effects of the substance. For example, although alcohol is a CNS depressant, signs and symptoms of withdrawal signify a hyperalert physiologic response.

TREATMENT OF SUBSTANCE USE DISORDER

SUDs cannot be cured with medications alone. However, medications can sometimes alleviate the effects of drug intoxication, attenuate withdrawal symptoms, or somewhat decrease craving and likelihood of relapse. For example, pleasurable and intoxicating effects of opioids appear to be caused by their action as agonists on μ-opioid receptors. Competitive μ-opioid receptor antagonists, such as naloxone, acutely reverse many opioid effects, including symptoms of intoxication. To date, specific antagonists for most other substances are unavailable. Similarly, reversal of withdrawal syndromes caused by substances of abuse is not always possible. Benzodiazepines are used for ethanol withdrawal because of cross tolerance with ethanol. For long-term medication management, patients addicted to opioids can be maintained on a regimen of medically managed, orally administered opioids (ie, substitution therapy) compared with more dangerous illicit opioid use. Regardless of the pharmacotherapy chosen, medications should always be used as adjuncts to a comprehensive psychosocial approach.[11]

Patient Encounter 2

A 26-year-old man is brought to the emergency department after he is found unconscious in a restaurant parking lot. The patient is somnolent and has slow and shallow breathing. His physical examination reveals miosis, bradycardia, and cyanosis. The patient slurs his speech when attempting to answer questions.

Which of the patient's signs and symptoms are suggestive of opioid intoxication?

How is the medication antidote for opioid intoxication used?

TREATMENT OF INTOXICATION SYNDROMES

LO 5 KEY CONCEPT Treatment goals for acute intoxication of ethanol, opioids, CNS stimulants, and cannabinoids include (a) management of psychological/psychiatric manifestations of intoxication, such as aggression, hostility, and psychosis and (b) management of medical manifestations of intoxication, such as respiratory depression, hyperthermia, hypertension, cardiac arrhythmias, and stroke. In all cases of intoxication that require medical intervention, referral to and participation in substance abuse treatment programs is desirable.

Alcohol Intoxication

Desired outcomes are appropriate management of medical problems, prevention of harmful behaviors, and stabilization of mood. Most cases of mild-to-moderate alcohol intoxication, including cases with blood alcohol concentrations (BACs) at lower limits of legal intoxication, do not require formal treatment. Providing a safe environment and reassurance until alcohol effects have dissipated is sufficient in most cases. Initially, BACs may continue to rise if gastrointestinal (GI) absorption is still occurring. Otherwise, BACs generally decrease at a rate of 15 to 20 mg/dL (0.015%–0.02% or 3.3–4.3 mmol/L) per hour. Table 36–3 lists the physiologic effects of alcohol at various BACs; however, tolerant individuals may not show the same level of symptoms at a given BAC as nontolerant individuals.

At more severe levels of intoxication, confusion, stupor, coma, and death may occur. Clinicians must rule out other causes of these serious adverse events, because patients may combine alcohol with other substances, sustain head or other injuries, or have vitamin deficiencies and electrolyte abnormalities. If consciousness is impaired, give thiamine by the intravenous (IV)

Table 36–2

Commonly Used Instruments for Assessing Patients with Substance Use Disorders[7-9]

Instrument	Purpose	Values and Interpretation
Addiction Severity Index (ASI)	Assessment tool Semi-structured interview that addresses seven problem areas: medical status, employment and support, alcohol use, drug use, legal status, family and social status, and psychiatric status Questions include frequency, duration, and severity of problems in the past 30 days or lifetime for various substances Clinician or technician-administered	200 items Patient and interviewer ratings included Interviewer severity ratings of "need for additional treatment" and composite scores to measure severity Composite score normative data from nationally representative sample of treatment programs is available for those seeking to compare a patient's ASI data with national data (www.tresearch.org); otherwise, comparisons with previous (eg, baseline) composite scores are useful
Alcohol Use Disorders Identification Test (AUDIT) Alcohol Use Disorders Identification Test—Consumption (AUDIT-C)	Screening tool Evaluates quantity and frequency of drinking, physiologic dependence on alcohol, and harmful use Clinician or self-administered	10 items; maximum score = 40 Score of ≥ 8 identifies heavy drinkers and those with possible alcohol use disorders AUDIT-C is an abbreviated 3-item version
CAGE Questionnaire	Screening tool Used to identify the presence of problematic drinking Clinician or self-administered	4 items; maximum score = 4 Score of ≥ 2 is positive and suggests problem drinking Positive screen prompts the need for further assessment
Clinical Institute Withdrawal Assessment-Alcohol, Revised (CIWA-Ar)	Assessment tool Gold-standard alcohol withdrawal assessment; used as part of a symptom-triggered approach Clinician-administered	10 items; maximum score = 67 < 10: mild withdrawal 10–18: moderate withdrawal > 18: severe withdrawal Monitor scores over time; ≥ 8–10 (depending on institutional protocols or co-occurring conditions) indicates need for medication
Clinical Opiate Withdrawal Scale (COWS)	Assessment tool Used to follow the course of opioid withdrawal symptoms and effectiveness of medication regimens Clinician-administered	11 items Score of 0 (asymptomatic) to 4 or 5 (severely symptomatic) for each item based on intensity of signs and symptoms 5–12: mild withdrawal 13–24: moderate withdrawal 25–36: moderately severe withdrawal > 36: severe withdrawal Monitor scores over time; higher scores may indicate need for medication; no standard cut-off exists
Fagerström Test for Nicotine Dependence	Assesses extent of nicotine tolerance, dependence, and craving	6 items Higher scores may predict greater difficulty quitting 0–2: very low 3–4: low 5: moderate 6–7: high 8–10: very high

or intramuscular (IM) route at 100 mg/day for at least 3 days. If hypoglycemia is suspected, administer thiamine before glucose-containing fluids to prevent precipitation of acute **Wernicke syndrome** (see Alcohol Withdrawal section). Interactions between alcohol and medications may also occur. **Table 36–5** details drug–drug interactions associated with substances of abuse.[16]

Behaviorally, patients may insist on driving, become aggressive and agitated, or otherwise become a danger to themselves or others. Indeed, most suicidal behaviors among those dependent on alcohol occur while they are intoxicated. Antipsychotics lower the seizure threshold and are best avoided. However, in some instances, agitation may require treatment with an oral or IM antipsychotic. Sedation with benzodiazepines has been used but, in the presence of alcohol, respiratory depression can be dangerous or even fatal.

Opioid Intoxication

The word *opioid* refers to the class of medications and substances that exert their action through the opioid system. Opioids encompass a wide range of substances, including naturally occurring (eg, morphine) and synthetic (eg, oxycodone).

Acutely intoxicated patients usually present with miosis, euphoria, slow breathing, slow heart rate, low blood pressure, and constipation. Seizures may occur with certain agents, such as meperidine. Monitor patients carefully to avoid cardiac and respiratory depression and death from opioid overdose. One strategy is to reverse intoxication using naloxone 0.4 to 2 mg IV every 2 to 3 minutes up to 10 mg; the IM, subcutaneous, or intranasal (IN) route may be used if IV access is not available. Naloxone is shorter acting than most abused opioids and may require readministration at periodic intervals; otherwise, patients could lapse into cardiopulmonary arrest after a symptom-free

Table 36–3

Signs and Symptoms of Drug Intoxication for Select Substances[6,11-14]

Drug	Behavioral Effects	Physiologic Effects
Ethanol	Changes in mood and behavior, inappropriate aggressive or sexual behavior, impaired judgment; possibly progressing to somnolence and coma as the blood level increases	Blood levels 0.02%–0.1% (20–100 mg/dL or 4.3–21.7 mmol/L): Euphoria, disinhibition, slight impairment (eg, reaction time) Blood levels 0.1%–0.2% (100–200 mg/dL or 21.7–43.4 mmol/L): Dysphoria, significant impairment (eg, balance, speech, vision) Blood levels 0.2%–0.3% (200–300 mg/dL or 43.4–65.1 mmol/L): Marked ataxia, mental confusion, nausea, vomiting Blood levels 0.3%–0.4% (300–400 mg/dL or 65.1–86.8 mmol/L): Severe dysarthria, amnesia, hypothermia Blood levels > 0.4% (400 mg/dL or 86.8 mmol/L): Coma, decreased respiration or respiratory arrest, aspiration of gastric contents, airway obstruction by flaccid tongue, drop in blood pressure and body temperature
Opioids	Drowsiness, sedation, slurred speech, impaired memory and attention, psychomotor retardation	Nausea, vomiting, respiratory depression (dose-related), stupor, coma, constipation common with chronic use, itching, miosis, hypothermia, bradycardia
CNS stimulants	Elated mood, anxiety, panic, impaired judgment, violent behavior, paranoia, delusions, hallucinations (tactile or auditory, rarely visual), increased motor activity, compulsive or stereotyped behavior (eg, skin picking)	Neurologic/Neuromuscular: mydriasis, headache, tremor, hyperreflexia, muscle twitching, flushing, hyperthermia or cold sweats, rhabdomyolysis (possibly resulting in renal failure), dyskinesias, seizures, coma Cardiovascular: tachycardia, hypertension, vasoconstriction, arrhythmias, myocardial infarction, cerebral hemorrhage GI: nausea, vomiting, weight loss
Cannabinoids	Anxiety, impaired judgment, social withdrawal	Euphoria, impairment motor coordination, tachycardia, xerostomia, conjunctival injection, increased appetite

CNS, central nervous system; GI, gastrointestinal.

interval of reversed intoxication. In addition, naloxone can induce withdrawal symptoms in opioid-dependent patients, so patients may awaken feeling distressed and agitated. Buprenorphine intoxication may be more difficult to reverse.[17]

Secure the airway and ensure breathing in cases of opioid overdose. In some cases, intubation and manual or mechanical ventilation may be required to avoid oxygen desaturation leading to brain hypoxia or anoxia and brain damage or death.

Recently, new opportunities for "take-home" naloxone have emerged in an effort to prevent overdose deaths. The US Food and Drug Administration (FDA) approved a naloxone auto-injector and IN naloxone for this purpose.[16,17] The IN naloxone

Table 36–4

Signs and Symptoms of Drug Withdrawal for Select Substances[6,12-15]

Drug	Timeline	Symptoms
Ethanol	As levels decrease:	
	Early symptoms	Tremor, nausea, vomiting, tachycardia (> 110 beats/minute), hypertension (> 140/90 mmHg), headache, insomnia
	Peak (24 hours)	Seizure-activity (usually 1 or 2 grand mal type, but can be numerous and possibly fatal)
	72–96 hours	Delirium tremens
	Onset at any time	Hallucinations (usually visual)
Opioids	For shorter-acting opioids (eg, heroin, morphine), withdrawal may begin 6–24 hours after last dose and last for about 1 week; with longer acting opioids (eg, methadone), may take up to 2–4 days for withdrawal to emerge and will last longer	EENT: lacrimation, mydriasis, rhinorrhea GI: nausea, vomiting, diarrhea Cardiovascular: increased heart rate and blood pressure CNS: irritability, restlessness, yawning Musculoskeletal: increased body temperature, piloerection
CNS stimulants	Stage 1: immediately following binge	Craving, intense dysphoria, depression, anxiety, agitation
	Stage 2: within 1–4 hours	Dysphoria, desire for sleep
	Stage 3: 3–4 days	Hypersomnia, increased appetite, craving may dissipate but return later
Cannabinoids	Withdrawal symptom onset typically within 24–72 hours; peaks within 1 week	Severity reflects degree and duration of cannabinoid use; symptoms include irritability, anxiety, sleep abnormalities, depressed mood, headache, tremors, sweating, chills
Tobacco	Begins within 24 hours of cessation; peaks within 1–2 weeks; may persist for months	Severity reflects degree and duration of nicotine use; symptoms include irritability, anxiety, frustration, craving, difficulty concentrating, decreased heart rate, increased appetite

CNS, central nervous system; EENT, ears, eyes, nose, and throat; GI, gastrointestinal.

Table 36–5

Clinically Relevant Drug Interactions with Substances or Medications Used to Treat Substance Use Disorders[16]

Drug	Interacting Drug	Type of Interaction
Amphetamines	MAOIs	Pharmacodynamic interaction resulting in increased blood pressure; possibly hypertensive emergency or stroke; AVOID combination
	Sodium bicarbonate	Sodium bicarbonate increases renal tubular reabsorption of amphetamine, resulting in prolonged amphetamine elimination half-life; closely monitor
Buprenorphine	Atazanavir	Combination of buprenorphine and atazanavir (without ritonavir) results in both lower atazanavir levels and higher buprenorphine levels; AVOID combination
	CYP3A4 inhibitors	May raise buprenorphine levels; monitor for greater than expected effects
Bupropion	MAOIs	Neurotoxicity; AVOID combination
	Substances that lower seizure threshold	Use caution when initiating other medications that lower the seizure threshold; AVOID bupropion in patients at risk for experiencing alcohol withdrawal
Cigarette smoking	CYP1A2 substrates	Cigarette smoking (but not NRT) induces CYP1A2, increasing metabolism of CYP1A2 substrates (eg, theophylline, olanzapine); may need to increase substrate dose when patient begins to smoke or decrease substrate dose if smoking is stopped
Disulfiram	Alcohol-containing solutions	Disulfiram reaction; AVOID combination
	Metronidazole	Combination has led to CNS effects (eg, psychosis); AVOID combination
	Benzodiazepines	Disulfiram (weakly) inhibits CYP1A2, 2C9, and 3A4; many benzodiazepines are metabolized via these pathways and doses may need to be lowered; lorazepam and oxazepam undergo conjugation and are alternatives
	Cocaine	Disulfiram decreases clearance of cocaine; may have increased or prolonged cocaine effects with combination
	Phenytoin	Disulfiram decreases metabolism of phenytoin, resulting in higher phenytoin levels; phenytoin dose may need to be reduced; because phenytoin undergoes nonlinear metabolism, it is difficult to predict magnitude of increase in blood levels; AVOID combination if possible
Ethanol (alcohol)	Acetaminophen	Chronic ethanol use increases hepatotoxicity risk when acetaminophen is used in high doses
	Bupropion	Abrupt discontinuation of alcohol with bupropion use may lower seizure threshold; AVOID bupropion in patients at risk for experiencing alcohol withdrawal
	Cefotetan or metronidazole	Disulfiram-type reaction may occur when these anti-infectives are combined with alcohol; AVOID combination
	Methotrexate	Risk of hepatotoxicity may be increased in those who chronically drink large amounts of alcohol; AVOID methotrexate in this population if possible; otherwise, monitor LFTs
	MAOIs	Ethanol DOES NOT interact with MAOIs; however, tyramine may be a component of aged alcoholic drinks, such as red wines or tap beers
	Tapentadol	Ethanol may result in higher maximum serum levels of extended-release tapentadol; AVOID combination
Methadone	Carbamazepine	Carbamazepine is a potent CYP3A4 inducer, and methadone is primarily metabolized via CYP3A4; if used together, may need to increase methadone dose to avoid withdrawal
	CYP3A4 inhibitors	May result in higher methadone levels; methadone dose adjustment should be based on clinical judgment, but a dose decrease may be necessary
	Didanosine	Methadone decreases oral absorption of didanosine; monitor the therapeutic effects of didanosine as a dose increase may be necessary
	Efavirenz	Efavirenz is a CYP3A4 inducer; efavirenz decreases methadone levels and has precipitated methadone withdrawal; may need to increase methadone dose
	MAOIs	Potential serotonin syndrome when MAOIs are combined with methadone; AVOID combination
	Nevirapine	Nevirapine is a CYP3A4 inducer and may decrease methadone levels, resulting in withdrawal complaints; may need to increase methadone dose
	QTc-prolonging medications	Medications that prolong the QT interval (eg, ziprasidone) should be AVOIDED with methadone when possible due to additive QT-prolonging effects
	St. John's wort	St. John's wort is a CYP3A4 inducer; caution dictates to AVOID combination; methadone withdrawal symptoms have been noted with this combination
	Zidovudine	Methadone increases zidovudine levels, likely via methadone inhibition of both metabolic and renal clearance of zidovudine; may need to decrease zidovudine dose to avoid toxicity
Naltrexone	Opioid analgesics	Blockade of pain relief; use nonopioid analgesics and treatment approaches

CNS, central nervous system; CYP, cytochrome P450; LFT, liver function test; MAOI, monoamine oxidase inhibitor; NRT, nicotine replacement therapy.

is commonly used in nonmedical settings due to ease of use. Most states allow for distribution of naloxone to third parties or first responders. Educate patients and caregivers on naloxone, including when to use, how to assemble, proper administration, and notifying emergency services.[18]

Stimulant (Cocaine and Amphetamines) Intoxication

Desired outcomes of stimulant intoxication treatment are appropriate management of medical and psychiatric complications. Medical problems include hyperthermia, hypertension, arrhythmias, chest pain, stroke, and seizures. Some problems are related to route of administration, such as nosebleeds or infections with IN or IV administration, respectively. Psychiatric effects include anxiety, aggression, and psychosis.[14]

Notably, stimulant intoxication is the only stimulant use disorder for which specific pharmacotherapy has demonstrated effectiveness. Recommended medications in acute settings include benzodiazepines, aspirin, nitroglycerin, nitroprusside, and phentolamine.[14] The American Heart Association guidelines indicate that acute use of β-blockers is not recommended and may lead to worsening cocaine-related chest pain and hypertension secondary to unopposed α-receptor mediated vasoconstriction.[19]

Cocaine is short-acting, and a single benzodiazepine may provide sufficient treatment for anxiety reactions. Depending on benzodiazepine half-life, multiple doses may be required for longer-acting amphetamine intoxication. Antipsychotics can manage psychosis, and psychotic symptoms usually respond rapidly in the absence of other co-occurring psychiatric disorders.[14]

Cannabinoid (Marijuana, etc) Intoxication

No established treatment recommendations exist for cannabinoid intoxication. Symptomatic treatment (eg, tachycardia, anxiety, and paranoia) is commonly used. Potent synthetic cannabinoids are the exception and may require aggressive benzodiazepine treatment for intense symptoms of anxiety or psychosis. These intense psychiatric symptoms are theorized to result either from the potent full-agonist cannabinoids that are used to prepare them or from the lack of cannabidiol in synthetic products.[14] Cannabidiol has been associated with antipsychotic effects.[20]

TREATMENT OF WITHDRAWAL SYNDROMES

LO 5

KEY CONCEPT Treatment goals for withdrawal from ethanol, opioids, CNS stimulants, and cannabinoids include (a) a determination if pharmacologic treatment of withdrawal symptoms is necessary, (b) management of other medical manifestations, and (c) referral to the appropriate program for long-term substance abuse treatment. Desired outcomes in the treatment of withdrawal syndromes are to ensure patient safety, comfort, and successful transition to longer-term maintenance treatment. Referral to specialized SUD treatment is strongly recommended after treatment of withdrawal. Rapid referral can introduce patients to the concept of recovery while they still vividly recall the negative consequences from using substances. Achieving a drug-free state by detoxification and then rehabilitation with a focus on total abstinence, or a reduction in substance use for some individuals, is the ideal outcome.

Alcohol Withdrawal

Alcohol withdrawal is characterized as either uncomplicated or complicated. Each differs in terms of pharmacologic treatment.

▶ *Uncomplicated Alcohol Withdrawal*

Uncomplicated alcohol withdrawal is the more commonly observed syndrome and, as the name implies, is not complicated by seizures, **delirium tremens** (DTs), or hallucinosis. Symptoms are typically rated using a validated scale, such as the Clinical Institute Withdrawal Assessment-Alcohol, revised (CIWA-Ar) (Table 36–2). The recommended CIWA-Ar threshold score for treating uncomplicated alcohol withdrawal with medications is 8 to 10. The risks of not treating high-scoring patients with medications are seizures and DTs, and those with a prior history of seizures or DTs have increased risk for subsequent episodes. There is some evidence for "kindling" during successive episodes of alcohol withdrawal, such that symptom severity and complications increase with additional withdrawal episodes.[12,21,22]

Benzodiazepines are the treatment of choice for uncomplicated alcohol withdrawal.[9,11] Anticonvulsants, such as carbamazepine, sodium valproate, and gabapentin, have been used; however, they are not as well-studied. The most commonly used benzodiazepines are lorazepam, diazepam, and chlordiazepoxide. They differ in three major ways: (a) pharmacokinetic properties, (b) routes for administration, and (c) rapidity of onset of action due to the rate of GI absorption and rate of crossing the blood–brain barrier. Benzodiazepines are given using either a symptom-triggered approach or loading dose strategy. Adjunctive "as needed" medications are typically used, as well.[12]

Benzodiazepines can be administered using a symptom-triggered approach when withdrawal signs and symptoms are present.[23] When the CIWA-Ar is greater than or equal to 8, this "triggers" the administration of a benzodiazepine. For example, lorazepam is given at the recommended 1 to 2 mg dose. The CIWA-Ar is then repeated hourly after each administration during the first 24 hours until the patient is comfortably sedated. Due to its short half-life, lorazepam dosing on subsequent days may be necessary, and the risk of seizures may potentially be higher.

Longer-acting agents, such as diazepam and chlordiazepoxide, are often used via the loading dose strategy in which larger doses are given initially followed by a 3–5 day taper. Their long half-lives and active metabolites usually provide a natural taper without further medication administration. Diazepam may be "preferred" to chlordiazepoxide secondary to its faster onset of action (ie, quicker GI absorption and rapid CNS entry due to high lipophilicity). However, a faster onset of action may be associated with euphoria and is a treatment disadvantage. This approach may be accompanied by "as needed" short-acting benzodiazepine doses for breakthrough alcohol withdrawal symptoms.

Special Dosing Considerations Unlike chlordiazepoxide and diazepam, lorazepam is not metabolized into active compounds. It is excreted by the kidneys after glucuronidation. This is important because many patients with alcohol use disorder have compromised liver function. Therefore, when treatment is initiated before results of liver function tests (LFTs) are known, lorazepam may be preferred. Patients with liver disease may still be treated with diazepam or chlordiazepoxide at lower doses.[12]

LO 6

American Psychiatric Association (APA) guidelines recommend thiamine for patients being treated for moderate to severe alcohol use disorders to prevent or treat adverse neurologic symptoms.[11] However, there are inadequate data with regard to the most efficacious thiamine dose, frequency, and route of administration to prevent or treat Wernicke syndrome associated with alcohol use disorders.[24] The APA guidelines recommend thiamine 50 to 100 mg per day given IV or IM, although other guidelines recommend higher doses

(eg, thiamine 300 mg/day).[11,25] Administration of thiamine, essential for proper energy utilization by the CNS, must precede glucose-containing IV fluid administration, which can help prevent an acute exacerbation of Wernicke syndrome.

▶ *Complicated Alcohol Withdrawal*

Alcohol Withdrawal Seizures Alcohol withdrawal seizures, a medical emergency, should be treated in an inpatient setting. Withdrawal seizures are usually generalized and few in number. Although binge drinking and alcohol withdrawal can lead to status epilepticus, the occurrence of focal seizures or status epilepticus may also suggest another etiology. Management consists of keeping the airway open and preventing self-injury during convulsions. Benzodiazepines are the treatment of choice. Give diazepam 5 to 10 mg IV to terminate a seizure if IV access is available. Repeat dose in 5 minutes if seizures persist. Alternatively, lorazepam 4 mg IM may be given, followed by insertion of an IV line after convulsive movements subside. In the event of a recurrent seizure, lorazepam 2 mg IV may be administered if the patient received IM lorazepam. Avoid IM diazepam or chlordiazepoxide because of erratic absorption that complicates the timing of subsequent doses and can result in delayed oversedation. Intravenous benzodiazepines may depress respiration; therefore, they should only be administered if advanced cardiopulmonary support is available. When the patient can take oral medications, treatment may continue using either the symptom-triggered or loading dose strategy. Electrolyte imbalances can contribute to seizures and should be corrected.[22,26] Avoid phenytoin for preventing or treating alcohol-related seizures.[21] Phenytoin affects sodium channels rather than directly affecting γ-aminobutyric acid (GABA) and glutamate abnormalities indicative of alcohol withdrawal.

Alcohol Withdrawal Delirium (DTs) DTs is a medical emergency necessitating hospitalization. Signs and symptoms include hallucinations, delirium, severe agitation, fever, increased blood pressure and heart rate, and possible cardiac arrhythmias. Parenterally administered benzodiazepines are the treatment of choice.[23] The first-generation antipsychotic haloperidol is given for severe agitation unresponsive to benzodiazepines. Evidence does not support use of an antipsychotic as sole treatment.[26] Administer thiamine according to the previously described guidelines.

Opioid Withdrawal

It is rare to die from opioid withdrawal alone; however, underlying medical complications (eg, hypertension) and recent myocardial infarction increase risk of complications and death. Therefore, it is important to manage and stabilize any medical issues and then determine if hospitalization is appropriate. Evaluate patients with underlying medical problems for possible triage to an inpatient detoxification program to be followed up with either inpatient or outpatient substance abuse treatment. Withdrawal from opioids is commonly described by patients as resembling "a bad case of the flu." Symptoms include nausea; vomiting; diarrhea; anxiety; headaches; mydriasis; rhinorrhea; lacrimation; muscle, bone, and joint pain; piloerection; yawning; fever; increased heart rate; and hypertension.[13]

Use of clinical withdrawal scales (Table 36–2), such as the Clinical Opiate Withdrawal Scale (COWS), provides interrater reliability and clinical utility given their objective measurement of withdrawal severity. The baseline score assists in deciding whether to treat pharmacologically or to observe. As COWS scores increase (eg, 5 or greater), opioid substitution or a "symptoms-based approach" may be indicated. In severe withdrawal, either buprenorphine (ie, partial μ-opioid receptor agonist) or methadone (ie, full μ-opioid receptor agonist) are recommended for detoxification. Methadone is the gold-standard for treating opioid use disorders, but under current US law, methadone detoxification requires referral to a federally approved methadone detoxification program. The pharmacologic options for opioid withdrawal treatment in regular clinical settings are either opioid substitution with buprenorphine or a symptoms-based approach.[27]

▶ *Opioid Substitution*

LO 6

Treatment with μ-opioid receptor agonists is accomplished with either buprenorphine or methadone. Methadone can be used for opioid detoxification and long-term relapse prevention, particularly among patients with heavy opioid use. Methadone is also widely used to treat women during pregnancy. Given its extensive medical use restrictions (eg, used only in a federally approved opioid treatment program [OTP]) and wide availability of methadone detoxification regimens, this chapter focuses on buprenorphine. Refer to Chapter 34 for additional information on methadone.

Buprenorphine is a partial μ-opioid receptor agonist and is available in multiple formulations with varying pharmacokinetic profiles. For example, buprenorphine in combination with naloxone is available as a sublingual tablet, sublingual film, and buccal film.[16] Certain formulations (eg, sublingual film) may have greater buprenorphine bioavailability, and hence lower dosage requirements than other formulations (eg, sublingual tablets). Naloxone is poorly absorbed via the sublingual and buccal routes but is added to buprenorphine formulations to block opioid receptors if the medication is injected. Thus, naloxone has negligible effects when used appropriately while discouraging inappropriate IV use. Therefore, buprenorphine plus naloxone is the recommended formulation (versus buprenorphine alone) unless the patient is pregnant or hypersensitive to naloxone. Opioid antagonists, such as naloxone, have been associated with severe negative outcomes among pregnant women (eg, spontaneous abortion) and should be avoided in this population.[27]

LO 6

To initiate buprenorphine induction, a patient must be experiencing moderate to severe withdrawal, with the last opioid taken at least 12 to 24 hours earlier, depending on the half-life of the opioid used (ie, the longer an opioid's half-life, the longer a clinician should wait before initiating buprenorphine). Otherwise, buprenorphine will likely induce withdrawal because it has high affinity for μ-opioid receptors, displacing other full μ-opioid agonists, and is a partial rather than full agonist. Buprenorphine can be initiated following a protocol such as the example in Table 36–6.[8] There are generally two treatment approaches

Table 36–6

Sample Regimen[a] for Buprenorphine Induction Treatment of Opioid Withdrawal and Long-Term Relapse Prevention[8]

Day	Buprenorphine Sublingual/Buccal Dosage
1	2 mg every 2 hours (maximum, 8 mg on first day)
2	Start with total day 1 dose; additional 2–4 mg every 2 hours (maximum, 16 mg)
3	Start with total day 2 dose; additional 2–4 mg every 2 hours (maximum, 32 mg)
4–5	Maintain on dose required to alleviate withdrawal symptoms[b]

[a]For withdrawal from any opioid.

[b]Patient will likely be transitioned to long-term maintenance dose indefinitely.

Table 36–7

Symptoms-Based Treatment Approach for Opioid Withdrawal[8,11]

The following are examples of medications for withdrawal symptoms that cause distress:

1. Insomnia: trazodone 75–200 mg at bedtime
2. Headache, muscle aches, or pain: acetaminophen 500 mg–1000 mg every 6 hours
3. Noradrenergic hyperactivity: clonidine 0.1–0.2 mg every 6–8 hours; not to exceed 1.2 mg in 24 hours
4. Abdominal cramps: dicyclomine 10–20 mg every 6 hours
5. Constipation: milk of magnesia 30 mL daily
6. Diarrhea: loperamide 2 mg every 6 hours

once a final dose is established. Either the maintenance dose is prescribed or the dose is tapered and discontinued within 1 to 2 weeks (eg, 25% reduction per day as a general rule of thumb).

▶ *Symptoms-Based Treatment*

Symptomatic treatment focuses on minimizing withdrawal symptoms to increase patient comfort. Symptom-specific medications are often used as adjunct medication along with opioid substitution.[8,11] Examples of symptom-specific medications are listed in Table 36–7.

▶ *General Patient Guidelines for Outpatient Opioid Detoxification*

Patient safety is the highest priority. The first step is to educate patients about the course of withdrawal. Symptoms generally peak at 5 to 7 days and may last up to 2 weeks, depending on the half-life of the opioid used before detoxification. Educate patients on the side effects of medications used for detoxification. Balance the risk of adverse events with the potential benefits. Buprenorphine side effects include constipation, sedation, and headaches. Potential for serious overdose exists when buprenorphine is combined with benzodiazepines or other sedative–hypnotics.

Risk of developing physiologic tolerance to buprenorphine is high if used for prolonged periods. In this case, buprenorphine requires a slow taper to discontinuation. Withdrawal from buprenorphine is generally easier and less severe than withdrawal from a full agonist, such as methadone.[8] However, there is concern regarding a subset of patients who have difficulty discontinuing buprenorphine. The duration of buprenorphine treatment is specific to each patient's needs and resources, and difficulty in tapering the medication to discontinuation complicates this decision further.

Following detoxification, rehabilitation and acquiring recovery skills are tied to positive outcomes. This goal can be accomplished by either achieving detoxification on-site during rehabilitation or by quick and seamless transition from detoxification to a rehabilitation program. The more time that elapses between the two modalities, the greater the likelihood of treatment failure and relapse.

Stimulant (Cocaine, Amphetamines) Withdrawal

Cocaine and amphetamine withdrawal are grouped together because their symptom profiles as described in *DSM-5* are similar, and the physiologic basis of their withdrawal syndromes involves the DA neurotransmitter system.[6,14] Stimulants of this group also include methylphenidate, but not nicotine and caffeine, which have different neurophysiologic mechanisms of action. Major adverse complications of stimulant withdrawal are profound depression with suicidal thoughts, and the primary treatment goal is suicide prevention. Therefore, unless suicidality warrants hospitalization, stimulant withdrawal can be treated in outpatient setting with psychological support and reassurance with an emphasis on patient safety. Medications have been studied to alleviate withdrawal symptoms and cravings, but inconsistent results preclude any recommendations for their routine use. Refer patients with stimulant use disorder for substance abuse treatment because of the high risk for continued use either during or immediately following stimulant withdrawal.

Cannabinoid (Marijuana, Hashish) Withdrawal

Symptoms of cannabinoid withdrawal are primarily behavioral. For example, significant anxiety may accompany cannabinoid withdrawal, which can lead many individuals to resume substance use. This is particularly problematic following heavy and prolonged use. Management of withdrawal focuses on these behavioral symptoms as there are no FDA-approved medications specifically targeted at cannabinoid withdrawal.

GENERAL APPROACH TO THE TREATMENT OF SUBSTANCE USE DISORDERS

KEY CONCEPT A multimodal and comprehensive approach is preferred when treating patients with SUDs given the heterogeneous nature of addiction. Pharmacologic treatment is always adjunctive to psychosocial therapy. Steps to be taken in the management of SUDs are similar for all substances and are highlighted in the Patient Care Process.[11]

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Address comorbid psychiatric conditions such as anxiety, depression, insomnia, pain, and continued smoking. All of these conditions increase risk of relapse to substance use. Although complete abstinence may be desirable, decreasing substance use and negative consequences may be sufficient in certain cases (ie, the "harm reduction" concept).[28]

Nonpharmacologic Therapy

Although pharmacologic agents may help prevent relapse, psychotherapy is the core therapeutic intervention. Psychotherapy typically addresses 1 or more of the following:

- Motivation enhancement to stop or reduce substance use
- Coping skills education
- Providing alternative reinforcement
- Managing painful affect (eg, dysphoria)
- Enhancing social support and interpersonal functioning

A thorough review of psychosocial approaches is beyond the scope of this chapter and are available elsewhere.[11] However, a few of the commonly used techniques are cognitive-behavioral therapy, motivational-enhancement therapy, and other behavioral therapies (eg, community reinforcement).

Pharmacologic Therapy

▶ *Maintenance Treatment*

KEY CONCEPT Certain pharmacologic agents are helpful for long-term maintenance in patients with SUDs. Typically, these medications exert their effects by one of the following theorized mechanisms: (a) drug substitution therapy with an agonist, (b) blocking drug effects with an antagonist, and (c) miscellaneous relapse prevention medications with indirect mechanisms of action. Medications from each of these categories are discussed in greater detail in the following paragraphs for alcohol, opioid, cannabinoid, stimulant, and tobacco use disorders.

▶ *Alcohol Use Disorder*

The FDA-approved medications to treat alcohol use disorder are naltrexone (oral and depot), acamprosate, and disulfiram. Practice guidelines recommend naltrexone and acamprosate as first-line agents.[25,29] However, in motivated patients or with supervised administration to ensure adherence, disulfiram is another option.[30]

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Naltrexone Naltrexone is a competitive opioid receptor antagonist that decreases alcohol intake, craving for alcohol, and alcohol-induced euphoria (ie, reduces positive reinforcement of drinking).[3] Naltrexone is more efficacious than placebo for a variety of drinking measures.[29] According to a recent meta-analysis, it significantly improves abstinence rates, decreases relapse rates, and has a safety profile similar to placebo.[31] Predictors of naltrexone efficacy may include family history of alcohol use disorder and a specific μ-opioid receptor gene polymorphism.[32] In the landmark COMBINE study, which assessed the efficacy of behavioral intervention, medical management, medications, and their combinations for treatment of alcohol use disorder, naltrexone with medical management was associated with a higher percent of days abstinent than other interventions.[33] An oversimplified interpretation of this complex study suggests that naltrexone is effective (eg, higher percent of days abstinent), but acamprosate offers no discernable advantage.[33]

Naltrexone is available as an oral tablet and long-acting IM injection. Naltrexone is dosed 50 mg once daily, with a range from 25 to 100 mg. A 25 mg test-dose is commonly given, then increased to 50 mg/day as tolerated. While specific dosage adjustments are unavailable, caution is warranted in patients with severe hepatic or renal impairment.[16] Adherence to naltrexone strongly affects drinking outcomes; therefore, a long-acting IM formulation is available. Administered as 380 mg once monthly, the injection results in significantly greater reductions in heavy drinking days compared with placebo injection.[34]

Common side effects include nausea, headache, insomnia, and nervousness. Injectable naltrexone is associated with injection site reactions. Because naltrexone can precipitate withdrawal in patients who are opioid dependent, withhold the first dose for 7 to 10 days after last opioid use and give only when the urine drug screen for opioids is negative. Naltrexone can be hepatotoxic, albeit typically not at oral doses less than 250 mg/day or at recommended injectable dose of 380 mg once monthly. Baseline and periodic LFTs are recommended.[16]

Naltrexone can block effects of opioid receptor agonists, rendering them therapeutically ineffective (Table 36–5). Given that opioid agonists are a mainstay of pain management, alternative pain treatment (eg, conscious sedation) may be required in patients receiving naltrexone maintenance.

Educate patients taking naltrexone to carry a pocket warning card or wear a medical bracelet. In the event that emergency pain management is needed, the patient will be insensitive to opioid analgesia unless potentially toxic doses are administered. Warn patients of the potential for opioid overdose under two conditions. First, dosing with opioids to reverse opioid insensitivity (ie, naltrexone's competitive blockade of opioid receptors) requires high doses of opioids that can cause respiratory depression and death. Second, following chronic opioid receptor antagonist therapy, patients are likely to have reduced tolerance to opioids, thereby increasing risk of respiratory depression and death when previously tolerated doses of opioids are used.[16]

Acamprosate Acamprosate appears to be a glutamatergic N-methyl-D-aspartate receptor antagonist and may affect GABA.[3] Alcohol acutely inhibits glutamatergic function. During acute and postacute alcohol withdrawal, increased activity of the glutamate system is caused by upregulation of receptors combined with absence of alcohol-related inhibition. Thus, acamprosate may correct glutamate/GABA imbalances that occur following chronic alcohol use (eg, reduce negative reinforcement associated with craving and withdrawal).[3,16]

Generally, trials assessing efficacy of acamprosate have shown mixed results. This may be partly attributable to differences in research methodologies, such as varying levels of abstinence required in trials before acamprosate initiation.[29] Notably, in the aforementioned COMBINE study, acamprosate appeared to offer no treatment advantage,[33] but a recent meta-analysis suggests it is more efficacious than placebo.[35] Another meta-analysis suggests that acamprosate may be more effective at maintaining abstinence, whereas naltrexone may more effectively reduce heavy drinking and craving.[36] Despite variable methodologies and results, sufficient evidence demonstrates that acamprosate is more effective than placebo, although differences may be modest.

The dose of acamprosate is 666 mg orally three times daily. It is not metabolized by the liver and is excreted unchanged by the kidneys. Consequently, it is contraindicated in patients with severe renal impairment (creatinine clearance less than or equal to 30 mL/min [0.50 mL/s]), and dose reduction is necessary when creatinine clearance is between 30 and 50 mL/min (0.50 and 0.83 mL/s). Closely monitor renal function in elderly patients to ensure proper dosing. Common side effects are nausea, diarrhea, and CNS effects, including insomnia, anxiety, and depressive symptoms.[16]

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Disulfiram Disulfiram irreversibly blocks the enzyme aldehyde dehydrogenase, a step in the metabolism of alcohol.[16] This results in increased blood levels of the toxic metabolite, acetaldehyde. As acetaldehyde levels increase, patients experience the disulfiram-ethanol reaction consisting of the following symptoms: decreased blood pressure, increased heart rate, chest pain, palpitations, dizziness, flushing, sweating, weakness, nausea, vomiting, shortness of breath, blurred vision, and syncope. Symptom severity increases with amount of alcohol consumed, and emergency treatment may be warranted. Psychologically, disulfiram works to deter drinking due to the knowledge that the aversive disulfiram–ethanol reaction occurs if alcohol is consumed.[30] Efficacy of disulfiram directly depends on medication adherence and can be effective when procedures for enhancing adherence are used.[30,37]

The usual starting dose of disulfiram is 250 mg once daily. It can be started at 500 mg once daily for the first 1 to 2 weeks, and the range is 125 to 500 mg/day.[16] Compared with 250 mg, the larger dose is recommended if a patient does not experience a disulfiram–ethanol reaction after alcohol consumption. The smaller dose is given when intolerable side effects are experienced at higher doses or for elderly patients. Use disulfiram with caution in patients with renal and hepatic impairment. Dosing begins only after the BAC reaches zero (ie, 12–24 hours after the last drink) and after the patient is educated on the consequences of drinking with disulfiram.

Disulfiram is contraindicated in patients with cardiovascular or cerebrovascular disease, hypersensitivity to thiuram derivatives, and the anti-infective, metronidazole. Common side effects are rash, drowsiness, and metallic or garlic-like taste. Less common, but concerning, adverse effects include neuropathies, psychosis, and hepatotoxicity.[16] Given the serious

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nature of these adverse effects, baseline and periodic monitoring is recommended. If LFTs are greater than three times the upper limit of normal values, withhold disulfiram and repeat testing every 1 to 2 weeks. When LFTs return to normal, they may be repeated every 1 to 6 months.[38] Although elevated LFTs may signal disulfiram-induced hepatotoxicity, it may also indicate the patient was nonadherent to treatment and resumed alcohol consumption. Psychosis has been reported with doses exceeding 500 mg/day and may be related to disulfiram's inhibition of DA β-hydroxylase, resulting in increased DA activity. Nevertheless, patients with schizophrenia or other co-occurring psychiatric disorders have received disulfiram at usual doses without difficulties.[39]

The disulfiram–ethanol interaction serves as disulfiram's mechanism of action. Depending on the dose of disulfiram, sensitivity to disulfiram, amount of alcohol consumed, and metabolism, patients may be at risk for an adverse interaction with alcohol for 2 to 14 days after stopping disulfiram (5 days on average) and should be educated accordingly. Table 36–5 lists relevant disulfiram interactions.

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Universally accepted treatment algorithms for alcohol use disorder treatment are lacking. Table 36–8 lists patient-specific factors that can guide medication selection.[38]

▶ *Opioid Use Disorder*

After conclusion of withdrawal, patients may not feel their usual selves for some time and could relapse to using opioids, just to "feel normal." Long-term use of opioids results in brain changes, and the brain might not readily return to its prior homeostasis. The goal of treatment is to encourage stability, both in the body and in the patient's life. If an individual is not successful in quitting opioids (eg, because of withdrawal symptoms or postacute craving), then maintenance treatment should be considered.

Opioid Agonists Methadone and buprenorphine are first-line medications for maintenance treatment, also called **medication-assisted treatment**, of opioid use disorder. Methadone is a full μ-opioid receptor agonist, and methadone maintenance treatment can only be provided in federally approved OTPs.[27] The other first-line agent for maintenance treatment, which will be the focus of this chapter, is buprenorphine. Alternatively, the long-acting naltrexone injection is FDA approved for prevention of opioid relapse, but its place in long-term treatment of opioid use disorder remains to be established.

The more widely available office-based opioid treatment (OBOT) exclusively uses buprenorphine, a partial μ-opioid receptor agonist, typically in formulations also containing naloxone.[8] Recently, the FDA approved a subcutaneous injection given every month and subdermal implants that deliver medication continuously for up to 6 months.[16] Under the Drug Addiction Treatment Act of 2000 and the Comprehensive Addiction and Recovery Act of 2016, clinicians may prescribe buprenorphine in the outpatient office-based setting once requirements (eg, training) are met. When these criteria are met, qualified providers obtain a separate "X" Drug Enforcement Administration number.[8]

Patients receiving buprenorphine maintenance should sign a treatment contract requiring full adherence, financial responsibility for treatment, adherence to office policies, and agreement to provide random urine samples for drug screens. Instruct patients to bring their prescribed medication for pill counts at every visit. In the event of OBOT failure, the alternative to buprenorphine maintenance is referral to an OTP for methadone administration. A recent meta-analysis indicates that methadone may offer an advantage over buprenorphine for select outcomes (eg, retention in treatment).[40] Therefore, there are circumstances under which referral to methadone maintenance remains the preferred treatment option.

Although there are no treatment algorithms to guide medication selection, there are protocols for some medications that assist with dosing and titration. For example, the extensive buprenorphine treatment protocol available from SAMHSA provides guidelines on how to dose buprenorphine from induction to maintenance treatment.[8] The effective maintenance dose of buprenorphine (with or without naloxone) is usually between 8 and 24 mg/day.[16] Initiate buprenorphine at the low end of the dosing range for elderly patients. Reduce initial and

Table 36–8

Alcohol Use Disorder Medication Decision Grid[38]

Pretreatment Indicator	Acamprosate	Disulfiram	Oral Naltrexone	Injectable Naltrexone
Renal failure	X	A	A	A
Significant liver disease	A	C	C	C
Coronary artery disease	A	C	A	A
Chronic pain	A	A	C	C
Current opioid use	A	A	X	X
Psychosis	A	C	A	A
Unwilling or unable to sustain total abstinence	A	X	A	A
Risk factors for poor medication adherence	C	C	C	A
Diabetes	A	C	A	A
Obesity that precludes intramuscular injection	A	A	A	X
Family history of alcohol use disorders	A	A	+	+
Bleeding or other coagulation disorders	A	A	A	C
High level of craving	A	A	+	+
Opioid use disorder in remission	A	A	+	+
History of postacute withdrawal syndrome	+	A	A	A
Cognitive impairment	A	X	A	A

+ = particularly appropriate; A = appropriate to use; C = use with caution; X = contraindicated.

Patient Encounter 3

A 35-year-old woman presents to the outpatient clinic for a medication therapy management appointment. She is diagnosed with schizophrenia and seasonal allergies and takes the following medications: olanzapine 15 mg once daily, loratadine 10 mg once daily, and a once daily multivitamin. The patient smokes approximately 1 pack of cigarettes per day and denies alcohol or illicit drug use. Laboratories are within normal limits.

What approach can assist the clinician in addressing the patient's tobacco use?

Is the patient a candidate for all first-line tobacco cessation pharmacotherapies?

How will smoking cessation affect the patient's current medications?

titration doses for patients with hepatic impairment and monitor for signs of toxicity or overdose.[16]

▶ *Cannabinoid Use Disorder*

There are no proven pharmacotherapies for treatment of cannabinoid use disorder. Pharmacotherapy trials have emerged in the literature, but universally accepted medication treatment strategies have yet to emerge.[41]

▶ *Stimulant Use Disorder*

There are no proven pharmacotherapies for treatment of stimulant use disorder. Combine medications with psychosocial approaches. The APA guidelines suggest three medications as possible treatment options: topiramate, disulfiram, and modafinil.[11,42] Disulfiram shows promise, possibly due to its inhibition of DA β-hydroxylase which converts DA to NE. The resulting increase in DA levels may counter DA deficiency states that are believed to underlie cocaine withdrawal and craving.[42]

▶ *Tobacco Cessation*

Nonpharmacologic Behavioral treatment, delivered by a variety of clinicians, increases abstinence rates. The 5 As model below can be used by all clinicians.[15]

- Ask about tobacco use.
- Advise to quit.
- Assess willingness to make a quit attempt.
- Assist in quit attempt.
- Arrange follow-up.

Provide tobacco cessation education to all patients who use tobacco, and assist those interested to achieve cessation. It is now standard practice for clinicians to screen for tobacco use, provide all patients who use tobacco with brief advice and assistance with appropriate medications to quit, or provide referral to specialized services when needed.[15]

Electronic cigarette use has grown considerably in recent years. Preliminary evidence suggests they may be useful for smoking cessation; however, long-term safety is unknown. They appear to contain toxins similar to those found in tobacco smoke, albeit at lower levels.[43,44] The FDA recently gained regulatory authority over electronic cigarettes, allowing them to restrict sales to minors and ensure products contain proper health warnings.[45]

Pharmacologic According to tobacco use practice guidelines, first-line medications for tobacco use disorder are nicotine replacement therapy (NRT), bupropion sustained-release (SR), and varenicline (Table 36–9).[15]

Symptomatic detoxification and maintenance for tobacco use disorders is achieved with any single or combination of the currently available NRTs.[15] Similar to opioid receptor agonists, NRTs act as substitution therapy as safer alternatives to tobacco use. While NRTs are generally considered safe, their pregnancy category D classification means the decision to use NRT for pregnant women must be made on a case-by-case basis. One meta-analysis of nearly 700 pregnant women concluded that there is inadequate evidence to determine whether NRT is safe or effective in pregnancy.[46] According to practice guidelines, pregnant women should be encouraged to quit without use of medication.[15] Given the various NRT products available, choice of NRT formulation depends on various factors, including patient preference.[11]

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Two nonnicotine medications are FDA approved for the treatment of tobacco use disorders: bupropion SR and varenicline. Bupropion is an antidepressant that blocks reuptake of DA and NE; in addition, it appears that one of its metabolites is a nicotinic antagonist. These mechanisms may help explain how bupropion reduces nicotine reinforcement, withdrawal, and craving.[3] Bupropion is contraindicated in patients with seizure disorders, eating disorders, and patients withdrawing from alcohol or sedative–hypnotics.[16] Varenicline is an $\alpha_4\beta_2$ nicotinic acetylcholine partial agonist. Varenicline decreases withdrawal and craving and prevents reinforcing effects of nicotine if the patient relapses.[3] Warnings include seizures and cardiovascular adverse events (eg, angina).[16] Both bupropion SR and varenicline have been associated with psychiatric disturbances when used for smoking cessation.[47]

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As shown in Table 36–10, various NRTs, bupropion SR, and varenicline increase abstinence rates at 6 months compared to placebo.[15] Combining NRTs (eg, nicotine patch and "as needed" gum) is common. A recent meta-analysis concluded that NRT, bupropion SR, and varenicline all improve smoking cessation rates. Varenicline was more effective than single NRT or bupropion SR, but varenicline and combination NRT were equally effective.[48]

OUTCOME EVALUATION

KEY CONCEPT A major component of successful SUD treatment is to monitor use of medications and identify a mechanism for long-term support of sobriety that might be appropriate for a specific patient such as Alcoholics Anonymous, Narcotics Anonymous, or recovery programs for health care professionals.

To determine immediate treatment outcomes for patients with intoxication and withdrawal syndromes, evaluate parameters such as blood pressure, heart rate, respirations, body temperature, and mental status. Select validated and standardized instruments to monitor the responsiveness of withdrawal syndromes to medical treatment. To determine the overall effectiveness of your health system for the treatment of substance-related disorders, monitor outcomes using sentinel events such as the rates of

Table 36–9

First-Line Medications for Treatment of Tobacco Use Disorder[15,16]

Medication	Dosing and Administration[a]	Adverse Effects, Warnings, and Precautions[b]
Nicotine patch (7, 14, and 21 mg)	Apply 1 patch/day to nonhairy area on the upper body; rotate application sites Use 21 mg for 4–6 weeks, 14 mg for 2 weeks, then 7 mg for 2 weeks if > 10 cigarettes/day Use 14 mg for 6 weeks, then 7 mg for 2 weeks if ≤ 10 cigarettes/day Duration: 8–12 weeks	Skin irritation, insomnia, vivid dreams Remove patch at bedtime if sleep disturbances occur and apply new patch in the morning
Nicotine gum (2 and 4 mg)	Chew slowly until gum tingles, then "park" in cheek until tingle is gone; repeat Avoid eating or drinking for 15 minutes before or during use Use 4 mg if first cigarette is smoked within 30 minutes of waking; otherwise, use 2 mg dose Use 1 piece every 1–2 hours for 1–6 weeks, then 1 piece every 2–4 hours for 7–9 weeks, then 1 piece every 4–8 hours for 10–12 weeks Maximum: 24 pieces of gum/day Duration: 12 weeks (or as needed)	Sore mouth, hiccups, dyspepsia, insomnia Limit swallowing excess saliva to avoid GI irritation
Nicotine lozenge (2 and 4 mg)	Avoid chewing; occasionally move lozenge around mouth until completely dissolved Avoid eating or drinking for 15 minutes before or during use Use 4 mg if first cigarette is smoked within 30 minutes of waking; otherwise, use 2 mg dose Use 1 piece every 1–2 hours for 1–6 weeks, then 1 piece every 2–4 hours for 7–9 weeks, and 1 piece every 4–8 hours for 10–12 weeks Maximum: 20 lozenges/day Duration: 3–6 months	Hiccups, cough, heartburn, nausea, insomnia Limit swallowing excess saliva to avoid GI irritation
Nicotine nasal spray (0.5 mg delivered to each nostril)	Do not inhale during administration 1 dose = 1 spray in each nostril Use 1–2 doses/hour Maximum: 5 doses/hour; 40 doses/day Duration: 3–6 months; taper	Nasal irritation or congestion, changes in smell Avoid in patients with reactive airway disease Dependence risk is higher than other formulations
Nicotine inhaler (4 mg in each cartridge)	Inhale ("puff") lightly 80 times/cartridge Cold temperature decreases nicotine delivery; store in warm area (eg, pocket) Avoid eating or drinking for 15 minutes before or during use Use 6–16 cartridges/day Maximum: 16 cartridges/day Duration: Up to 6 months; taper	Mouth and throat irritation (improves with use), cough, rhinitis, sneezing
Bupropion sustained-release	Dosing: 150 mg once daily for 3 days, then 150 mg twice daily Start 1–2 weeks before quit date	Neuropsychiatric events (eg, mood disturbances) when used for smoking cessation
Varenicline	Dosing: 0.5 mg once daily for 1–3 days, then 0.5 mg twice daily for 4–7 day, then 1 mg twice day on day 8 and after Renal dosing (CrCl < 30 mL/min [< 0.50 mL/s]): 0.5 mg once daily with a maximum of 0.5 mg twice daily Start 1 week before quit date	CNS: insomnia, abnormal dreams, neuropsychiatric events (eg, depression, suicidal thoughts) GI: dose-related nausea

[a]NRT dosage adjustments for renal or hepatic impairment are not established. Severe impairment may affect nicotine clearance.

[b]Avoid NRT in patients with recent myocardial infarction, arrhythmias, or unstable angina.

CNS, central nervous system; CrCl, creatinine clearance; GI, gastrointestinal; NRT, nicotine replacement therapy.

cardiopulmonary arrest, seizures, discharges against medical advice, patient violence, and use of physical restraints. The ultimate goal is to enable the transition of patients to formal substance use treatment when indicated.

Important outcome indicators to evaluate postintoxication and/or postwithdrawal treatment can be divided into three major groups: decreased consumption of substances, decreased problems associated with substance use, and improved psychosocial functioning. When complete abstinence has not been achieved, quantify the consumption of substances using quantity–frequency measures, rates of abstinence, and time to first relapse as determined by interviews, self-report, and biological markers such as urine and blood tests. The ASI (Table 36–2) assesses alcohol and drug-related problems in various domains, and provides a more comprehensive picture of the patient's life.

KEY CONCEPT Clinicians must be familiar with "essential" resources, many of which are in the public domain. Table 36–11 provides a list of these resources which provide useful information for clinical management, research, teaching, and policy development purposes.

Table 36–10

Six-Month Postquit Smoking Abstinence Rates and Associated Odds Ratios[a,15]

Medication	Abstinence Rate (%)	Odds Ratio (95% CI)
Placebo	13.8	1.0
NRTs		
Nicotine gum (6–14 weeks)	19.0	1.5 (1.2–1.7)
Nicotine patch (6–14 weeks)	23.4	1.9 (1.7–2.2)
Nicotine gum (> 14 weeks)	26.1	2.2 (1.5–3.2)
Nicotine patch (> 14 weeks)	23.7	1.9 (1.7–2.3)
Non-NRTs		
Bupropion SR	24.2	2.0 (1.8–2.2)
Varenicline (1 mg/day)	25.4	2.1 (1.5–3.0)
Varenicline (2 mg/day)	33.2	3.1 (2.5–3.8)
Combination Strategies		
Nicotine patch (> 14 weeks) + ad lib gum or spray	36.5	3.6 (2.5–5.2)
Nicotine patch + bupropion SR	28.9	2.5 (1.9–3.4)

[a]Meta-analysis; 83 studies included.

CI, confidence interval; NRT, nicotine replacement therapy; SR, sustained-release.

Table 36–11

Essential Substance Use Disorder Treatment Resources

Source	Website	Example Highlight
American Psychiatric Association	www.psych.org	Clinical practice guidelines
American Society of Addiction Medicine	www.asam.org	Principles of Addiction Medicine textbook
National Institute on Alcohol Abuse and Alcoholism	www.niaaa.nih.gov	Alcohol Research & Health journal
National Institute on Drug Abuse	www.drugabuse.gov	Education resources
Substance Abuse and Mental Health Services Administration	www.samhsa.gov	National Survey on Drug Use and Health Treatment Improvement Protocols

Patient Care Process

Collect Information:

- Conduct a medication history for prescription, nonprescription, herbal, and dietary supplement use. Identify medication allergies and associated reactions.
- Retrieve a state prescription drug-monitoring program report.
- Document medical history, family history (eg, SUDs, psychiatric disorders), social history (eg, alcohol, tobacco, and illicit substance use), physical assessment, and mental status examination findings.
- Document other factors (eg, transportation, employment) that may impact treatment.
- Determine the patient's preferences, beliefs, and functional goals.
- Consider the use of screening and assessment instruments (Table 36–2).
- Assess the patient's readiness to change.

Assess the Information:

- Assess medication appropriateness, efficacy, safety, and adherence.
- Review laboratory tests (eg, electrolytes, liver and renal function, drug screen, HIV test).
- Assess previous periods of abstinence and factors that worked to achieve this.

Develop a Care Plan:

- Substance *intoxication*: Management is typically supportive. The most important goal is to maintain cardiopulmonary function. If consciousness is impaired, obtain blood chemistries to help identify causative substance and rule out other etiologies. Observe patient until intoxication has resolved.
- Substance *withdrawal*: Select instrument to monitor withdrawal symptoms and guide medication use (Table 36–2). Severe symptoms (eg, seizures) require inpatient treatment.
- Medication management is an adjunct to psychosocial approaches for achieving recovery.
- Align treatment (eg, detoxification versus longer-term treatment) with patient goals.

Implement the Care Plan:

- Educate the patient and the patient's support system about SUDs, medications, adverse effects, and adverse effect management. Ensure the patient has access to medications.
- Discuss the importance of medication adherence and psychosocial treatment approaches.
- Provide referrals for the treatment of co-occurring medical conditions or complications.
- Reduce stress and risk factors for relapse and improve attitude toward wellness.

Follow-up: Monitor and Evaluate:

- Assess treatment effectiveness, safety, and adherence regularly. Make changes as needed.
- Evaluate progress toward treatment goals (eg, improved coping skills, functioning, and relapse prevention).
- Continuously monitor for triggers, cravings, substance use, and relapse. Provide support.

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Abbreviations Introduced in This Chapter

APA	American Psychiatric Association
ASI	Addiction Severity Index
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood alcohol concentration
CAGE	Cut down, angry/annoyed, guilty, eye opener
CIWA-Ar	Clinical Institute Withdrawal Assessment–Alcohol, Revised
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	Corticotropin-releasing factor
DA	Dopamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders,* 5th edition
DTs	Delirium tremens
FDA	US Food and Drug Administration
GABA	γ-aminobutyric acid
GI	Gastrointestinal
IM	Intramuscular
IN	Intranasal
IV	Intravenous
LFT	Liver function test
NA	Nucleus accumbens
NE	Norepinephrine
NRT	Nicotine replacement therapy
NSDUH	National Survey on Drug Use and Health
OBOT	Office-based opioid treatment
OTP	Opioid treatment program
PFC	Prefrontal cortex
SAMHSA	Substance Abuse and Mental Health Services Administration
SR	Sustained-release
SUD	Substance use disorder
VTA	Ventral tegmental area

REFERENCES

1. Substance Abuse and Mental Health Services Administration, Results from the 2015 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H–51, HHS Publication No. (SMA) 16–4984. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2016.
2. The Neurobiology of Drug Addiction. National Institute on Drug Abuse. Available from: http://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-i-introduction-to-brain. Accessed July 10, 2018.
3. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th ed. New York, NY: Cambridge University Press; 2013.
4. Beveridge TJR, Roberts DCS. The anatomy of addiction. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. The ASAM Principles of Addiction Medicine, 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:36–48.
5. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35(1):217–238.
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
7. Rush AJ, First MB, Blacker D, eds. Handbook of Psychiatric Measures, 2nd ed. Arlington, VA: American Psychiatric Publishing; 2008.
8. Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04–3939. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2004.
9. Substance Abuse and Mental Health Services Administration. Detoxification and substance abuse treatment. Treatment Improvement Protocol (TIP) Series, No. 45. HHS Publication No. (SMA) 13–4131. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2006.
10. Volkow ND, Warren KR. Drug addiction: the neurobiology of behavior gone awry. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. The ASAM Principles of Addiction Medicine. 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:3–18.
11. American Psychiatric Association. Practice guideline for the treatment of patients with substance use disorders, 2nd ed. Arlington, VA: American Psychiatric Association; 2006.
12. Wartenberg AA. Management of alcohol intoxication and withdrawal. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. The ASAM Principles of Addiction Medicine, 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:635–651.
13. Tetrault JM, O'Connor PG. Management of opioid intoxication and withdrawal. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. The ASAM Principles of Addiction Medicine, 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:668–684.
14. Wilkins JN, Danovitch I, Gorelick DA. Management of stimulant, hallucinogen, marijuana, phencyclidine, and club drug intoxication and withdrawal. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. The ASAM Principles of Addiction Medicine, 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014: 685–709.
15. Fiore MC, Jaén CR, Baker TB, et al. Treating tobacco use and dependence: 2008 update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service, 2008.
16. Lexi-Comp Online. Hudson, OH: Lexi-Comp, Inc.; 2011. Available from: www.lexi.com. Accessed May 13, 2018.
17. Elzey MJ, Fudin J, Edwards ES. Take-home naloxone treatment for opioid emergencies: a comparison of routes of administration and associated delivery systems. Expert Opin Drug Deliv. 2017;14:1045–1058.
18. Substance Abuse and Mental Health Services Administration. SAMHSA opioid overdose prevention toolkit. HHS Publication No. (SMA) 16–4742. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2016.
19. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation. 2008;117:1897–1907.
20. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy. 2013;33(2):195–209.
21. Muncie HL, Yasinian Y, Oge L. Outpatient management of alcohol withdrawal syndrome. Am Fam Physician. 2013;88:589–595.
22. Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med. 2014;371:2109–2113.
23. Cassidy EM, O'Sullivan I, Bradshaw P, et al. Symptom-triggered benzodiazepine therapy for alcohol withdrawal syndrome in the emergency department: a comparison with the standard fixed dose benzodiazepine regimen. Emerg Med J. 2012;29:802–804.
24. Day E, Bentham PW, Callaghan R, et al. Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. Cochrane Database Syst Rev. 2013;7:CD004033.

25. Lingford-Hughes AR, Welch S, Peters L, Nutt DJ. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J Psychopharmacol. 2012;26:899–952.
26. Mirijello A, D'Angelo C, Ferrulli A, et al. Identification and management of alcohol withdrawal syndrome. Drugs. 2015;75:353–365.
27. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) national practice guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9:358–367.
28. Wodak A. The harm reduction approach to prevention and treatment. In: Ries RK, Fiellin DA, Miller SC, Saitz R, eds. The ASAM Principles of Addiction Medicine. 5th ed. Philadelphia, PA: Wolters Kluwer Health; 2014:466–479.
29. American Psychiatric Association. Practice guideline for the pharmacological treatment of patients with alcohol use disorder. Arlington, VA: American Psychiatric Association, 2018.
30. Swift RM, Aston ER. Pharmacotherapy for alcohol use disorder: current and emerging therapies. Harv Rev Psychiatry. 2015;23:122–133.
31. Jarosz J, Miernik K, Wachal M, et al. Naltrexone (50 mg) plus psychotherapy in alcohol-dependent patients: a meta-analysis of randomized controlled trials. Am J Drug Alcohol Abuse. 2013;39:144–160.
32. Garbutt JC, Greenblatt AM, West SL, et al. Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence. Addiction. 2014;109:1274–1284.
33. Anton RF, O'Malley SS, Ciraulo DA, et al., for the COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE Study: a randomized controlled trial. JAMA. 2006;295(17):2003–2017.
34. Aboujaoude E, Salame WO. Naltrexone: a pan-addiction treatment? CNS Drugs. 2016;30:719–733.
35. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014;311:1889–1900.
36. Maisel NC, Blodgett JC, Wilbourne PL, et al. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction. 2013;108:275–293.
37. Fuller RK, Branchey L, Brightwell DR, et al. Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. JAMA. 1986;256:1449–1455.
38. Center for Substance Abuse Treatment. Incorporating alcohol pharmacotherapies into medical practice. Treatment Improvement Protocol (TIP) Series 49. HHS Publication No. (SMA) 09–4380. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009.
39. Sinclair JM, Chambers SE, Shiles CJ, Baldwin DS. Safety and tolerability of pharmacological treatment of alcohol dependence: comprehensive review of evidence. Drug Saf. 2016;39:627–645.
40. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2:CD002207.
41. Marshall K, Gowing L, Ali R, Le Foll B. Pharmacotherapies for cannabis dependence. Cochrane Database Syst Rev. 2014;12:CD008940.
42. Haile CN, Kosten TR. Pharmacotherapy for stimulant-related disorders. Curr Psychiatry Rep. 2013;15:415.
43. Hajek P, Etter JF, Benowitz N, et al. Electronic cigarettes: review of use, content, safety, effects on smokers, and potential for harm and benefit. Addiction. 2014;109:1801–1810.
44. Hartmann-Boyce J, McRobbie H, Bullen C, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2016;9:CD010216.
45. FDA's New Regulations for E-Cigarettes, Cigars, and All Other Tobacco Products. U.S. Food and Drug Administration. Available from: https://www.fda.gov/tobaccoproducts/labeling/rulesregulationsguidance/ucm394909.htm. Accessed May 13, 2018.
46. Coleman T, Chamberlain C, Cooper S, Leonardi-Bee J. Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. Addiction. 2011;106:52–61.
47. FDA Drug Safety Communication: FDA revises description of mental health side effects of the stop-smoking medications chantix (varenicline) and zyban (bupropion) to reflect clinical trial findings. U.S. Food and Drug Administration. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm532221.htm. Accessed May 13, 2018.
48. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;5:CD009329.

37 Schizophrenia

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LEARNING OBJECTIVES

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

LO

1. Recognize signs and symptoms of schizophrenia and be able to distinguish among positive, negative, and cognitive impairments associated with the illness.
2. Explain potential pathophysiologic mechanisms that are thought to underlie schizophrenia.
3. Identify treatment goals for a patient with schizophrenia.
4. Recommend appropriate antipsychotic medications based on patient-specific data.
5. Compare side-effect profiles of individual antipsychotics.
6. Educate patients and families about schizophrenia, treatments, and the importance of adherence to antipsychotic treatment.
7. Describe components of a monitoring plan to assess the effectiveness and safety of antipsychotic medications.

INTRODUCTION

LO 1

Schizophrenia is a challenging disorder often requiring life-long treatment. The disorder may have many pathophysiological pathways that ultimately manifest with psychotic symptoms, including positive symptoms such as hallucinations and delusions, as well as disordered thinking. Commonly, these symptoms are accompanied by cognitive impairment (abnormalities in thinking, reasoning, attention, memory, and perception), impaired insight and judgment, and negative symptoms including loss of motivation (**avolition**), loss of emotional range (restricted affect), and a decrease in spontaneous speech (poverty of speech). Cognitive impairments and negative symptoms account for much of the poor social and functional outcomes. Schizophrenia is the fourth leading cause of disability among adults and is associated with substantially lower rates of employment, marriage, and independent living compared with population norms. However, earlier diagnosis, treatment, advances in research, and newer treatment developments have led to better outcomes with the potential for remission and recovery.

EPIDEMIOLOGY AND ETIOLOGY

Approximately 0.7% of the world population suffers from schizophrenia, with symptoms typically presenting in late adolescence or early adulthood.[1] Prevalence is equal in men and women, but symptoms appear earlier in men with first hospitalization typically occurring at 15 to 24 years compared to 25 to 34 years in women.

The etiology of schizophrenia remains unknown. A genetic basis is supported by the fact that first-degree relatives of patients with schizophrenia carry a 10% risk of developing the disorder, and when both parents have the diagnosis, the risk to their offspring is 40%. For monozygotic twins, the concordance rate is about 50%. Many genes have been weakly associated with the development of schizophrenia; however, there is probably no single "schizophrenia gene." Research continues to explore candidate genes, loci, and copy number variants, hoping to better understand the genetic contribution.[2] Possibly, when a genetic liability is present, environmental stimuli may trigger expression of the illness. Some data suggest intrauterine exposure to significant stress, viral or bacterial infections may be a risk factor; however, more research is needed.

PATHOPHYSIOLOGY

The dopamine hypothesis, the oldest pathophysiologic theory, proposes that psychosis is caused by excessive dopamine in the brain. This hypothesis followed the discovery that chlorpromazine, the first antipsychotic medication, was a postsynaptic dopamine antagonist. Drugs that cause an increase in dopamine (eg, cocaine and amphetamines) worsen or cause psychotic symptoms, and medications that decrease dopamine (eg, antipsychotics) improve psychotic symptoms. However, data reveal a more complicated picture with both hyperdopaminergic and hypodopaminergic brain regions in schizophrenia. Hyperdopaminergic activity in the mesolimbic pathway contributes to positive symptoms of psychosis, while hypoactivity of the **mesocortical pathway** in the prefrontal cortex may contribute to negative symptoms. Thus, a more modern reworking of the dopamine hypothesis is the "dysregulation hypothesis," which takes these findings into account and also focuses primarily on presynaptic dopamine.[3] It is possible, however, that the hypothesized dopamine abnormalities may represent changes occurring secondary to other pathophysiologic abnormalities. Other implicated neurotransmitter systems include a combined dysfunction of the dopamine and glutamate neurotransmitter systems. It is hypothesized that glutamate, possibly through malfunctioning *N*-methyl-D-aspartate (NMDA) receptors, impacts dopaminergic activity in the mesolimbic and mesocortical pathways. NMDA antagonists such as phencyclidine (PCP) and ketamine can elicit

LO 2

Patient Encounter Part 1

A 19-year-old man was admitted to the inpatient psychiatric unit after he barricaded himself in his bedroom at his parents' house and refused to eat. His parents report that they have been concerned about their son for several years. While in high school, he struggled academically, had difficulty making friends, and did not participate in any activities. At home, he spent most of his time in his bedroom. He graduated from high school 1 year ago and enrolled in the local community college. He dropped out after a few weeks because he could not concentrate and was skipping classes. Since that time, he has been at home and spends his days isolated in his bedroom watching Netflix. The patient was seen about 6 months ago by his primary care provider. He was diagnosed with major depressive disorder and was started on sertraline, but there was no improvement. His mother states that about 1 month ago, the patient began refusing meals stating that she was poisoning his food. He became more suspicious and fearful of others and barricaded himself in his room. When his parents tried to encourage him to come out of his room to go see a doctor, he started throwing furniture around his room and yelling that he did not want to leave. His parents had to call the police to bring their son to the emergency room.

In the emergency room, he was administered lorazepam 2 mg IM. He is now calm and cooperative. He answers questions with only a "yes" or "no" and frequently looks over his shoulder. The patient's mother and father state that they tried to be supportive of their son, but they just don't understand his odd behaviors and they express concern over his lack of friends and participation in activities. The patient states he "doesn't really miss" doing these things, and he doesn't want to be pressured to do them. His mother also worries that he has strange eating habits and that his sleep is "off"—up at night and sleeping too much during the day.

What diagnoses are suggested by this presentation?

What additional information would help to clarify the diagnosis and why?

Should the patient's parents be involved in his care?

a state resembling schizophrenia, including positive and negative symptoms and cognitive impairments.[3] There is evidence for the serotonergic system in schizophrenia as evidenced by serotonin-induced hallucinations and serotonin modulation of second-generation antipsychotics (SGAs).[4] It is notable that to date, antipsychotics without any primary or secondary dopamine-modulating properties have been ineffective for the treatment of positive symptoms of schizophrenia.

CLINICAL PRESENTATION AND DIAGNOSIS

In addition to the positive, negative, and cognitive symptoms of schizophrenia, people with schizophrenia may sometimes be uncooperative, suspicious, hostile, anxious, or aggressive. Psychotic and depressive symptoms may lead to poor hygiene and impaired self-care. Sleep and appetite disturbances may be present, and people with schizophrenia may have difficulty living independently, forming close relationships with others, and initiating or maintaining employment. Co-occurring medical and substance use disorders are common with cigarette smoking and illicit drug use about four to five times more prevalent than the general population.[5,6]

KEY CONCEPT A diagnosis of schizophrenia is made clinically because there are no psychological assessments, brain imaging, or laboratory examinations that confirm the diagnosis.

The diagnosis is made by ruling out other causes of psychotic symptoms and meeting specified diagnostic criteria. When present, a family history of mental illness supports the diagnosis. The commonly accepted diagnostic criteria for schizophrenia are from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*)[7] (Table 37–1).

KEY CONCEPT Patients presenting with odd behaviors, illogical thought processes, fixed false beliefs, and hallucinations should be comprehensively assessed to rule out other diagnoses or contributing factors.[8]

At minimum, patients with psychotic symptoms should have a medical workup at the time of admission to rule out other diagnoses or contributing factors, such as medical illnesses, infections, or other psychiatric or substance use disorders. Often, people with

Table 37–1

Diagnostic Criteria for Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be 1, 2, or 3:
   1. Delusions
   2. Hallucinations
   3. Disorganized speech (eg, frequent derailment or incoherence)
   4. Grossly disorganized or catatonic behavior
   5. Negative symptoms (ie, diminished emotional expression or avolition)

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved before onset (or when onset is in childhood or adolescence, there is a failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meets Criterion A (ie, active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (eg, odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (a) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms or (b) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (eg, drug of abuse or medication) or another medical condition.

F. If there is a history of autism spectrum disorder or communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

psychosis are poor historians and the gathering of collateral information is necessary. Co-occurring substance abuse, medical illnesses, and psychosocial stressors often confound the diagnosis.

COURSE AND PROGNOSIS

Treatment of schizophrenia has been associated with poor long-term outcomes in the past; however, with earlier treatment and better care, many people can achieve remission and recovery is possible. Without early intervention, there are traditionally intermittent acute psychotic episodes with a downward decline in psychosocial functioning. Though many of the more dramatic and acute symptoms may fade with time, severe residual symptoms may persist. Involvement with law enforcement is common for vagrancy, loitering, and disturbing the peace. Life expectancy is shortened primarily because of suicide, cardiovascular disease, accidents, and compromised self-care. Lifetime risk of suicide for people with schizophrenia is 5% to 10%, and it is estimated that suicide risk in this population exceeds that in the general population more than eightfold.[9] Persistent adherence with a tolerable medication regimen improves prognosis, while relapse without antipsychotic medication exceeds 50% in the year following discontinuation of antipsychotic treatment.

The onset of schizophrenia can be rapid with acute psychosis presenting as the first symptom, or can be insidious with negative symptoms and social impairments predating psychosis by many years. Whether insidious or acute, the period around the diagnosis is difficult for patients, families, and clinicians. Patients may hide symptoms from family and friends and isolate themselves from social support networks. Gradual development of psychosis and the misunderstanding of symptoms can delay diagnosis and treatment. Recent data suggest that people treated early in their illness may have a better prognosis. Therefore, the first challenge of optimal therapy is to initiate treatment closer to the onset of psychosis.

TREATMENT

Desired Outcomes

KEY CONCEPT The goals of treatment are to reduce symptomatology and psychotic relapses and to improve functional and social outcomes.[10] Patients should receive comprehensive treatment as early as possible and earlier treatment can lead to better outcomes.[11] In the past, the primary treatment goal was to decrease positive symptoms and associated hostile and aggressive behaviors. Newer approaches also focus on functional and social outcomes.

LO 3

Clinical Presentation of Schizophrenia

General

Schizophrenia is a chronic disorder of thought and affect, causing significantly impaired vocational and interpersonal function. Onset is usually preceded by gradual social withdrawal, diminished interests, changes in appearance and hygiene, changes in cognition, and bizarre or odd behaviors. The clinical presentation of a person with schizophrenia is extremely varied.

Symptoms

Psychotic symptoms (positive symptoms):

- Hallucinations (distortions or exaggeration of perception)
  - Most frequently auditory, can also be visual, olfactory, gustatory, and tactile.
  - Can be voices or thoughts that feel distinct from the person's mind.
  - Voices may be threatening or commanding (eg, commanding the person to perform a particular action).
- Delusions (fixed false beliefs)
  - Beliefs despite invalidating evidence
  - May be bizarre in nature
  - Often paranoid in nature which may cause suspiciousness
- Thought disorder (illogical thought and speech)
  - Loosening of associations
  - Tangentiality
  - Thought blocking
  - Concreteness
  - Circumstantiality
  - Perseveration
  - Thinking and speech may be incomprehensible and illogical

Negative symptoms:

- Impoverished speech and thinking
- Lack of social drive (avolition)
- Flatness of emotional expression
- Apathy
- May be primary or occur secondarily to medication side effects, mood disorder, environmental understimulation, or demoralization
- The best strategy for differentiating primary from secondary negative symptoms is to observe for their persistence over time despite efforts at resolving the other causes

Cognitive impairments (diminished function in the following):

- Attention
- Processing speed
- Verbal, visual memory, and working memory
- Problem solving
- There is a loss of, on average, one standard deviation of preillness IQ, with the average IQ between 80 and 84.

Laboratory and Other Diagnostic Assessments

LO 1

An initial psychotic workup includes a thorough neurologic, medical, and laboratory evaluation to rule out other causes

- Electrolytes
- Blood urea nitrogen
- Serum creatinine
- Urinalysis
- Liver and thyroid function profile
- Syphilis serology
- Serum pregnancy test
- Urine toxicology

Though antipsychotic medications may improve combativeness, hostility, sleep, and appetite, other aspects of the illness are less responsive to treatment. Improvements in negative symptoms, cognitive functioning, social skills, and judgment generally require adjunctive treatments and a longer period to improve.

General Approach to Treatment

LO3 LO7

The concept of recovery has become an increasingly prominent treatment goal. Treatment planning increasingly includes providing recovery-oriented services to people with schizophrenia. A range of nonpharmacologic interventions are now part of the long-term strategy to improve functioning. Implementation of evidence-based practice and prescribing behaviors has led to the use of interventions that promote a remission or recovery attitude, and new data suggest that 1 in 7 people with schizophrenia can achieve full recovery.[12,13] Moreover, recent attempts to improve and measure patient satisfaction and to include shared decision making have fostered patient empowerment and hope.

KEY CONCEPT The cornerstone of treatment is antipsychotic medications, and most patients with schizophrenia relapse when not medicated. Treatment with antipsychotic medications should begin as soon as psychotic symptoms are recognized. Many patients are on lifelong antipsychotic medication because nonadherence and discontinuation are associated with high relapse rates. Often, adjunctive medications may also be necessary for specific symptoms or comorbid diagnoses. If other symptoms are present, such as depression and anxiety, these symptoms should be aggressively treated. Nonpharmacologic and psychosocial treatments should also play an important role in treatment.

LO3 LO4

Antipsychotic Treatment

In the United States, we have two general classes of antipsychotic medications, the first-generation antipsychotics (FGAs; typical antipsychotics) and SGAs (atypical antipsychotics). The SGAs include risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone, brexpiprazole, cariprazine, and clozapine. Clozapine, the prototype SGA, is currently reserved for treatment-resistant schizophrenia because of its unusual side-effect profile (see below). All antipsychotic medications share a common mechanism of dopamine antagonism, although there is significant variation among the agents. Dopaminergic antagonism is important in both treatment of symptoms and potential for medication-induced side effects. Of the four main dopaminergic pathways in the brain, positive symptoms are associated with hyperdopaminergic activity in the mesolimbic pathway, so blockade in this area is thought to reduce psychotic symptoms. However, blockade of dopamine activity in the other three main pathways may worsen some symptoms or lead to side effects. For example, hypodopaminergic activity in the mesocortical pathway may be associated with negative symptoms and cognitive symptoms, and further reducing dopamine activity could exacerbate these issues. Blockade of dopaminergic activity in the nigrostriatal pathway can lead to motor-related side effects, and blockade of dopaminergic activity in the tuberoinfundibular pathway may

Patient Encounter Part 2

PPH: The patient was seen 6 months ago by his primary care doctor and was diagnosed with major depressive disorder due to his lack of participation in activities, which was felt to be anhedonia. He was started on sertraline but had no improvement. This is his first psychiatric hospitalization.

PMH: He had a history of bedwetting until he was 14 years old but does not have any history of head trauma or seizure disorder.

SH: He grew up with his mother, father, and one sister, who is 2 years older than him. His sister is in her last year of college and upon interviewing her, she states "my brother was always a little odd and had a hard time making friends." His mother says he was always anxious—he often complained of stomach aches and headaches and did not want to go to school. He also refused to stay at other children's homes overnight. He drinks alcohol occasionally but does not use marijuana or other substances of abuse. He does smoke cigarettes and started smoking at age 14 years. He smokes 1 PPD. He has never held a job. He has no health insurance.

FH: His grandfather had an alcohol problem, and his great uncle has a history of psychiatric hospitalization, though the specific circumstances are unknown. His mother and aunt reportedly have depression.

Mental Status Examination

Appearance: Appears disheveled, dressed in dirty clothes, and hair looks like it has not been washed or brushed for several days. No abnormal movements. Poor eye contact. He is distracted and is looking around the room and over his shoulder.

Speech: Soft with one word answers

Mood: Nervous. Says he feels "normal." Denies feeling depressed.

Affect: Guarded and anxious with restricted range. He denies feeling sad, guilty, hopeless, or helpless.

Thought content: He is an adequate historian but has a tendency to leave out detail. He denies hearing voices but is very afraid that his mother is trying to poison his food. He thinks others may also be trying to poison him with arsenic or polonium and is refusing to eat. Sometimes, he feels that others know his thoughts. He has passing thoughts of suicide but no plan. He denies homicidal thoughts.

Thought processes: Vague, tangential, and illogical.

Cognition: Grossly intact.

Insight and judgment: Insight and judgment are poor. He does not believe he has a mental illness.

Given this additional information, how has your differential diagnosis changed?

What medications would you consider to be first-line options, and why?

What are the goals of initial treatment?

lead to prolactin elevation and related side effects.[3] Differences in dopaminergic and nondopaminergic receptor antagonism and receptor affinity across the antipsychotic agents and classes lead to differing potential for dopamine-related side effects.

KEY CONCEPT Compared with the FGAs, the SGAs are associated with a lower risk of motor side effects (tremor, stiffness, restlessness, and dyskinesia).

With the introduction of SGAs in the 1990s, the use of FGAs has progressively decreased, and FGAs have less than 10% market share of the antipsychotics used for schizophrenia. This decline occurred because of the touted better side-effect profile and other possible benefits of SGAs in nonpsychotic domains of the illness. However, a large landmark study (the Clinical Antipsychotics Trials of Intervention Effectiveness [CATIE trial]; $n > 1400$) examined the effectiveness of SGAs relative to a midpotency FGA, perphenazine. The study revealed that the FGA was equal to the SGAs for the primary endpoint of time to discontinuation of medication.[14] SGAs have historically been much more expensive than the FGAs; however, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and clozapine are now available in generic formulations. In conclusion, when selecting an antipsychotic, the risk-to-benefit profile becomes fundamental and the varying side-effect profiles must be considered.

LO 4 LO 5

Second-Generation (Atypical) Antipsychotics

FGAs exert most of their effects through dopamine-receptor blockade at the dopamine$_2$ (D_2) receptor. SGAs may have different receptor-binding profiles that contribute to their "atypicality." This possibly includes greater serotonin to dopamine antagonism, dopamine antagonism with rapid dissociation, partial dopamine antagonism and serotonin$_{1A}$ (5-HT$_{1A}$) partial agonism. Despite heterogeneous receptor binding, the efficacy among the SGAs is similar.[14] However, due to differences in specific receptor binding affinity, side-effect risks may vary between these agents. Additionally, recent data for SGAs and lower doses of FGAs document similar overall efficacy with an effect size for acute treatment of 0.30 to 0.60 for most antipsychotics.[15] These findings have led to a modest resurgence of FGA use. Only clozapine, however, has demonstrated superior efficacy and that is in treatment-resistant patients. An important distinction of the SGAs is their lower propensity to cause acute **extrapyramidal symptoms** (EPSs) and **tardive dyskinesia** (TD). TD risk with SGAs is 1.5% annually in adults (< 54 years of age) compared to approximately a 5% annual risk with FGA treatment.[16] However, side effects such as weight gain, the potential for glucose dysregulation, and lipid abnormalities may be caused by treatment with these agents. Weight gain may be caused by a combination of lifestyle and medication interaction with neurotransmitter systems that may increase appetite and food intake (serotonergic, histaminergic, and dopaminergic), and, although all antipsychotics may be associated with weight gain, certain SGAs such as clozapine, olanzapine, quetiapine, and risperidone may offer greater risk. Similarly, risk of lipid abnormalities mirrors the risk for weight gain. Risk for glucose dysregulation or new-onset diabetes generally follows the risk of agents with most weight gain potential, although it is important to note that clozapine and olanzapine have been associated with diabetic ketoacidosis in the absence of significant weight gain in isolated cases.

KEY CONCEPT The SGAs are heterogeneous with regard to side-effect profiles. Many SGAs carry an increased risk for weight gain and for the development of glucose and lipid abnormalities; therefore, careful monitoring is essential. Dosing and comparative side effects of SGA are shown in Tables 37–2 and 37–3.

▶ *Risperidone*

Risperidone, a benzisoxazole derivative, was the initial first-line oral SGA to become available generically. It has high binding affinity to both serotonin 2$_A$ (5-HT$_{2A}$) and D_2 receptors and binds to α_1 and α_2 receptors, with very little blockade of cholinergic receptors.[17] Risperidone is also approved for relapse prevention and is associated with significantly lower relapse rates than long-term haloperidol treatment.[18] At doses less than or equal to 6 mg/day, EPSs are low, although higher doses are associated with a greater incidence of EPS. Risperidone is often associated with elevated prolactin to a greater extent than most other SGAs and FGAs. Elevated prolactin levels can, but do not always, lead to amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction. Mild to moderate weight gain and mild elevations in serum lipids and glucose may occur.

▶ *Olanzapine*

Olanzapine has greater affinity for 5-HT$_{2A}$ than for D_2 receptors. It also has affinity at the binding sites of D_4, D_3, 5-HT$_3$, 5-HT$_6$, α_1-adrenergic, muscarinic$_{1–5}$ ($M_{1–5}$), and histamine$_1$ (H_1) receptors.[19] In the CATIE trial, olanzapine was associated with the longest time to treatment discontinuation,[14] suggesting it may differ from the other SGAs in effectiveness. Olanzapine has a low rate of EPS and causes slight, transient prolactin elevations. Olanzapine causes significant weight gain across the dosage range, similar to that seen with clozapine and greater than that observed with the other SGAs. Olanzapine is also associated with hypertriglyceridemia, increased fasting glucose, and new-onset type 2 diabetes (ie, metabolic syndrome). Among the first-line SGAs, it is associated with the greatest elevations in these metabolic parameters.[14]

▶ *Quetiapine*

Quetiapine, structurally related to clozapine and olanzapine, has high affinity for 5-HT$_{2A}$ receptors and lower affinity for D_2 and D_1 receptors. It has some affinity for α_1, α_2, and H_1 receptors but very little for muscarinic receptors. Quetiapine may be beneficial for anxiety and depression. Motor side effects and prolactin elevations are uncommon. Orthostasis occurred in 4% of subjects in clinical trials. Sedation is generally transient. Mild weight gain and minor elevations in triglycerides can occur. Use of quetiapine with agents that can prolong the QTc interval or in patients with prolonged QTc should be avoided. Quetiapine has been associated with some dose-related decreases in thyroid hormones.

▶ *Ziprasidone*

Ziprasidone was developed to block D_2 receptors but also to bind with greater affinity to central 5-HT$_{2A}$ receptors. It has a binding affinity ratio of 11:1 for 5-HT$_{2A}$:D_2 receptors. It has a relatively high affinity for 5-HT$_{2C}$, 5-HT$_{1D}$, α_1-adrenergic, and D_1 receptors.[20] It should be taken with food, as this results in absorption levels twice that of fasting administration. Liability for EPS, weight gain, and lipid elevations is low but does occur. Ziprasidone causes some prolongation of the QTc interval in adults. However, overdose data and pharmacokinetic interaction data show little evidence that significant QTc prolongation occurs. Use of ziprasidone with agents that can prolong the QTc interval or in patients with existing diseases associated with prolonged QTc should be avoided. Drug-reaction with eosinophilia and systemic symptoms (DRESS) has occurred rarely.

▶ *Aripiprazole*

Aripiprazole has both antagonist and agonist activity at the D_2 receptor. Aripiprazole is also a partial agonist at 5-HT$_{1A}$

Table 37–2

Second-Generation (Atypical) Antipsychotics

Second-Generation Antipsychotic	Usual Oral Starting and Target Dose (mg/day) (Schizophrenia)	Maximum Oral Dose Likely to Be Beneficial (mg/day)	Available Dosage Forms
Aripiprazole (Abilify; Aristada [aripiprazole lauroxil injection])	Initial: 10–15 Target: 15–30	30	• 2-, 5-, 10-, 15-, 20-, and 30-mg tablets • 1-mg/mL oral solution • 10- and 15-mg orally disintegrating tablets • IM 9.75 mg/1.3 mL • Abilify Maintena extended-release 300- and 400-mg vial powder for suspension or prefilled syringe long-acting injection • Aristada extended-release 441, 662, 882, and 1064-mg prefilled syringes
Asenapine (Saphris)	Initial: 5 twice daily Target: 10–20 total daily dose	10–20	• 2.5-, 5-, and 10-mg sublingual tablets
Brexpiprazole (Rexulti)	Initial: 1 Target: 2–4	4	• 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets
Cariprazine (Vraylar)	Initial: 1.5 Target: 1.5–6	6	• 1.5-, 3-, 4.5-, and 6-mg capsules
Clozapine (Clozaril, Fazaclo, Versacloz, also available generically)	Initial: 12.5–25 Target: 300–450	500–800	• 12.5-, 25-, 50-, 100-, and 200-mg tablets • FazaClo (orally disintegrating tablets) 12.5-, 25-, 100-, 150-, and 200-mg • Versacloz (oral suspension) 50 mg/mL
Iloperidone (Fanapt)	Initial: 1 twice daily Target: 12–24 total daily dose	24	• 1-, 2-, 4-, 6-, 8-, 10-, and 12-mg tablets
Lurasidone (Latuda)	Initial: 40 Target: 40–160	160	• 20-, 40-, 60-, 80-, and 120 mg tablets
Olanzapine (Zyprexa, also available generically)	Initial: 5–10 Target: 10 –20	30–40[a]	• 2.5-, 5-, 7.5-, 10-, 15-, and 20-mg tablets • Orally disintegrating tablets: 5, 10, 15, and 20 mg • IM 10 mg vial (after reconstitution, ~5 mg/mL) • Zyprexa Relprevv 210-, 300-, and 405-mg/vial powder for suspension long-acting injection
Paliperidone (Invega)	Initial: 6 Target: 3–12	12	• 1.5-, 3-, 6-, and 9-mg tablets • Invega Sustenna 39-, 78-, 117-, 156-, and 234-mg prefilled syringes • Invega Trinza 273-, 410, 546-, or 819 mg
Quetiapine (Seroquel, also available generically)	Regular release Initial: 25 twice daily Target: 300–750 Extended release Initial: 300 Target 400–800	800	• 25-, 50-, 100-, 200-, 300-, and 400-mg tablets • Seroquel XR (extended-release tablets) 50-, 150-, 200-, 300-, and 400-mg tablets
Risperidone (Risperdal, also available generically)	Initial: 1–2 Target: 4–6	6–8	• 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets • 1 mg/mL (30 mL) solution • orally disintegrating tablets: 0.25-, 0.5-, 1-, 2-, 3-, and 4-mg tablets • Risperdal Consta long-acting injectable 12.5-, 25-, 37.5-, and 50-mg vial/kit
Ziprasidone (Geodon, also available generically)	Initial: 20 twice daily Target: 120–160 total daily dose	160–240[a]	• 20-, 40-, 60-, and 80-mg capsules • IM 20 mg/mL

[a]Outside product labeling guidelines.

IM, intramuscular.

receptors, an antagonist at 5-HT_{2A} receptors, and has affinity for D_3 receptors. Additionally, it has moderate affinity for α_1 and H_1 receptors with no appreciable affinity for the M1 receptor.[21] In CYP2D6-poor metabolizers, start dosing with one-half the usual dose with adjustment to clinical efficacy. Sedation, nausea, and vomiting are the most often seen side effects. Elevations in weight, lipids, and glucose are generally negligible, and aripiprazole is not associated with elevations in serum prolactin. In fact, patients switched to aripiprazole from other antipsychotic agents may experience decreases in prolactin.

► *Paliperidone*

Paliperidone is the 9-hydroxy (9-OH) metabolite of risperidone. The efficacy of risperidone and paliperidone is similar. Receptor

LOS

Table 37–3

Comparative Side Effects Among the SGAs and Haloperidol

Side Effect	Cloz	Risp[a]	Olan	Quet	Zip	Ari	Ilo	Asen	Lur	Brex	Carip	Hal
Anticholinergic side effects	+++	±	++ (Higher doses)	+	±	±	±	+	±	±	±	±
EPS at clinical doses	+	+	±	±	±	±	+	+	+	±	+	++
Dose-dependent extrapyramidal symptoms	0	++	+	0	+	±	+	+	+	+	+	+++
Orthostatic hypotension	+++	++	+	++	+	+	++	+	+	±	±	++
Prolactin elevation	0	+++	+	±	+	0	+	±	±	±	0	+
QTc prolongation	+	±	±	+	+	±	+	+	+	±	±	±
Sedation	+++	+	+	++	+	+	++	+	+	+	+	+
Seizures	++	±	±	±	±	±	±	±	±	±	±	±
Weight gain	+++	++	+++	++	+	+	+	+	+	+	±	±
Glucose dysregulation	++	+	++	+	±	±	±	±	±	±	±	±
Lipid abnormalities	+++	+	+++	++	±	±	±	±	±	±	±	±

[a]Side effects similar for paliperidone.

0, absent; ±, minimal; +, mild or low risk; ++, moderate; +++, severe; SGA, second-generation antipsychotic.

Cloz, clozapine; Risp, risperidone; Olan, olanzapine; Quet, quetiapine; Zip, ziprasidone; Ari, aripiprazole; Ilo, iloperidone; Asen, asenapine; Lur, lurasidone; Brex, brexpiprazole; Carip, cariprazine; Hal, haloperidol.

binding affinity is also similar between the two agents, with paliperidone having a greater affinity at 5-HT_{2A} compared with D_2 receptors. Unlike many other antipsychotic medications, paliperidone is mostly excreted unchanged, a potential advantage in patients with liver impairment, although adjustment may need to be made in renal impairment. Patients should be told to expect to see the shell of the tablet in the stool because it may not dissolve in the digestive tract.[22] Side effects of paliperidone are expected to be similar to those of risperidone, including the potential for dose-related EPS and prolactin elevation.[22]

▶ *Iloperidone*

Iloperidone is indicated for acute treatment of adults with schizophrenia. It exhibits high affinity for $5HT_{2A}$, dopamine D_2, and D_3 receptors and acts as an antagonist at these, as well as at the $5HT_{1A}$ and norepinephrine α_1/α_{2C} receptors. Doses must be titrated because of the risk of orthostatic hypotension, and dosing should be reduced by half in CYP2D6 poor metabolizers. Common adverse reactions include dizziness, dry mouth, fatigue, orthostatic hypotension, tachycardia, and weight gain. Dizziness, tachycardia, and weight gain were twice as common with higher dose (20–24 mg total daily dose) versus lower doses (10–16 mg total daily dose).[23] Use of iloperidone with agents that can prolong the QTc interval or in patients with diseases that are associated with prolonged QTc should be avoided.

▶ *Asenapine*

Asenapine is approved for the acute treatment of schizophrenia in adults. Its mechanism of action is thought to be its antagonistic activity at $5HT_{2A}$ and D_2 receptors. It also exhibits a high affinity for other serotonergic and dopaminergic receptors, as well as α_1- and α_2-adrenergic receptors and H_1 receptors. Asenapine tablets must be placed under the tongue and allowed to dissolve completely; tablets should not be chewed or swallowed. Patients should not drink or eat for 10 minutes after administration. No added benefit was seen with doses above 10 mg twice daily, but adverse effects increase. Common adverse effects include somnolence, dizziness, and akathisia. It has shown little effect on metabolic parameters and weight change. Labeling for asenapine was modified to address rare occurrence of hypersensitivity reactions, including anaphylaxis and angioedema.[24]

▶ *Lurasidone*

Lurasidone antagonizes D_2 and $5HT_{2A}$ receptors. It also has moderate affinity as an antagonist at α_{2C}, is a partial agonist at $5HT_{1A}$, and is an antagonist at α_{2A}-receptors. Lurasidone should be taken with caloric intake of at least 350 calories (~1.5 kJ) for maximal absorption. Adverse reactions reported in at least 5% of patients (and at least twice the placebo rate) include somnolence, akathisia, nausea, parkinsonism, and agitation. Lurasidone has shown only a small effect on body weight and causes minimal changes in other metabolic parameters.[24]

▶ *Brexpiprazole*

Brexpiprazole is a partial agonist at 5-HT_{1A}, D_2 and D_3 receptors. It is also an antagonist of 5-HT2A, 5-HT2B, 5-HT7, α_1A, α1B, α1D, α2C, and H1 receptors. It has negligible affinity for muscarinic receptors. In CYP2D6 poor metabolizers, usual dosage should be reduced by one-half. This medication is slightly less stimulating and has less akathisia than aripiprazole. The most commonly occurring side effects are weight gain and akathisia.[25]

▶ *Cariprazine*

Cariprazine is a dopamine D_3-preferring D_2/D_3 receptor partial agonist. It is given once daily and has a long half-life; thus, side effects should be monitored for several weeks after initiation or a dose change. Most common side effects are akathisia, EPS, nausea, vomiting, somnolence, and restlessness. Those having a known hypersensitivity reaction to cariprazine should not be treated with the medication.[26]

First-Generation (Typical) Antipsychotics

The FGAs are high-affinity D_2-receptor antagonists. During chronic treatment, they block 65% to 80% of D_2 receptors in the striatum and other dopamine tracts in the brain.[25] Clinical response is generally associated with 60% D_2-receptor blockade, while 70% and 80% are associated with hyperprolactinemia and EPS, respectively. During the 1990s, SGAs began to replace FGAs as first-line therapy.

Doses for FGAs are frequently given as **chlorpromazine equivalents**, which are defined as the FGA equipotent dose with 100 mg of chlorpromazine. The target dose recommendation for

Patient Encounter Part 3

The patient started treatment with risperidone in the hospital and was titrated to 6 mg/day. He was feeling less paranoid, began to eat again, and his sleep pattern normalized. He has now been out of the hospital for 3 months and came in for his regular appointment with his outpatient psychiatrist. While he was in the waiting room, he was noticed to be pacing around and seemed to be very restless. The patient told the doctor that he was unable to sit and he felt better when walking around. The patient's mother stated that her son seemed more agitated and his symptoms were getting worse again. She was concerned he might be readmitted to the hospital. It was also noted that the patient had gained 12 lbs (5.4 kg). After much discussion with the patient and his mother, the decision was made to switch him from risperidone to aripiprazole. The doctor informed the patient that he would call him in a few days to see how he was feeling. The doctor also encouraged him to exercise regularly and eat a healthy diet that is low in carbohydrates, and referred him to a dietician.

What symptom was the patient experiencing on risperidone? What other treatments could have been considered besides switching agents?

Discuss the differences in the side-effect profiles of risperidone and aripiprazole.

acute psychosis is 400 to 600 chlorpromazine equivalents unless the patient's history indicates that dose may not be tolerated. Generally, maintenance therapy is 300 to 600 chlorpromazine equivalents daily. Dosing and available dosage forms are shown in Table 37–4. All FGAs are equally efficacious when studied in equipotent doses in groups of patients. Relative potency of FGA agents is related to side-effect profile, with lower potency agents such as chlorpromazine demonstrating higher risk of anticholinergic and cardiovascular side effects and higher potency agents such as haloperidol displaying more potent EPS side effects. However, an individual patient may not respond equally to each antipsychotic. Selection of a particular antipsychotic is based on patient variables, such as the need to avoid certain side effects or drug–drug interactions or previous patient or family history of response. Long-acting formulations of FGA medications are shown in Table 37–5.

Side Effects of the First-Generation Antipsychotics

As previously mentioned, the low-potency FGA agents are less likely to cause EPS than the high-potency agents (see Table 37–4). Of note, high-potency and mid-potency agents may cause less EPS than once believed and were similar to SGAs in the CATIE trial.[14]

The FGAs are commonly associated with early onset EPS (including akathisia [motor or subjective restlessness], dystonia [muscle spasm], and pseudoparkinsonism [akinesia, tremor, and rigidity]) caused by dopamine antagonism in the nigrostriatal pathways. SGAs also may have these side effects. Akathisia, or the feeling of restlessness, occurs in 20% to 40% of FGA patients. Roughly half of the cases of akathisia present within 1 month of FGA initiation, though it may present within 5 to 10 days after the first dose or after an increase in dosage. Younger people and those taking high doses of high-potency antipsychotics are at greater risk for development of akathisia.

Acute dystonic reactions are abrupt in onset and are usually seen within 24 to 96 hours after a first dose or increase in dosage. Characteristic signs and symptoms include abnormal positioning or spasm of the muscles of the head, neck, limbs, or trunk. Dystonia may occur in 10% to 20% of patients. There is higher risk for dystonia in young male patients and those taking high-potency FGAs.

Pseudoparkinsonism may be present in 30% to 60% of people treated with FGAs. The onset of symptoms is usually within 1 to 2 weeks after dose initiation or dose increase. Clinical presentation may include cogwheel rigidity, pill-rolling hand movements, resting tremor, shuffling gait, stooped posture, and mask facies. Risk factors include older age, female gender, high doses, and possibly those with depressive symptoms. Anticholinergic medications are used for treatment of dystonic reactions and pseudoparkinsonism, while β-blocking agents are generally first line for akathisia.[27]

Table 37–4

First-Generation (Typical) Antipsychotics[a]

Class	Agent (Brand Name)	Dosage Range (mg/day)	Chlorpromazine Equivalents (mg)	Available Formulations
Butyrophenone	Haloperidol (Haldol)	5–30	2	T, LC, I
Dibenzoxazepine	Loxapine (Loxitane, Adasuve)	20–100	10	C, IP
Diphenylbutylpiperidine	Pimozide (Orap)	1–10	1–2	T
Phenothiazines	Chlorpromazine (Thorazine)	300–800	100	T, I
	Fluphenazine (Prolixin)	2–40	2	T, L, LC, I
	Perphenazine (Trilafon)	8–64	8–10	T
	Thioridazine (Mellaril)	300–800	100	T
	Trifluoperazine (Stelazine)	15–30	5	T
Thioxanthenes	Thiothixene (Navane)	5–60	4	C

[a]Low-potency antipsychotics include thioridazine, mesoridazine, and chlorpromazine. High-potency antipsychotics include haloperidol, fluphenazine, thiothixene, and pimozide.

C, capsule; I, injection; IP, inhalation powder; LC, liquid concentrate; L, liquid solution, elixir, or suspension; T, tablet.

Table 37–5

Antipsychotic Dosing of Long-Acting Preparations

Drug	Starting Dose	Maintenance Dose	Comments
Aripiprazole long-acting injection (Abilify Maintena)	400 mg monthly Give 14 consecutive days of concurrent oral aripiprazole (10–20 mg) or current oral antipsychotic after first injection	300–400 mg monthly	Establish tolerability with oral agent first Dosage adjustments for CYP2D6 poor metabolizers, and in persons who take strong CYP2D6 or 3A4 inhibitors; recommend to avoid use if strong 3A4 inducer Available as 300, 400 mg kits
Aripiprazole lauroxil (Aristada)	441 if 10 mg/day oral 662 if 15 mg/day oral 882 if 20 mg/day or more oral Give 21 days of concurrent oral aripiprazole overlapping with first dose	Average 441–882 monthly or 882 every 6 weeks or 1064 every 2 months	Dose adjustments for CYP2D6 poor metabolizers, and persons who take strong CYP2D6 or 3A4 inhibitors; or CYP3A4 inducers > 2 weeks Available as 441, 662, 882, or 1064 mg prefilled syringes
Haloperidol decanoate	10–20 × oral haloperidol daily dose; in the elderly use 10–15 × oral haloperidol daily dose; Generally 100–450 mg/month Initial dose should not exceed 100 mg regardless of previous dose requirements (if > 100 mg, give 3–7 days apart) Oral supplementation may temporarily be necessary for first 2–3 injections unless loading dose given	10–15 × oral haloperidol daily dose, generally 50–300 mg/month	Deep IM injection generally with 21-gauge needle; maximum volume per injection site should not exceed 3 mL Available in 50 and 100 mg/mL (5-mL vials and 1-mL ampules)
Fluphenazine decanoate	Approximately 12.5 mg injection = 10 mg oral daily dose; usual starting dose 12.5–25 mg; generally 12.5–mg/2–3 weeks Give ½ oral dose after first injection, discontinue oral after second injection	Based on starting dose and clinical response but usually 2–4 weeks; doses above 50 mg increase cautiously in 12.5 mg increments; do not exceed 100 mg Generally 12.5–25 mg dosed at 2–4-week intervals (may be up to 6 weeks in some cases)	Can be administered IM or SC; 21-gauge needle, must be dry Should not exceed 100 mg; when dosing above 50 mg, should increase in increments of 12.5 mg Available in 25 mg/mL (5-mL vials)
Olanzapine (Zyprexa Relprevv)	To target oral 10 mg/day dose: Either 210 mg/2 weeks or 405 mg/4 weeks during first 8 weeks To target oral 15 mg/day dose: 300 mg/2 weeks for first 8 weeks To target 20 mg/day oral dose: 300 mg/2 weeks Establish tolerance with oral administration prior to initiation	To target oral 10 mg/day dose: after 8 weeks, give 150 mg/2 weeks or 300 mg/4 weeks To target oral 15 mg/day dose: after 8 weeks, 210 mg/2 weeks or 405 mg/4 weeks To target 20 mg/day oral dose: continue with 300 mg/2 weeks	Gluteal injection, 19-gauge needle Do not confuse with rapid-acting IM injection Must reconstitute with included diluent Measure amount to inject from vial (there will be remaining suspension in vial) Zyprexa Relprevv Patient Care Program: 3-hour observation period; patient must be accompanied to destination No refrigeration needed, use within 24 hours, or immediately once suspension is in syringe Available as 210, 300, 405 kits
Paliperidone monthly (Invega Sustenna)	Initiate with 234 mg on day 1 and 156 mg 1 week later, both in deltoid muscle Establish tolerance with oral administration prior to initiation	Recommended monthly maintenance dose is 117 mg (range, 39–234 mg)	First two doses must be given in the deltoid muscle; after that, monthly doses given in either the deltoid or gluteal muscle Adjust dose in mild renal impairment; avoid in moderate to severe impairment Available as 39-, 78-, 117-, 156-, and 234-mg prefilled syringes

(*Continued*)

Table 37–5

Antipsychotic Dosing of Long-Acting Preparations (*Continued*)

Drug	Starting Dose	Maintenance Dose	Comments
Paliperidone (every 3 months) (Invega Trinza)	If monthly 78 mg, 273 mg/3 months If monthly 117 mg, 410 mg/3 months If monthly 156 mg, 546 mg/3 months If monthly 234 mg, 819 mg/3 months Only initiate after at least 4 months of paliperidone monthly injections.	273–819 mg/3 months	Adjust dose in mild renal impairment; avoid in moderate to severe impairment Available as 273-, 410-, 546-, or 819-mg prefilled syringes
Risperidone long-acting injection (Risperdal Consta)	25 mg every 2 weeks Previous antipsychotics should be continued for 3 weeks after initial dose of risperidone long-acting injection	25–50 mg every 2 weeks	Recommended to establish tolerability with oral risperidone prior to initiation of long-acting injection Lower starting dose of 12.5 mg may be appropriate in some patients with renal/hepatic impairment Available in 12.5-, 25-, 37.5-, and 50-mg vial/kit; must use needle supplied with kit, administer IM

IM, intramuscular; SC, subcutaneous.

TD is a movement disorder characterized by abnormal choreiform (rapid, objectively purposeless, irregular, and spontaneous) and athetoid (slow and irregular) movements beginning late in relation to initiation of antipsychotic therapy. It usually develops over several months or after at least 3 months of cumulative exposure to antipsychotics. When antipsychotics are tapered or discontinued, there is typically a transient worsening of abnormal movements, and movements may be irreversible in some cases. Risk factors for TD include older age; longer duration of antipsychotic treatment; and presence of EPS, substance abuse, and mood disorders. SGAs have a lower risk of approximately 2% to 4% risk of TD than FGAs (5%–6%).[16] A variety of approaches have been used for treating TD including switching to clozapine, using high dose vitamin E, and, most recently, the approval of new Food and Drug Administration (FDA)-approved medications for TD, valbenazine and deutetrabenazine, which inhibit vesicular monoamine transporter 2 (VMAT2).[27]

Neuroleptic malignant syndrome (NMS), a life-threatening emergency characterized by severe muscular rigidity, autonomic instability, and altered consciousness, can occur uncommonly with all FGAs and may also occur with SGAs. Rapid dose escalation, use of high-potency FGAs at higher doses, and younger patients have a higher risk of NMS. When NMS is diagnosed or suspected, antipsychotics should be discontinued and supportive, symptomatic treatment begun (eg, antipyretics, cooling blanket, intravenous fluids, oxygen, monitoring of liver enzymes, and complete blood cell count). Benzodiazepines and dantrolene are recommended treatments along with intensive care management as needed.[27]

Dermatologic side effects, photosensitivity, and cataracts may occur with the phenothiazine FGAs. Sedation is mediated by H_1 receptor antagonism; anticholinergic side effects (constipation, blurred vision, dry mouth, and urinary retention) are caused by M_1-receptor antagonism; and α_1-receptor blockade is associated with orthostatic hypotension and tachycardia (Table 37–6). QTc prolongation may occur with the lower potency FGAs, and thioridazine has a black-box warning for QTc prolongation.

Pharmacologic Treatment Guidelines and Algorithms

There have been a variety of treatment recommendations published for schizophrenia. The American Psychiatric Association (APA) Practice Guidelines for Schizophrenia[8] were introduced in 2004 with a 2009 update, the Texas Implementation of Medication Algorithms (TIMA) were updated in 2008,[28] and the Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations[29] were published in 2009. More recent guidelines are available from the World Federation of Societies of Biological Psychiatry Guidelines (WFSBP),[30] British Association of Psychopharmacology (BAP),[31] and the National

Table 37–6

Side Effects of First-Generation Antipsychotics

	Relative Potency	Extrapyramidal Symptoms	Sedation	Anticholinergic Side Effects	Cardiovascular Side Effects	Seizure Effects/QTc Prolongation
Chlorpromazine	100	++	++++	+++	++++	++
Thioridazine	100	++	++++	++++	++++	+++
Loxapine	10	+++	+++	++	+++	+
Perphenazine	8–10	+++	++	++	++	+
Trifluoperazine	2–5	+++	++	++	++	+
Thiothixene	4	+++	++	++	++	+
Fluphenazine	2	++++	++	++	++	+
Haloperidol	2	++++	+	+	+	+

+, very low; ++, low; +++, moderate; ++++, high.

Institute for Health and Care Excellence (NICE) guidelines.[10] While guidelines from the early 2000s generally recommend SGAs as first-line treatment, more recent guidelines generally suggest first-line treatment with either an FGA or SGA. Choice of the FGA/SGA is guided by side-effect profiles and patient clinical characteristics. Treatment with a given drug should be continued for 4 to 6 weeks to assess response and then a second antipsychotic should be started with the aim of crossing over to monotherapy with a different agent in conjunction with psychosocial support. Use of two antipsychotic medications concomitantly is discouraged due to increased side effect burden and paucity of data for increased efficacy.

Treatment Adherence

Antipsychotic nonadherence is estimated to occur in at least 40% to 50% of patients with schizophrenia. Patients who are nonadherent have about a fourfold greater risk of a relapse than those who are adherent.[32] Neurocognitive deficits, poor insight, and paranoid symptoms may hamper adherence, and identification of nonadherence by caretakers and providers can be challenging. Antipsychotic side effects such as EPS, weight gain, sexual dysfunction, substance use, and negative symptoms may all contribute to treatment nonadherence. For patients who have relapsed several times because of nonadherence, have a history of dangerous behavior, or risk a significant loss of social or vocational gains when relapsed, treatment with long-acting injection (LAI) should be encouraged. However, more recent data suggest that both FGA and SGA LAIs are more effective at reducing rehospitalization risk compared to oral treatment,[33] and thus may be considered for all patients as a routine treatment option. Risperidone, paliperidone, olanzapine, and aripiprazole are available as LAIs. In general, oral tolerability of these agents should be ensured prior to initiating LAI. Dosing and other information about these formulations is shown in Table 37–5.

Special Populations

▶ *Dosing in Renal and Hepatic Impairment*

Table 37–7 shows dosing guidance on specific antipsychotic medications.

▶ *Children and Adolescents*

Around 10% to 30% of patients with schizophrenia have psychotic symptoms before their 18th birthday. The diagnosis of schizophrenia in children and adolescents is often challenging, and the differential diagnosis includes autistic spectrum disorders, attention-deficit/hyperactivity disorder, and language or communication disorders. The existence of prominent hallucinations or delusions helps make the diagnosis because they are not prominent in other disorders. Children and adolescents developing schizophrenia before age 18 years have premorbid abnormalities such as withdrawal, odd traits, and isolation. Treatment for psychotic children and adolescents ideally is intensive, comprehensive, and structured. Early intervention in psychosis services such as NAVIGATE should be employed in first-episode schizophrenia.[34] Pharmacologic treatment is indicated if psychotic symptoms cause significant impairments or interfere with other interventions. Children and adolescents are more vulnerable to EPS, particularly dystonias, than are adults. Because of concerns about EPS and TD in children and adolescents, it is recommended that antipsychotic therapy be initiated with SGAs. Aripiprazole, risperidone, quetiapine, olanzapine, paliperidone, and lurasidone are approved by the FDA for the treatment of schizophrenia in adolescent patients. Initiation and target dosing is lower for adolescents than adults.

Agents with significant sedative and anticholinergic side effects are not preferred because they can interfere with school performance. Compared with adults, children and adolescents tend to gain more weight when taking these agents.

▶ *Elderly*

Psychotic symptoms in late life (after 65 years of age) generally result from an ongoing chronic illness; however, a small percentage of patients develop psychotic symptoms *de novo*, defined as late-life schizophrenia. Other illnesses with psychotic symptoms are common in this population; approximately one-third of patients with Alzheimer disease, Parkinson disease, and vascular dementia experience psychotic symptoms.

Antipsychotics can be safe and effective for the treatment of schizophrenia in the elderly, if used at lower doses than those commonly used in younger adults. Older adults are particularly vulnerable to the side effects of the FGAs, and TD risk is over threefold risk in elderly patients.[16]

Orthostasis, estimated to occur in 5% to 30% of geriatric patients, is a major contributing factor to falls that often lead to injuries and loss of independence. Low-potency antipsychotics and clozapine are more likely to cause significant orthostasis. Antipsychotics may cause or worsen anticholinergic effects, including constipation, dry mouth, urinary retention, and cognitive impairment. Greater antipsychotic-associated impairment in cognitive functioning may occur in the elderly compared to younger adults. In the elderly, this can lead to decreased independence, a very problematic issue. As a result of data showing a statistically significant increase in mortality in elderly dementia patients taking SGAs, a black-box warning was added to the manufacturer's information for all antipsychotics. Patients and families should be informed of this risk before using these agents in patients with dementia. Dosing in the elderly is initiated lower, and titration is slower than in younger adults. Maximum doses are often half of adult doses (see Table 37–7).

▶ *Co-Occurring Substance Use Disorder*

Alcohol and illicit drug use is about threefold higher in schizophrenia than the general population.[5] The most common drugs of abuse are cannabis, cocaine, and alcohol. Substance use often worsens the clinical course and complicates treatment. People with schizophrenia having substance use disorder are more likely to be nonadherent with treatment. They may have a poorer response rate to the FGAs, more severe psychosis, and higher rates of relapse and rehospitalization than people without co-occurring disorders. EPS may occur more frequently in substance-using patients, and alcohol use is a risk factor for developing TD. It is important to incorporate a dual treatment approach for substance use disorders and schizophrenia with nonpharmacologic and pharmacologic treatments.[35]

▶ *Treatment-Resistant Schizophrenia*

For 20% to 30% of people with schizophrenia, first-line antipsychotic treatment is ineffective and another 30% of people have a partial treatment response.[30] A consensus guideline on the definition of Treatment Resistant Schizophrenia (TRS) was recently published. This guideline suggests a standard definition of TRS defined as (a) moderately severe illness as defined by rating instruments with a persistence of at least 5 years, (b) moderate

Table 37–7

Second-Generation Antipsychotic Dosing Recommendations for Special Populations

Medication	Pediatric	Geriatric	Renal Impairment	Hepatic
Aripiprazole	Ages 13–17 years (schizophrenia): Initiate 2 mg every day, increasing to 5 mg daily after 2 days and target of 10 mg after several days, 30 mg/day maximum	No oral adjustment necessary	No adjustment necessary	No adjustment necessary
Asenapine	No pediatric FDA indication for schizophrenia (bipolar I indication only)	No adjustment necessary	No adjustments necessary	No adjustment necessary for mild to moderate impairment, but use not recommended in severe impairment
Brexpiprazole	No pediatric FDA indication	Experience is limited; low dose initiation, up to 3 mg/day kinetics similar to adults with MDD in safety/tolerability trial	CrCl < 60 mL/min (1.0 mL/s): maximum 3 mg	Moderate to severe: maximum 3 mg
Cariprazine	No pediatric FDA indication	Experience is limited; low dose initiation	CrCl < 30 mL/min (0.50 mL/s): not recommended	Mild to moderate: no adjustment required; severe: not recommended
Clozapine	No pediatric FDA indication	Experience is limited; low dose and slow titration	Adjustments may be necessary with significant impairment; no specific recommendations available	Adjustments may be necessary with significant impairment; no specific recommendations available
Iloperidone	No pediatric FDA indication	No adjustment necessary	No adjustment information provided, but unlikely necessary	No adjustment needed for mild impairment; exercise caution with moderate impairment; not recommended for severe impairment
Lurasidone	Ages 13–17 years (schizophrenia): Initial dose, 40 mg/day with target dose of 40–80 mg/day	No adjustment required	With moderate to severe renal impairment, recommended starting dose 20 mg daily; do not exceed 80 mg daily	With moderate impairment, initial dose 20 mg daily; max dose 80 mg daily With severe impairment, initial dose 20 mg daily, max dose 40 mg daily
Olanzapine	Oral: Ages 13–17 years (schizophrenia): Initial dose, 2.5–5 mg orally every day with target dose of 10 mg/day; maximum dose, 20 mg/day Long-acting injection: Not approved in children	Oral: 5 mg/day, if escalation needed use caution Long-acting injection: Consider starting dose of 150 mg every 4 weeks for elderly or debilitated patients	Oral: In renal impairment, no adjustment usually necessary; however, consider a lower initial dose of 5 mg/day Long-acting injection: No information given	Oral: No dosage adjustment noted in prescribing information except in combination with fluoxetine Long-acting injection: No information given
Paliperidone	Oral: Ages 12–17 years (schizophrenia) Dose by body weight: < 51 kg, initiate 3 mg/day oral, increase at increments of > 5 days; maximum, 6 mg/day At least 51 kg, initiate at 3 mg/day, increase at increments of > 5 days, maximum of 12 mg/day	Oral: For patients with normal renal function, no adjustment is required, but if renal impairment guidance is available	Long-acting injection: CrCl 50–79 mL/min (0.83–1.32 mL/s); initiate with 156 mg IM day 1, 117 mg IM 1 week later, with maintenance at 78 mg IM monthly CrCl < 50 mL/min (0.83 mL/s): Use not recommended Oral: CrCl 50–79 mL/min (0.83–1.32 mL/s): 3 mg once daily initiation, maximum 6 mg/day CrCl between 10 and 49 mL/min (0.17–0.82 mL/s): 1.5 mg once daily initiation; maximum, 3 mg/day CrCl < 10 mL/min (0.17 mL/s): Use not recommended	Long-acting injection: No dosage adjustment needed for mild or moderate impairment; no guidance given for severe impairment Oral: No dose adjustment is required for mild or moderate impairment

(*Continued*)

Table 37–7

Second-Generation Antipsychotic Dosing Recommendations for Special Populations (*Continued*)

Medication	Pediatric	Geriatric	Renal Impairment	Hepatic
Quetiapine	Regular-release tablets: Indicated for schizophrenia (ages 13–17 years): Initiate 25 mg twice daily; recommended target dose 400–800 mg/day; maximum, 800 mg/day Extended-release tablets: Initiate 50 mg/day; recommended target dose 400–800 mg	Regular-release tablets: Slower dose escalation and a lower target dose Extended-release tablets: Initiate at 50 mg/day and increase at 50-mg/day increments based on response or tolerance	No dosing recommendations for renal dysfunction	Regular-release tablets: Lower starting dose (25 mg) and slower titration may be needed Extended-release tablets: Should be initiated with 50 mg/day, increasing in 50-mg/day increments
Risperidone	Oral: Pediatric ages 13 years and older (schizophrenia): Initiate at 0.5 mg orally daily, adjusting at intervals of at least 24 hours and in increments of 0.5–1 mg/day as tolerated Recommended target dose, 3 mg/day	Long-acting IM: Initial dose, 25 mg IM every 2 weeks with a 3-week oral crossover; may consider 12.5 mg starting dose Oral: Initiate at 0.5 mg twice daily; may increase by 0.5 mg twice daily, increases above 1.5 mg twice daily done at intervals of at least 1 week	Long-acting IM: Patients with renal impairment should receive titrated doses of oral risperidone before initiation of IM (more detail in prescribing information) Oral: Recommended initial dose in CrCl < 30 mL/min (0.50 mL/s), 0.5 mg twice daily; dose may be increased by 0.5 mg twice daily, but increases above 1.5 mg twice daily should be done at intervals of at least 1 week. Clearance of risperidone is decreased by 60% in patients with moderate-to-severe renal disease (CrCl < 60 mL/min [1.0 mL/s])	Long-acting IM: Titrate with oral risperidone (see renal dosing) Oral: Recommended initiation in Child-Pugh Class C (see renal dosing)
Ziprasidone	No pediatric indication	No official adjustment recommended; consider starting at lower end of the dosage range	Oral doses: No adjustment necessary for mild to moderate renal impairment IM doses: Use with caution because of cyclodextrin sodium excipient	No adjustment necessary for mild to moderate hepatic impairment; however, caution is warranted

CrCl, creatinine clearance; FDA, Food and Drug Administration; IM, intramuscular.

or worse functional impairment, (c) treatment with at least two different antipsychotics given at adequate doses (a dose equivalent to at least 600 mg of chlorpromazine) for an adequate duration (6 weeks), (d) meeting minimum criteria of being adherent to current treatment, and (e) ideally having one prospective antipsychotic trial.[36]

Clozapine Clozapine remains the only drug with proven superior efficacy and approved by the FDA for TRS.[15] It is efficacious after nonresponse to other SGAs, in partially responsive patients and patients who have had a poor response to other medication for years. According to published guidelines and recommendations, clozapine should be considered after two failed antipsychotic trials,[10,27,29,31] but may be considered sooner if the individual patient situation warrants.[8,30] Additionally, it has a beneficial effect for aggression and suicidality and is FDA approved for reducing the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder.[37]

It remains unknown which pharmacologic properties account for clozapine's superior efficacy. Clozapine interacts with a multitude of receptors but notably has a low affinity for D_2 receptors, antagonism of D_1 receptors, and is a 5-HT_{2A} antagonist.

Clozapine's use is limited by the regulatory requirements resulting from the risk for severe neutropenia (ANC < 0.5×10^9/L [or $0.5 \times 10^3/mm^3$], was termed agranulocytosis previously). This is a rare but potentially life-threatening side effect occurring in < 1% of people treated. The required long-term hematologic monitoring (Table 37–8) can be a barrier for both patients and care providers. Other rare side effects include seizures and myocarditis. Other common unpleasant side effects include sedation, dizziness, constipation, enuresis, weight gain, and hypersalivation. Registration for clozapine must first occur prior to dispensing using a Clozapine REMS website.

The optimal plasma level of clozapine is a minimum trough level of 918 to 1071 nmol/L (300–350 ng/mL or mcg/L), usually corresponding to a daily dose of 200 to 400 mg, although dosage must be individualized. Males and smokers tend to require higher doses to achieve the targeted blood level due to more rapid metabolism.

▶ *Acutely Psychotic and Agitated Patients*

Psychiatric emergencies occur in emergency departments, psychiatric units, medical facilities, and outpatient settings.

Table 37–8

Monitoring of Absolute Neutrophil Count During Clozapine Treatment

	General Population	BEN Population
Initiation to 6 months	Initiate if ANC ≥ 1.5 × 10^9/L; weekly monitoring for 6 months as long as ANC remain ≥ 1.5 × 10^9/L	Initiate if ANC ≥ 1.0 × 10^9/L (obtain at least 2 baseline levels); weekly monitoring for 6 months if ANC remain ≥ 1.0 × 10^9/L
6–12 months	Every 2 week monitoring for 6 months as long as ANC levels remain ≥ 1.5 × 10^9/L	Every 2 week monitoring for 6 months as long as ANC remain ≥ 1.0 × 10^9/L
After 12 months of therapy	Every 4 week monitoring as long as ANC levels remain ≥ 1.5 × 10^9/L	Every 4 week monitoring as long as ANC levels remain ≥ 1.0 × 10^9/L
ANC 1.0–1.49 × 10^9/L	**Mild neutropenia (general population)** 1.0 to 1.49 × 10^9/L (confirm with repeat ANC within 24 hours) Recommendation to continue treatment Monitor ANC three times weekly until ANC ≥ 1.5 × 10^9/L, then return to patient's last normal range monitoring interval if appropriate	These ANC levels considered normal for BEN population, continue monitoring as generally indicated above
ANC 0.5–0.99 × 10^9/L	**Moderate neutropenia (general population)** ANC 0.5–0.99 × 10^9/L (confirm with repeat ANC within 24 hours) Recommend hematology consult; interrupt treatment if clozapine-induced neutropenia is suspected. Resume treatment once ANC is ≥ 1.0 × 10^9/L Monitor ANC daily until ANC ≥ 1.0 × 10^9/L, then three times weekly until ANC ≥ 1.5 × 10^9/L, then check weekly × 4 weeks, then return to patient's last normal range ANC interval, if appropriate	**BEN neutropenia** 0.5–0.99 × 10^9/L (confirm with repeat ANC within 24 hours) Recommend hematology consult Continue treatment Monitor ANC thrice weekly until ANC ≥ 1.0 × 10^9/L or up to patient's known baseline Once at ANC ≥ 1.0 × 10^9/L or patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last normal BEN range ANC monitoring interval, if appropriate
ANC < 0.5 × 10^9/L	**Severe neutropenia (general population)** Daily ANC until ANC ≥ 1.0 × 10^9/L, then three times weekly until ANC ≥ 1.5 × 10^9/L Recommend hematology consultation Interrupt treatment for suspected clozapine-induced neutropenia; no rechallenge unless benefits > risks If patient is rechallenged, resume treatment as a new patient under "normal range" monitoring once ANC ANC ≥ 1.5 × 10^9/L	**BEN severe neutropenia** Daily ANC until ≥ 0.5 × 10^9/L, then thrice weekly until ANC ≥ patient's baseline Recommend hematology consultation Interrupt treatment for suspected clozapine-induced neutropenia. Do not rechallenge unless benefit > risk. If patient is rechallenged, resume treatment as a patient under normal range monitoring once ANC ≥1.0 × 10^9/L or at patient's baseline
Whenever clozapine is discontinued	Weekly for at least 4 weeks from day of discontinuation	Weekly for at least 4 weeks from day of discontinuation

ANC, absolute neutrophil count (10^9/L is equivalent to 10^3/mm^3); BEN, benign ethnic neutropenia.

Although nonpharmacologic interventions such as relaxation techniques and decreasing sensory stimulation are most ideal for initial management, acutely psychotic and agitated patients also require pharmacologic interventions. Short-acting, intramuscular (IM) formulations are available for a number of FGAs (haloperidol most frequently) as well as the SGAs (aripiprazole, ziprasidone, and olanzapine). IM benzodiazepines are commonly used in addition to IM antipsychotics. IM lorazepam is generally suggested as it is the only benzodiazepine with rapid and complete IM absorption. Concomitant IM olanzapine and benzodiazepines may cause cardiorespiratory depression and should be avoided if possible. Loxapine oral inhalation is also available for acute agitation but is restricted to a REMS program and to enrolled health care facilities with onsite equipment and personnel to handle bronchospasm.

▶ *Pregnancy and Lactation*

Women with schizophrenia have higher rates of unwanted pregnancies and obstetric complications (eg, stillbirth, infant death, preterm delivery, low infant birth weight, and infants who are small for gestational age). Prolactin-related effects secondary to certain FGA and SGA treatments have led to infertility in the past. Irregular menstruation also complicated the ability to plan for pregnancies and potential false protection with sexual activity. When pregnancy occurs, the management of pregnancy and lactation in females with schizophrenia should include a multidisciplinary team and the patient's family should be involved if possible. The decision to continue antipsychotic must be weighed by the risks and benefits. The fetus is at risk for antipsychotic side effects but also the risk of relapse with schizophrenia during pregnancy is associated with a higher risk of birth complications. Guidelines suggest that antipsychotics are increasingly being used in pregnancy. Older data suggested teratogenic effects; however, larger and more recent epidemiologic studies find the majority of antipsychotics to be associated with no greater risk. Patients should still be cautioned that while the risk is low, congenital malformations have occurred rarely. There is now more published safety data with SGAs than FGAs. The safety data for FGAs is primarily for haloperidol. Low-potency phenothiazines may increase the risk of congenital abnormalities when used in the first trimester. There is some

Patient Encounter Part 4

The patient's aripiprazole dose was titrated to 30 mg once daily, which he was maintained on for 8 weeks. He returned again for follow-up with his outpatient psychiatrist who noted the patient was markedly worse. The patient looked disheveled and was answering questions with only a "yes" or "no." The patient admitted that he often skips his aripiprazole because he feels he does not need it. His mother reported that she does not observe him taking his medication but has suspected that he has not been taking it for at least a couple of weeks. The physician suggests that the patient consider getting "a shot" of aripiprazole once a month, then he would not need to take a pill every day. The patient's mother readily agrees that this is a reasonable solution. The patient is initially reluctant to get "a shot" but finally agrees, as he does not want to get into power struggles with his mother about whether or not he is taking his medication.

Over the next several months, he is more stable on the long-acting intramuscular form of aripiprazole, and he has not gained further weight. His eating habits are normal. He is less anxious, and his sleep is better.

How would a clinician discuss the advantages of taking a long-acting intramuscular medication?

What aripiprazole long-acting formulations are available?

What dose of aripiprazole LAI (Abilify Maintena) is appropriate for someone taking oral aripiprazole 30 mg once daily?

What if the patient was taking a strong CYP 3A4 inhibitor?

evidence to suggest a higher risk of congenital malformations with risperidone; however, this risk difference is only slightly higher at 5% versus 3% in the general population comparative group. If pregnancy occurs during antipsychotic treatment, continuation of previous antipsychotic is preferred to decrease relapse risk. Data do suggest that mothers who are pregnant have about a twofold risk of developing gestational diabetes; thus, monitoring and promoting healthy eating is very important. Babies born to mothers taking SGAs may also have increased birth weights compared to nonexposed mothers.[35,38] A labeling change for antipsychotic medications has been implemented by the FDA to address the potential risk for EPS and symptoms of withdrawal in newborns whose mothers were treated with antipsychotics in the third trimester. Withdrawal symptoms may include agitation, abnormal muscle tone (increased or decreased), tremor, sleepiness, and difficulty in breathing or feeding, which may last for hours to days after delivery. In some newborns, specific treatment for withdrawal is not needed, whereas in others, longer hospital stays may be required.

Although SGAs are excreted in breast milk, most case reports document a low frequency of deleterious effects on the infant. Breast feeding while on clozapine should be avoided.[35,38]

Pharmacokinetics

Most antipsychotics are, at least to some extent, metabolized by hepatic CYP450 metabolic enzymes to water-soluble compounds that are excreted by the kidneys (Table 37–9).[39] Unlike the other antipsychotics, ziprasidone is mostly metabolized by aldehyde oxidase, a metabolic system independent of the CYP450 system. Paliperidone, the 9-OH metabolite of risperidone, is mostly excreted unchanged in the urine, although up to one-third may be metabolized. The transmembrane energy-dependent efflux transporter P-glycoprotein may limit the ability of drugs to penetrate the blood–brain barrier and therefore impact pharmacologic activity in the brain. Antipsychotics currently known to use this pathway include perphenazine, haloperidol, fluphenazine, quetiapine, risperidone, paliperidone, aripiprazole, and olanzapine.[40]

Additive side effects may occur with combined drug therapies, and a few clinically significant drug interactions are notable (see Table 37–9). Cigarette smoking decreases serum concentrations of clozapine and olanzapine by induction of CYP1A2. Although antipsychotics are highly protein bound, protein-binding interactions are generally not clinically significant. Absorption of most antipsychotics is not affected by food, with the exception of lurasidone and ziprasidone. The mean maximum concentration of lurasidone increases threefold when administered with food, and ziprasidone's absorption is increased by 60% to 70% when given with meals.

Ziprasidone, iloperidone, and quetiapine have potential to prolong the QTc interval. Using them with other agents that prolong the QTc interval should be undertaken with caution. These other agents include, but are not limited to, quinidine, sotalol, chlorpromazine, droperidol, mesoridazine, pimozide, thioridazine, gatifloxacin, halofantrine, mefloquine, moxifloxacin, and pentamidine. Combining higher doses of ziprasidone, iloperidone, or quetiapine with ketoconazole or erythromycin should be undertaken cautiously.

Added pharmacodynamic effects are possible when combining antipsychotics with other drugs that can cause sedation, hypotension, anticholinergic symptoms, and weight gain or metabolic abnormalities.

Adjunct Treatments

The judicious use of pharmacologic therapies other than antipsychotics is often necessary for the treatment of motor side effects, anxiety, depression, mood elevation, and TRS that does not respond to clozapine. Anticholinergic medications (eg, benztropine, 1–2 mg twice daily; trihexyphenidyl, 1–3 mg thrice daily; and diphenhydramine, 25–50 mg twice daily) are used to treat EPS. They may be prescribed prophylactically with high-D_2-binding agents or in patients at risk for EPS or for treatment of EPS. β-Blockers (eg, propranolol 30–120 mg/day) are sometimes effective for patients who develop akathisia. In some situations, such as on an inpatient unit, the concomitant use of benzodiazepines (eg, lorazepam 1–3 mg/day) with the SGAs may be necessary for agitation.[27]

More recent guidelines suggest that regular assessment of depressive symptoms in schizophrenia is important and that waiting for the effect of antipsychotics to work instead of immediately adding an antidepressant is recommended. Evidence suggests that SGAs may be more effective than FGAs for depressive symptoms in people with schizophrenia; however, this evidence is limited.[35] Antidepressants may be useful for patients with schizophrenia who have depressive symptoms in the stable phase of schizophrenia; however, these agents may have the potential to worsen symptoms in the acute phase.[35] Because suicide risk may be increased, aggressive treatment may

Table 37–9

Metabolism and Drug Interactions with Antipsychotics

Antipsychotic	Major Metabolic Pathways	Other Metabolic Pathways	Increase Antipsychotic Concentrations	Decrease Antipsychotic Concentrations
Aripiprazole	CYP 3A4	CYP 2D6	Fluvoxamine, ketoconazole	Carbamazepine
Asenapine	Glucuronidation by UGT1A4 and CYP 1A2	CYP 3A4, CYP 2D6	Fluvoxamine	
Brexpiprazole	CYP 3A4, 2D6		Itraconazole, clarithromycin, ketoconazole, quinidine, paroxetine, fluoxetine	Rifampin, St. John's wort
Cariprazine	CYP 3A4	CYP 2D6	Itraconazole, ketoconazole	Rifampin, carbamazepine (use not recommended with strong CYP3A4 inducer)
Chlorpromazine	CYP 2D6	CYP 1A2, CYP 3A4		
Clozapine	CYP 1A2	CYP 3A4, CYP 2D6, CYP 2C19, CYP 2C9	Fluvoxamine, ciprofloxacin, paroxetine	Cigarette smoking
Fluphenazine	CYP 2D6		Paroxetine	
Haloperidol	CYP 2D6, CYP 3A4	CYP 1A2	Fluvoxamine, fluoxetine, ketoconazole	Carbamazepine
Iloperidone	CYP 2D6, CYP 3A4	CYP 1A2, CYP 2E1	Ketoconazole, fluoxetine, paroxetine	
Loxapine	CYP 1A2, CYP 2D6, CYP 3A4			
Lurasidone	CYP 3A4		Ketoconazole, diltiazem	Rifampin
Olanzapine	CYP 1A2, Glucuronidation by UGT1A4	CYP 2D6	Fluvoxamine, ciprofloxacin, paroxetine	Cigarette smoking
Paliperidone	CYP 2D6, CYP 3A4 (in vitro, but limited role in vivo)		Divalproex sodium, paroxetine	Carbamazepine (via increased renal elimination)
Perphenazine	CYP 2D6		Fluvoxamine, fluoxetine, paroxetine	
Pimozide	CYP 3A4	CYP 1A2	Strong CYP 2D6 inhibitors, CYP 3A4 inhibitors	CYP 3A4 inducers
Quetiapine	CYP 3A4	CYP 2D6	Fluvoxamine, ketoconazole	Carbamazepine
Risperidone	CYP 2D6	CYP 3A4	Fluoxetine, paroxetine	Carbamazepine
Thioridazine	CYP 2D6	CYP 2C19	Fluvoxamine	Cigarette smoking
Thiothixene	CYP 1A2		CYP 1A2 inhibitors	CYP 1A2 inducers
Trifluoperazine	CYP 1A2		CYP 1A2 inhibitors	CYP 1A2 inducers
Ziprasidone	Aldehyde oxidase	CYP 1A2, CYP 3A4	Fluvoxamine, ketoconazole	Carbamazepine

CYP450, cytochrome P450 isoenzyme.

be necessary when depression is present. The selective serotonin reuptake inhibitors (SSRIs) are the preferred agents, but they may inhibit the CYP450 enzymes, thus raising plasma concentrations of clozapine, olanzapine, and haloperidol. Mood stabilizers, such as lithium and the anticonvulsants, have been used adjunctively with the antipsychotics to treat the affective component of schizoaffective disorder.[35]

For patients with an inadequate response to clozapine, limited treatment options are available for these patients. A number of augmentation strategies have been tried, including FGAs, SGAs, mood stabilizers (eg, lithium, valproate, and topiramate), minocycline, antidepressants, transcranial magnetic stimulation (TMS), and **electroconvulsive therapy** (ECT). Though controlled trial results are mixed, some data support the adjunctive use of risperidone, lamotrigine, or aripiprazole in clozapine-treated patients.[30]

Psychosocial Treatment

KEY CONCEPT Psychosocial support helps improve functional outcomes. Residual symptoms often persist such as avolition, isolation, and impaired social functioning, limiting participation in social, vocational, and educational endeavors. Psychosocial interventions, as adjuncts to pharmacotherapy, are designed to improve psychosocial functioning, self-esteem, and life satisfaction. In the United States, psychosocial treatments are less frequently used than in Europe, but their use is on the rise and current guidelines suggest nonpharmacologic strategies in conjunction with antipsychotic treatment. There are much data to support family education in decreasing relapse rates and vocational support to improve vocational outcomes. A few of the best-supported and most promising approaches to psychosocial rehabilitation are social skills training (SST), cognitive behavioral therapy (CBT), and cognitive remediation (CR). In addition, psychoeducation, supported employment, Assertive Community Treatment (ACT), and Medical Home care models have improved outcomes.[12,41]

Patient Education

KEY CONCEPT Education of the patient and family regarding the benefits and risks of antipsychotic medications and the importance of treatment adherence must be ongoing and integrated into pharmacologic management. Medication management discussions offer an opportunity to provide illness and treatment education including the nature and course of schizophrenia, and can serve as a time to hear the patient's life goals. Key considerations include:

Patient Encounter Part 5

The patient has remained on aripiprazole long-acting injection for nearly a year, but the patient's paranoia returned and he felt agitated on the drug. Over the next 2 years, he was switched to various other agents including ziprasidone, perphenazine, and olanzapine, to which he only had a partial response. At his most recent outpatient appointment, the doctor suggested that he might benefit from a trial of clozapine, but the patient was not sure if clozapine was right for him. In a separate phone call to his parents, his doctor reviewed the pros and cons of the clozapine trial. The patient and his parents discussed everything they discussed with the doctor and agreed to a trial of clozapine.

Why is his clinician considering a clozapine trial?

What are the rare serious side effects of clozapine versus the common manageable side effects?

The patient still smokes cigarettes. How will cigarette smoking affect clozapine therapy?

LO 6

- Involve families in the education and treatment plans because family psychoeducation may decrease relapse, improve symptomatology, and enhance psychosocial and family outcomes.[40]
- Be clear that there is no cure for schizophrenia and that medication can be effective to decrease and improve many symptoms.
- Explain common and rare but dangerous side effects.
- Stress the importance of medication and treatment adherence for improving long-term outcomes.
- Decision making on the best course of treatment should be a shared process.

OUTCOME EVALUATION

Developing a good working alliance with the patient is essential. In the absence of a solid therapeutic relationship, patients are frequently reluctant to share their beliefs, personal experiences, and life goals.

Symptom Monitoring

Many assessments are available to objectively rate positive and negative symptoms, level of function, and life satisfaction. The most commonly used scales in clinical trials to measure symptoms include:

- Positive and Negative Symptom Scale (PANSS)
- Brief Psychiatric Rating Scale (BPRS)
- Clinical Global Impression (CGI) Scale
- Calgary Depression Scale for Schizophrenia (CDSS)

LO 7

Using these scales on a regular basis, particularly when switching medications or changing doses, is a more reliable means of monitoring symptoms. Symptom assessments cannot capture the full range of possible improvements, but they can be useful in deciding whether a medication is having substantial benefit.

Side-Effect Monitoring

LO 7

KEY CONCEPT Regularly monitor for side effects and overall health status.[27,31] Perform orthostatic blood pressure measurements and vital sign assessments before initiating antipsychotics and regularly throughout treatment. Ask about prolactin-related side effects such as impaired menstruation, libido, and sexual performance regularly. At baseline check body weight, fasting glucose, and lipid profile, and repeat these measurements 12 weeks after initiation of medication and then yearly.[42] For patients at higher risk of developing diabetes and those who gain weight, check body weight more often (Table 37–10). Every effort should be made to help with weight and metabolic side effects.[6,43–45] Metformin may be an option in addition to nonpharmacologic techniques for weight loss or attenuation of weight gain.[46]

Additionally, perform baseline electrocardiography for patients with preexisting cardiovascular disease or risk for arrhythmia. With clozapine therapy, there is a risk for the development of severe neutropenia, which is greatest in the first 6 months of treatment. Required monitoring of absolute neutrophil count (ANC) is described in Table 37–8. Separate monitoring guidelines now exist for general patients and those with Benign Ethnic Neutropenia. Overall, encourage patients to have annual physical, gynecologic, and ophthalmologic examinations and regularly ask about physical health and side effects at each visit.

LO 7

Table 37–10

Cardiometabolic Monitoring Protocol for Patients on Second-Generation Antipsychotics

	Baseline	4 Weeks	8 Weeks	12 Weeks	Annually
Personal or family history[a]	X				X
Weight (BMI)	X	X	X	X	X
Waist circumference	X	X		X	X
Blood pressure	X	X		X	X
Fasting plasma glucose	X			X	X
Fasting plasma lipids	X			X	X
ECG	X				X

[a]Of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease.

Data from Refs. 30, 42, and 44.

Patient Care Process

Collect Information:

- Chief complaint and history of present illness
- Family history, psychiatric history (age when first diagnosed, time of first hospitalization for mental illness), medical history. Obtain collateral information from family, past medical records, and other providers to help clarify the psychiatric history.
- Social history (housing arrangements, social and vocational goals, support systems, employment, substance use history)
- Physical examination
- Key laboratory data and imaging studies
- Mental status examination
- Past and current medications (psychiatric and somatic, prescription, nonprescription, herbal or other dietary supplements)

Assess the Information:

- Review the patient's chief complaint, presenting symptoms, and history, including psychiatric history. Assess mental status examination for organization of thoughts and range of affect, presence of mood disturbance, likelihood of harm to self or others, and presence of hallucination, paranoia and/or delusions of control, evaluate judgment and insight.
- Assess medical records, including laboratory and imaging studies, to rule out medical causes of psychosis.
- Assess current treatments and outcomes of prior treatments for effectiveness and safety.
- Assess adherence to medications and willingness to take medications.

Develop a Care Plan:

- Identify medication-related problems.
- Determine the goals of therapy.
- Select or optimize the dose of an antipsychotic based on the side-effect profile that is most appropriate and acceptable to the patient.
- Collaborate with other health care professionals or caregivers in the development of the plan.
- Consider how income, insurance coverage, and access to care might influence pharmacotherapy choice.

Implement the Care Plan:

- Initiate, modify, discontinue, or administer the appropriate medication therapy.
- Educate patient and caregiver (with patient consent) about the illness, medication treatments, possible side effects, and goals of treatment.
- Discuss medication adherence and healthy lifestyle goals, including substance and cigarette use.
- Enlist adjunctive treatments, including psychosocial therapies to optimize outcomes.
- Coordinate referrals or transition of care to other health care professionals, such as social workers, home care nurses, or other medical specialists.
- Recommend placement of individuals in ACT, group homes, transitional housing, rehabilitation, or long-term care.
- Schedule follow-up appointments.

Follow-up: Monitor and Evaluate:

- Monitor medication therapy for effectiveness, using psychiatric rating scales when necessary.
- Monitor medication therapy for adverse events of antipsychotics using the AIMS, Simpson–Angus Scale, and Extrapyramidal Symptom Rating Scale.
- Monitor appropriate laboratory measures to prevent or minimize adverse effects, including metabolic abnormalities.
- Assess for emergence of new target symptoms.
- Monitor for adherence to the medication regimen.
- Optimize dosing and consider clozapine if criteria are met for treatment resistance.

Commonly used rating scales to monitor for EPS include the Simpson–Angus Scale (SAS) and the Extrapyramidal Symptom Rating Scale (ESRS). Akathisia is commonly monitored by the Barnes Akathisia Scale (BAS). The emergence of dyskinesias could represent the emergence of TD. Monitor patients on SGAs for TD at least annually, and patients taking FGAs at each visit. The most commonly used instrument to measure these symptoms is the Abnormal Involuntary Movement Scale (AIMS).

Abbreviations Introduced in This Chapter

5-HT	Serotonin
ACT	Assertive Community Treatment
AIMS	Abnormal Involuntary Movement Scale
ANC	Absolute neutrophil count
APA	American Psychiatric Association
BAS	Barnes Akathisia Scale
BPRS	Brief Psychiatric Rating Scale
CATIE	Clinical Antipsychotics Trials of Intervention Effectiveness
CBT	Cognitive behavioral therapy
CGI	Clinical Global Impression Scale
CR	Cognitive remediation
CYP450	Cytochrome P450 isoenzyme
D	Dopamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
ECT	Electroconvulsive therapy
EPS	Extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
H	Histamine
IM	Intramuscular
LAI	Long-acting injection
M	Muscarinic

NMDA	*N*-methyl-D-aspartate
NMS	Neuroleptic malignant syndrome
PANSS	Positive and Negative Symptom Scale
PCP	Phencyclidine
PORT	Schizophrenia Patient Outcomes Research Team
QTc	Corrected QT interval
SAS	Simpson–Angus Scale
SGA	Second-generation antipsychotic
SSRI	Selective serotonin reuptake inhibitor
SST	Social skills training
TD	Tardive dyskinesia
TIMA	Texas Implementation of Medication Algorithms
TMS	Transcranial magnetic stimulation
TRS	Treatment Resistant Schizophrenia
WBC	White blood cell

REFERENCES

1. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2:e141.
2. Kim Y, Zerwas S, Trace SE, Sullivan PF. Schizophrenia genetics: where next? Schizophr Bull. 2011;37(3):456–463.
3. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: update for the 21st century. J Psychopharmacol. 2015;29:97–115.
4. Halberstadt A, Geyer MA. Serotonergic hallucinations as translational models relevant to schizophrenia. Int J Neuropsychopharmacol. 2013;16:2165–2180.
5. Hartz SM, Pato CN, Medeiros H, et al. Comorbidity of severe psychotic disorders with measures of substance use. JAMA Psychiatry. 2014;7:248–254.
6. Andreade C. Cardiometabolic risks in schizophrenia and directions for intervention, 3: psychopharmacological interventions. J Clin Psychiatry. 2016;77:e1090–e1094.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
8. American Psychiatric Association. Practice guidelines for the treatment of patients with schizophrenia. Am J Psychiatry. 2004;161(2 suppl):1–56.
9. Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol. 2010;24(4 suppl): 81–90.
10. Psychoses and Schizophrenia in Adults: Prevention and Management. National Institute for Health and Care Excellence (NICE). Available from: https://www.nice.org.uk/Guidance/CG178. Accessed July 16, 2018.
11. Rubio JM, Correll CU. Duration and relevance of untreated psychiatric disorders, 1: psychotic disorders. J Clin Psychiatry. 2017;78:358–359.
12. Dixon LB, Dickerson F, Bellack AS, et al; Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychosocial treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):48–70.
13. Jaaskelainen E. Juola P, Hirvonen R, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013;39:1296–1306.
14. Lieberman JA, Stroup TS, McEvoy JP; The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in people with chronic schizophrenia. N Engl J Med. 2005;353(12):1209–1223.
15. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382:951–962.
16. Cornett E, Novitch M, Kaye AD, Kata V, Kaye AM. Medication induced tardive dyskinesia: a review and update. Ocshner. 2017;17:162–174.
17. Schotte A, Janssen PF, Gommeren W, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. Psychopharmacology. 1996;124(1–2):57–73.
18. Csernansky JG, Mahmoud R, Brenner R, Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med. 2002;346(1):16–22.
19. Richelson E. Receptor pharmacology of neuroleptics: relation to clinical effects. J Clin Psychiatry. 1999;60(suppl 10):5–14.
20. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther. 1995;275(1):101–113.
21. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology. 2003;28(8):1400–1411.
22. Dolder C, Nelson M, Deyo Z. Paliperidone for schizophrenia. Am J Health Syst Pharm. 2008;65(5):403–413.
23. Arif SA, Mitchell MM. Iloperidone: a new drug for the treatment of schizophrenia. Am J Health Syst Pharm. 2011;68:301–308.
24. Citrome L. Iloperidone, asenapine, and lurasidone: a brief overview of 3 new second generation antipsychotics. Postgrad Med. 2011;123(2):153–162.
25. Markovic M, Gallipani A, Patel KH. Brexpiprazole. Pharamacother. 2017;51:315–322.
26. Garnock-Jones KP. Cariprazine: a review in schizophrenia. CNS Drugs. 2017;31:513–525.
27. Hasan A, Falkai P, Wobrock T, Lieberman J, et al; WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry. 2013;14:2–44.
28. Moore TA, Buchanan RW, Buckley PF, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. J Clin Psychiatry. 2007;68(11):1751–1762.
29. Buchanan RW, Kreyenbuhl J, Kelly DL, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71–93.
30. Hasan A, Falkai P, Wobrock T, et al; World Federation of Societies of Biological Psychiatry (WFSBP) Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 1: update 2012 on acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry. 2013;13:318–378.
31. Barnes TRE, Schizophrenia Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2011;25(5):567–620.
32. Velligan DI, Sajatovic M, Hatch A, Kramata P, Docherty JP. Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. Patient Prefer Adherence. 2017;11:449–468.
33. Tihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29,823 patients with schizophrenia. JAMA Psychiatry. 2017;74:686–693.
34. Mueser KT, Penn DL, Addington J, et al. The NAVIGATE program for first-episode psychosis: rational, overview, and description of psychosocial components. Psychiatr Serv. 2015;66:680–690.

35. Hasan A, Falkai P, Wobrock T, et al; WFSBP Task Force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, Part 3: update 2015 management of special circumstances: depression, suicidality, substance use disorders and pregnancy and lactation. World J Biol Psychiatry. 2015;16:142–170.
36. Howes OD, McCutcheon R, Agid O. Treatment-resistant Schizophrenia: treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry. 2017;174:216–229.
37. Hill M, Fredudenreich O. Clozapine: key discussion points for prescribers. Clin Schizophr Relat Psychoses. 2013;6:177–185.
38. McAllister-Williams RH, Baldwin DS, Cantwell RJ, et al. British Association for Psychopharmacology consensus guidance on the use of psychotropic medication preconception, in pregnancy and postpartum. Psychopharmacol. 2017;31:519–552.
39. Spina E, Hiemke C, de Leon J. Assessing drug-drug interactions through therapeutic drug monitoring when administering oral second-generation antipsychotics. Expert Opin Durg Metab Toxicol. 2016;12:407–422.
40. Akamine Y, Yasui-Furukori N, Ieiri I, Uno T. Psychotropic drug-drug interactions involving P-glycoprotein. CNS Drugs. 2012;26:959–973.
41. Morin L Franck N. Rehabilitation interventions to promote recovery from schizophrenia: a systematic review. Front Psychiatry. 2017;8:100.
42. American Diabetes Association. Screening Guidelines for People on Second Generation Antipsychotics. Diabetes Care. 2004;27(2):596–601 or 2007;30(suppl 1):S4–S41.
43. Falissard B, Mauri M, Shaw K, et al. The METEOR study: frequency of metabolic disorders in patients with schizophrenia. Focus on first and second generation and level of risk of antipsychotic drugs. Int Clin Psychopharmacol. 2011;26:291–302.
44. Cooper SJ, Reynolds GP, Barnes TRE, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J Psychopharmacol. 2016;30:717–748.
45. Polcwiartek C, Kragholm K, Schjerning O, Graff C, Nielson J. Cardiovascular safety of antipsychotics: a clinical review. Expert Opinion on Drug Safety. 2016;5:679–688.
46. De Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. BMC Psychiatry. 2016;16:341.

38 Major Depressive Disorder

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LEARNING OBJECTIVES

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

LO

1. Explain the etiology and pathophysiology of major depressive disorder (MDD).
2. Identify the signs and symptoms of MDD.
3. Outline the treatment goals for a patient with MDD.
4. Recommend pharmacotherapy given a specific patient with MDD.
5. Develop a monitoring plan for a specific patient with MDD which includes the assessment of efficacy as well as adverse effects.
6. Predict, prevent, identify, and resolve potential drug-related problems.
7. Educate patients and caregivers on the proper use of antidepressant therapy.

INTRODUCTION

Major depression is a common, seriously disabling, disorder nonresponsive to volitional efforts to feel better. Individuals with major depressive disorder (MDD) experience pervasive symptoms affecting mood, thinking, physical health, work, and relationships. Suicide often results when MDD is inadequately diagnosed and treated.[1]

Over and under detection of MDD is an important consideration. Primary care providers have become increasingly involved in the management of MDD. Studies show that over detection of MDD can outnumber missed cases.[1] Antidepressants account for 15 of the top 200 prescription drugs dispensed in the United States.[2] Inadequate treatment remains a serious concern.[3]

EPIDEMIOLOGY AND ETIOLOGY

The lifetime and 12-month prevalence estimates for MDD are 16.2% and 6.6%, respectively.[4] Women are twice as likely as men to experience MDD.[5] In the United States, incidence peaks in the twenties. Many patients with MDD have comorbid psychiatric disorders, especially anxiety and substance use disorders.[5]

According to the World Health Organization (WHO), depression is the leading cause of disability worldwide and a major contributor to the overall global burden of disease.[6]

The etiology of depression is complex and is hypothetically due to a change in the brain neurotransmitters, primarily norepinephrine (NE), serotonin (5-HT), and dopamine (DA).[7]

Patient Encounter Part 1

A 43-year-old woman presents to the psychiatry clinic with complaints of depressed mood, poor sleep, and decreased appetite. She has lost 25 pounds (11.4 kg) in the last 2 months. She also has been isolating herself from other people, and has had crying spells. She says that she has been thinking about committing suicide, but she does not have a specific plan.

What symptoms of MDD does she have?

What medical or psychiatric issues could be contributing to her symptoms?

What additional information do you need to know before creating a treatment plan for this patient?

PATHOPHYSIOLOGY

LO 1

The cause of MDD is unknown but is probably multifactorial. Multiple theories abound, and practitioners suggest that development of depression likely involves a complex interaction of genetic predisposition, psychological stressors, and underlying pathophysiology. There are no currently accepted unifying theories to adequately explain the pathophysiology of depression.[7]

Genetics

First-degree relatives of MDD patients are about two to four times more likely to develop MDD compared with controls.[5] Adoption and twin studies also suggest that MDD is due to genetic influences.[8] Major depression has been associated with four different genes including polymorphisms in the glucocorticoid receptor gene NR3C1, the monoamine oxidase A gene, the gene for glycogen synthase kinase-3β, and a group-2 metabotropic glutamate receptor gene (GRM3).[9]

Stress

Major life stressors do not always cause depression. Nevertheless, there is an undeniable association between life stressors and depression, and there appears to be a significant causative interaction between life stressors and genetic predisposition. Although acute stressors may precipitate depression, chronic stressors cause longer episodes and are more likely to lead to **relapse** and **recurrence**.[10]

Biogenic Amine and Receptor Hypotheses

KEY CONCEPT The primary hypothesis is the biogenic amine hypothesis which states that a deficit of NE, DA, or 5-HT at the synapse is the cause of depression.[7] The fact that existing antidepressants increase synaptic monoamine concentrations supports this hypothesis (see Pharmacologic Therapy). One argument against this hypothesis is that patients with depression do not always have decreased monoamine levels. Additionally, monoamine levels are altered within hours of initiating antidepressant therapy, but **response** is delayed by 2 to 4 weeks or more.[7]

The receptor hypothesis suggests that depression is related to upregulation of **monoamine neurotransmitter** receptors in response to a depletion of monoamine neurotransmitters. In this hypothesis, chronic administration of antidepressants alters receptor sensitivity causing desensitization or downregulation of monoamine neurotransmitter receptors leading to therapeutic response.[7] Importantly, the time required for changes in receptor sensitivity correlates with antidepressant onset.[7] These hypotheses are clearly oversimplifications of the pathophysiology of depression. MDD probably involves a complex dysregulation of monoamine systems that modulate and are modulated by other neurobiological systems.

Other Neurobiological Hypotheses

At least three categories of peripheral hormones are associated with the pathophysiology of depression. They include (a) neurotrophic and other growth factors including brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), and insulin-like growth factor; (b) proinflammatory cytokines including interleukin-1β, interleukin-6, and tumor necrosis factor-α; and (c) the hypothalamic pituitary axis (HPA).[9]

Proinflammatory cytokines are increased in individuals with MDD, and antidepressants suppress the synthesis of these cytokines.[9] HPA axis regulation is impaired in depression, and antidepressants can attenuate the neuroendocrine response.[9] Similarly, BDNF is decreased in patients with MDD, and antidepressants reverse this response.[9]

CLINICAL PRESENTATION AND DIAGNOSIS

LO 2

The diagnosis of a major depressive episode (MDE) requires the presence of five depressive symptoms for a minimum of 2 weeks that cause clinically significant distress or impairment.[5] The diagnosis of MDD is based on the presence of one or more MDEs during a person's lifetime (Table 38–1).[5]

Differential Diagnosis

MDEs also occur in bipolar disorder. Individuals with bipolar disorder also experience hypomanic, manic, or mixed episodes (see Chapter 39) during the course of their illness, but individuals with MDD do not.[5]

Conditions that may mimic or coexist with MDD are anxiety, personality, and substance use disorders.[5] Several chronic medical conditions also have strong correlations with MDD. MDD is associated with a 65% increased risk of diabetes in elderly patients.[11] MDD is also strongly correlated with coronary artery disease.[11] Other medical disorders associated with depression include hypothyroidism, cancer, anemia, infections, electrolyte disturbances, folate deficiency, neurologic disorders, and cardiovascular and respiratory disease.[5,11] Identification and treatment of MDD in patients with chronic medical conditions is important. Inadequate recognition and undertreatment of depression may increase the mortality associated with these medical disorders.[11] Use of central nervous system (CNS) depressants, such as alcohol, benzodiazepines, or narcotics, is associated with an increased incidence of depression.[5,12] Some drugs that cause depressive symptoms include corticosteroids, contraceptives, phenobarbital, levetiracetam, topiramate, vigabatrin, gonadotropin-releasing hormone agonists, interferon-α, interleukin-2, varenicline, mefloquine, isotretinoin, propranolol, clonidine, methyldopa, and reserpine.[12]

Persistent depressive disorder (dysthymia) is a chronic form of depression that must be differentiated from MDD.[5] Many symptoms of dysthymia are similar to those of MDD, but they are chronic and milder.[5] Symptoms must be present for at least 2 years and may include sleep and appetite disturbances, lack of energy, poor self-image, and difficulty making decisions.[5] Individuals with dysthymia are more likely to develop MDD than the general population.[5]

Table 38–1

Clinical Presentation of Depression: Diagnostic Criteria for Major Depressive Episode[5]

At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning.

- Depressed mood[a]
- Markedly diminished interest or pleasure in usual activities[a]
- Increase or decrease in appetite or weight
- Increase or decrease in amount of sleep
- Increase or decrease in psychomotor activity (ie, agitation or retardation)
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think, concentrate, or make decisions
- Recurrent thoughts of death, suicidal ideation, or suicide attempt

The symptoms cause clinically significant distress or impairment in functioning.

The symptoms are not due to the direct physiologic effects of a substance or medical condition.

[a]One of these two symptoms must be present.

Data from American Psychiatric Association. Major Depressive Disorders. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association, 2013:160–168.

COURSE AND PROGNOSIS

MDD may affect an individual at any age including children and elderly, although, as previously stated, the incidence peaks in the 20s in the United States.[5] Some individuals will experience only one episode of depression, others will experience distinct episodes with few or no symptoms between, while others will rarely experience **remission**. The course of MDD varies markedly between patients.[5] KEY CONCEPT It is not uncommon for a patient to experience only a single MDE, but most patients with MDD experience multiple episodes. The longer an individual is in remission, the lower their risk of recurrence. Individuals with longer symptom duration, psychotic features, prominent anxiety, and severe symptoms predict lower recovery rates.[5] The risk of recurrence increases in individuals with persistent mild depressive symptoms, severe episodes, younger age, and in those with a history of previous episodes.[5,13]

MDD is a risk factor for suicide.[14] The WHO estimates that nearly 800,000 people die from suicide every year and suicide is the second leading cause of death among 15- to 29-year olds.[6]

TREATMENT

Desired Outcomes

LO 3 The goal of therapy for patients with MDD is resolution of depressive symptoms, return to **euthymia,** and prevention of relapse and recurrence of symptoms.[14] KEY CONCEPT One extremely important goal is prevention of suicide attempts. LO 3 Other desired outcomes include improving quality of life including normalization of functioning in areas such as work and relationships, minimization of adverse effects, and reduction of health care costs.[14]

Nonpharmacologic Therapy

Evidence supports efficacy of interpersonal and cognitive-behavioral therapy in the treatment of MDD. Psychotherapy alone is an initial treatment option for mild to moderate depression, and it may be useful when combined with pharmacotherapy for the treatment of severe depression.[14] This combination can be more effective than either treatment alone in severe or recurrent MDD.[14] Combination treatment may be helpful for patients with psychosocial stressors, interpersonal difficulties, or comorbid personality disorders.[14]

Electroconvulsive therapy (ECT) is a highly efficacious and safe treatment alternative for MDD. The response rate is about 70% to 90%, and it exceeds 50% for patients who have failed pharmacotherapy.[14] ECT may be beneficial for MDD that is complicated with psychotic features, severe suicidality, refusal to eat, pregnancy, or contraindication or nonresponse to pharmacotherapy.[14] Typically, 6 to 12 treatments are necessary with response occurring in 10 to 14 days.[14] When ECT is discontinued, antidepressants are initiated to help maintain response. In addition, some patients will receive maintenance ECT with/without antidepressants. Side effects after ECT include temporary confusion and retrograde and anterograde amnesia.[14]

Light therapy may be an effective alternative treatment for depression associated with seasonal (eg, winter) exacerbations.[15] Side effects can include eye strain and mania.[14,15]

Vagus nerve stimulation (VNS) was approved by the Food and Drug Administration (FDA) in 2005 for treatment-resistant depression.[14] A pulse generator is surgically implanted around the vagus nerve which sends signals to the brain that may help relieve depressive symptoms.[16] Adverse effects of VNS include alterations in patients' voice, hoarseness, dyspnea, and neck pain.[14]

Transcranial magnetic stimulation is a noninvasive and well-tolerated procedure that is FDA approved for use after one failed trial of an antidepressant.[14,17] Physical exercise may reduce depressive symptoms, but well-controlled studies are needed to verify this.[18]

Pharmacologic Therapy

Individual antidepressants, even those within the same class, have important pharmacologic differences (**Tables 38–2** and **38–3**).[7,19] Clinicians and treatment guidelines categorize antidepressants by pharmacologic mechanism of action, chemical structure or whether the medication is a "newer antidepressant" which includes all of the nonmonoamine oxidase inhibitors (MAOIs) and nontricyclic antidepressants (TCAs) or "older antidepressants" which includes the MAOIs and TCAs.

▶ *Selective Serotonin Reuptake Inhibitors*

The primary action of the selective serotonin reuptake inhibitors (SSRIs) is serotonin reuptake inhibition (SRI), although each agent in the class has unique pharmacological profiles.[7] For example, paroxetine has mild anticholinergic effects, citalopram has mild antihistaminic effects, and fluoxetine antagonizes the 5-HT2C receptor which may contribute to its antibulimia effects.[7]

Patient Encounter Part 2

PMH: History of chronic migraine headaches, irritable bowel syndrome.

Past Psych History: She has had multiple psychiatric hospitalizations with the last being 2 years prior to this admission. She has a history of MDD.

FH: Mother had diabetes mellitus and MDD, died at age 60; father had a history of alcoholism and died at age 58; brother is a recovering alcoholic.

SH: Completed 4 years of college with bachelor's degree. Most recently, employed as a representative in the pharmaceutical industry but position was eliminated about 3 months ago. Drinks socially—admits to drinking several glasses of wine nightly recently after loss of her job. Married with two teenage children. Denies tobacco use.

Current Meds:

- Sertraline 200 mg by mouth daily
- Propranolol LA 80 mg by mouth once daily
- Dicyclomine 10 mg by mouth three times daily as needed
- Aspirin/acetaminophen/caffeine by mouth as needed for migraine headache

ROS: Decreased sleep; decreased appetite; weight loss; all others noncontributory

PE:

VS: Ht 5'7" (170 cm), Wt 120 lbs (54.5 kg), weight loss of 25 lbs (11.4 kg) over past 8 weeks

MSE: Depressed mood, decreased sleep, decreased appetite, isolation, positive suicidal ideation without plan

Labs: Within normal limits. Urine drug screen—negative

Given this additional information, what is your assessment of the patient's condition?

Does she have risk factors for depression?

Identify treatment goals for the patient.

What nonpharmacologic and pharmacologic alternatives are available for this patient?

Table 38–2

Primary Pharmacologic Actions[a] of Antidepressants[7,9,20]

Action	MAOIs	TCAs	SSRIs	Bup	SNRIs	Vilaz	Traz	Nefaz	Mirtaz	Vorti
Monoamine oxidase inhibition	X									
Serotonin reuptake inhibition		X	X		X	X	X	X		X
Norepinephrine reuptake inhibition		X		X	X					
Dopamine reuptake inhibition				X						
α_2-Adrenergic receptor blockade									X	
Serotonin$_{1A}$ receptor agonist										X
Serotonin$_{1A}$ receptor partial agonist						X				
Serotonin $_{1B}$ receptor partial agonist										X
Serotonin $_{2A}$ receptor blockade							X	X	X	
Serotonin$_{2C}$ receptor blockade							X	X	X	
Serotonin$_3$ receptor blockade									X	X
Serotonin$_7$ receptor blockade										X
α_1-Adrenergic receptor blockade		X					X	X		
Histamine-1 receptor blockade		X					X		X	
Muscarinic cholinergic receptor blockade		X								

[a]See text for discussion of secondary pharmacologic actions.

Bup, bupropion; MAOI, monoamine oxidase inhibitor; Mirtaz, mirtazapine; Nefaz, nefazodone; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; Traz, trazodone; Vilaz, vilazodone; Vorti, vortioxetine.

▶ *Serotonin Norepinephrine Reuptake Inhibitors*

Venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran are 5-HT and NE reuptake inhibitors (SNRIs). Compared with venlafaxine and desvenlafaxine, which have primarily SRI activity and dose-related affinity for norepinephrine reuptake inhibition (NRI), duloxetine has more balanced SRI and NRI activities.[7] Levomilnacipran has higher activity at NRI than SRI.[7]

▶ *Norepinephrine Dopamine Reuptake Inhibitor*

Bupropion is an NE and DA reuptake inhibitor (NDRI). Bupropion's effects on NRI and DRI are weak but it is an efficacious antidepressant.[7] Bupropion is generally activating and may be especially useful at improving energy, alertness, as well as other symptoms of depression.[7]

▶ *Serotonin Antagonist and Reuptake Inhibitors*

Nefazodone and trazodone are 5-HT antagonists.[7] Their SRI activity is not as pronounced as that of the SSRIs, but they potently block 5-HT$_{2A}$ receptors, which allow more 5-HT to interact at postsynaptic 5-HT$_{1A}$ sites.[7] In addition, trazodone blocks histaminergic and α-adrenergic receptors, and nefazodone possesses weak NRI and α-adrenergic blocking properties.[7]

Table 38–3

Efficacy and Adverse Effect Profile Based on Pharmacology[7,9]

Pharmacologic Action	Result
SRI	Antidepressant and antianxiety efficacy (via interaction of 5-HT at 5-HT$_{1A}$ receptors) Anxiety, insomnia, sexual dysfunction (via interaction of 5-HT at 5-HT$_{2A}$ receptors) Anxiety, anorexia (via interaction of 5-HT$_{2C}$ receptors) Nausea, GI problems (via interaction of 5-HT at 5-HT$_3$ receptors)
NRI	Antidepressant efficacy Tremor, tachycardia, sweating, jitteriness, increased blood pressure
Dopamine reuptake inhibition	Antidepressant efficacy, euphoria, psychomotor activation, aggravation of psychosis
α_2-Adrenergic receptor blockade	Increase in serotonergic and noradrenergic activity—see actions of SRI and NRI above
Serotonin$_{1A}$ receptor agonist	Antianxiety, antidepressant augmentation, decreased blood pressure
Serotonin$_{1A}$ partial agonism	Antianxiety, antidepressant augmentation, decreased blood pressure, decreased heart rate
Serotonin$_{2A}$ receptor blockade	Antianxiety efficacy Increased REM sleep; decreased sexual dysfunction
Serotonin$_{2C}$ receptor blockade	Antianxiety efficacy Increased appetite or weight gain
Serotonin$_3$ receptor blockade	Antiemetic, decreased GI problems
Serotonin$_7$ receptor blockade	Antidepressant, modulates glutamate
α_1-Adrenergic receptor blockade	Orthostatic hypotension, dizziness, reflex tachycardia
Histamine-1 receptor blockade	Sedation, weight gain
Muscarinic cholinergic receptor blockade	Dry mouth, blurred vision, constipation, urinary hesitancy, sinus tachycardia, memory problems

GI, gastrointestinal; 5-HT, serotonin; NRI, norepinephrine reuptake inhibition; REM, rapid eye movement; SRI, serotonin reuptake inhibition.

▶ *Miscellaneous*

Vilazodone is best characterized pharmacologically as an SRI and a partial agonist at 5-HT_{1A} receptors. The 5-HT_{1A} effect is thought to reduce negative feedback on endogenous serotonin receptors which may improve the medication's antidepressant effect.[7] Vortioxetine is an agonist/antagonist/partial agonist at various 5-HT receptors.[20] Vortioxetine has affinity for β-adrenergic receptors which may be associated with side effects, and histaminic and acetylcholinergic receptors which may have a positive effect on memory.[20] Finally, mirtazapine is a **noradrenergic** and specific serotonergic antidepressant. It blocks presynaptic α_2 **autoreceptors** on noradrenergic neurons and **heteroreceptors** on serotonergic neurons, resulting in increases in NE and 5-HT synaptic concentrations.[7] Mirtazapine also blocks postsynaptic serotonergic receptors and histamine-1 receptors at lower doses inducing sleep and weight gain. At higher doses histaminic activity is offset by noradrenergic activity which reduces its effects on sleep and weight gain.[7,21]

▶ *Monoamine Oxidase Inhibitors*

MAOIs inhibit the enzyme responsible for the breakdown of 5-HT, NE, and DA.[7] There are two main forms of the MAO enzyme—MAO-A and MAO-B.[7] MAO-A and MAO-B are both located in the brain and MAO-A is also present in the gut. MAO-A is responsible for the breakdown of 5-HT, DA, NE, and tyramine.[7] MAO-B is responsible for the breakdown of dopamine, phenylethylamine, and tyramine.[7] Dietary restrictions limiting the consumption of tyramine are necessary for orally available MAOIs due to inhibition of MAO-A in the gut.[7] Dietary restrictions are not required for the transdermal formulation of selegiline at the starting dose of 6 mg/24 hours.[7]

▶ *Tricyclic Antidepressants*

The TCAs possess both SRI and NRI properties, but they also block other receptors, including α_1-adrenergic, histamine-1, and muscarinic cholinergic receptors, which contribute to side effects.[7]

Complementary and Alternative Treatments

St. John's wort (*hypericum perforatum*) is an herbal medication that has shown efficacy in mild to moderate depression, but minimal efficacy for moderate to severe depression.[14] It has mild MAO-inhibiting properties.[22] Many patients believe that herbal medications are devoid of adverse effects and drug interactions; however, St. John's wort can cause gastrointestinal (GI) irritation, headache, fatigue, and nervousness. It also triggers drug interactions through induction of CYP3A4 enzymes, as well as P-glycoprotein.[22] The safety and efficacy of St. John's wort combined with standard antidepressant medications remains unknown.[14,22]

Levels of s-adenosyl methionine (SAM-e), a naturally occurring compound in the body, tends to be lower in people with major depression.[23] It is sold as a nutritional supplement and lacks the standardization of medications that are FDA approved.

Low folate levels are associated with a greater risk of depression or a lack of response to antidepressants.[14] Because folic acid prevents neural tube defects in pregnancy and causes few to no adverse effects, it may be used in doses of 0.4 to 1 mg/day to improve the efficacy of the antidepressants.[14] L-methylfolate is the active metabolite of folate and is a prescription medical food approved for use in MDD along with an antidepressant.[18,24]

Low doses of omega-3 fatty acids (eicosapentaenoic, docosahexaenoic acid, or both) have been used adjunctively for major depression.[25] More studies are needed to establish their role in MDD.[14,25]

Adverse Effects

The adverse effects of the antidepressants are often a function of their underlying pharmacologic profiles (see Table 38–3).

The adverse effect profile of the SSRIs includes sexual dysfunction (eg, delayed or absent orgasms), CNS stimulation (eg, nervousness and insomnia), GI disturbances (eg, nausea and diarrhea), weight gain, anhedonia, and fatigue.[19] CNS stimulation, GI disturbances, headache, and fatigue are often transient and improve with time.[7] KEY CONCEPT Sexual dysfunction, common and challenging to manage, may lead to nonadherence.[26] Various strategies to manage antidepressant-induced sexual function include waiting for symptoms to subside, reducing the dosage, permitting periodic "drug holidays," prescribing adjunctive therapy, and switching antidepressants.[14,26] Some patients, however, report an improvement in sexual functioning as a result of improvement in depressive symptoms.[26] Reducing the dose and using drug holidays may weaken the antidepressant effects.[26] Clinicians often prescribe adjunctive therapy such as dopaminergic drugs (eg, bupropion), 5-HT_2 antagonists (eg, cyproheptadine), and phosphodiesterase inhibitors (eg, sildenafil) or simply switch to antidepressants with less likelihood of causing these effects, such as bupropion, mirtazapine, nefazodone, or vortioxetine.[26]

Bupropion causes insomnia, nightmares, decreased appetite, anxiety, and tremors, but the most concerning adverse effect is **seizures**.[14,19] Because of the risk for seizures, patients with a CNS lesion, history of seizure disorder, head trauma, anorexia, or bulimia should not receive bupropion.[14,24] The total daily dose of bupropion should not exceed 450 mg/day (immediate release and extended release), and any single dose of the immediate-release formulation should not exceed 150 mg.[24] The maximum dose of sustained release is 200 mg twice daily.[24] Insomnia and/or nightmares often respond to moving the last daily dose from bedtime to late afternoon.

The adverse effects of the SNRIs are similar to those of the SSRIs.[14] Nausea can be troublesome with venlafaxine and desvenlafaxine, which sometimes necessitates using lower starting doses and giving the medication with food.[14] A dose-related elevation in blood pressure can occur at higher doses, and blood pressure monitoring should be conducted for patients receiving venlafaxine or desvenlafaxine.[14] Duloxetine should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease owing to the potential for hepatic injury.[24]

Trazodone causes sedation, and it is used more often as an adjunct with other antidepressants for sleep than as an antidepressant.[14] **Priapism** is a rare but serious adverse effect in men taking trazodone.[14] There have been no reported cases of priapism with nefazodone.[14] Unfortunately, nefazodone has been associated with development of fatal **hepatotoxicity**, which led to a black-box warning and significant reduction in its use.[14]

Mirtazapine can cause sedation and weight gain by blocking histamine-1 receptors.[7] Despite being partially a serotonergic drug, it rarely causes serotonergic-related adverse effects because it also blocks various postsynaptic 5-HT receptors.[7] Although it carries a bolded warning for neutropenia due to a handful of cases reported during clinical trials, it is questionable whether neutropenia is more problematic with mirtazapine than other antidepressants.[14,27]

The TCAs cause sedative, anticholinergic, and cardiovascular adverse effects.[7] Although adverse effects are common, they can be serious in some cases. The tertiary TCAs (eg, amitriptyline, imipramine) are more sedating and anticholinergic than the secondary TCAs (eg, desipramine, nortriptyline).[14] The TCAs

Table 38–4

Relative Incidence of Adverse Effects of Newer Antidepressants[7,9]

Drug	Sedation	Activation	Weight Gain	Weight Loss	GI Upset	Sexual Dysfunction
Bupropion	+	++++	+	++	+++	+
Citalopram	+	+	+	+	++++	++++
Desvenlafaxine	++	+++	+	+	++++	++++
Duloxetine	+	+++	+	+	+++	++++
Escitalopram	+	++	+	+	++	++++
Fluoxetine	+	++++	+	+	++++	++++
Fluvoxamine	++	++	+	+	++++	++++
Levomilnacipran	+	+++	+	+	++	+
Mirtazapine	+++	+	++	+	+	+
Nefazodone	++	+	+	+	++	+
Paroxetine	++	++	+	+	++++	++++
Sertraline	+	+++	+	+	++++	++++
Venlafaxine	++	+++	+	+	++++	++++
Vilazodone	+	+	+	+	++++	++
Vortioxetine	+	+	+	+	++++	+

+, minimal; ++, low; +++, moderate; ++++, high; GI, gastrointestinal.

have a quinidine-like effect on the heart, which makes them toxic in overdose.[7] The average lethal dose of a TCA can occur with as little as 15 mg/kg in a young adult which is typically less than a 1-month supply.[19]

The relative incidence of adverse effects among the newer antidepressants is shown in Table 38–4.

Pharmacokinetic Parameters

Pharmacokinetic parameters related to the newer antidepressants are shown in Table 38–5. Several antidepressants are not highly protein bound; the most notable of these are venlafaxine, desvenlafaxine, and levomilnacipran.[24] The elimination half-lives of paroxetine, nefazodone, and venlafaxine are relatively short compared with the other agents.[24,28] Conversely, fluoxetine has a very long half-life (ie, 4–6 days) with chronic dosing, and its active metabolite (norfluoxetine) has an even longer half-life.[14,24] Because of this, a 5-week washout of fluoxetine is required before starting an MAOI, whereas a 2-week washout is generally considered sufficient for other serotonergic agents.[14] Several antidepressants have notable active metabolites including

Table 38–5

Pharmacokinetic Parameters of Newer Antidepressants[14,24,33]

Drug	Protein Binding (%)	Elimination Half-Life (hours)	Active Metabolite	Cytochrome P450	
				Substrate	Inhibitor
Bupropion	84	14–21	Yes	2B6	2D6 (+++)
Citalopram	80	35	Yes	3A4, 2C19	2D6 (+)
Desvenlafaxine	30	10–11.1	No	3A4 (minor)	2D6 (+)
Duloxetine	90	8–17	No	1A2, 2D6	2D6 (+++)
Escitalopram	56	27–32	No	3A4, 2C19	2D6 (+)
Fluoxetine	95	4–6 days with chronic dosing; 4–16 days (active metabolite)	Yes	2D6	2C (++) 2D6 (++++) 3A4 (++)
Fluvoxamine	80	15.6	No	None	1A2 (++++), 2C (++), 2D6 (+), 3A4 (+++)
Levomilnacipran	22	12	No	3A4	0
Mirtazapine	85	26 (males)–37 (females)	Yes	1A2, 2D6, 3A4	0
Nefazodone	99	2–4	Yes	None	3A4 (++++)
Paroxetine	93–95	15–21	No	2D6	2D6 (++++)
Selegiline	90	18–25	Yes	2B6, 2C9, 3A4/5	0
Sertraline	98	26	Yes	2C19, 2D6	2C (++), 2D6 (+), 3A4 (+)
Venlafaxine	27–30	5	Yes	2D6	2D6 (+)
Vilazodone	96–99	25	No	3A4	0
Vortioxetine	98	66	No	2D6, 3A4/5, 2C9, 2C19, 2A6, 2C8, 2B6	0

++++, high; +++, moderate; ++, low; +, very low; 0, absent.

amitriptyline (nortriptyline), imipramine (desipramine), and venlafaxine (desvenlafaxine), which have all been approved separately for the treatment of depression. Other antidepressants such as sertraline and citalopram also have active metabolites, but these metabolites (desmethylsertraline and desmethylcitalopram, respectively) are only about one-eighth as potent as the parent compounds for SRI activity.[29]

Drug Interactions

LO 6

Antidepressant drug interactions can be pharmacokinetic or pharmacodynamic resulting in a variety of drug-related problems. The usual pharmacodynamic drug interactions involve the "dirty receptors" blocked by some antidepressants (eg, H1, muscarinic).[7] TCAs can cause significant additive effects with other drugs that cause sedation, hypotension, or anticholinergic effects.[7,14] Similarly, trazodone can interact with other drugs that cause hypotensive and sedative effects.[14] By far, the most concerning pharmacodynamic interactions are hypertensive crisis and serotonin syndrome, which are both life-threatening. Hypertensive crisis is characterized by sharply elevated blood pressure, occipital headache, stiff or sore neck, nausea, vomiting, and sweating.[14] It may result during MAOI therapy if the patient takes a **sympathomimetic** drug, such as ephedrine, pseudoephedrine, phenylephrine, or **stimulants** such as amphetamines or methylphenidate or if the patient consumes foods rich in tyramine, such as tap beers, aged cheeses, fava beans, yeast extracts, liver, dry sausage, sauerkraut, or tofu.[14,30] There are extensive lists of foods and drinks that are not permitted during therapy with MAOIs, and these should always be provided to patients.[30] Because many over-the-counter (OTC) products contain sympathomimetics, patients should always be told to consult with their pharmacist or other clinician before using these drugs.[14]

Serotonin syndrome is characterized by confusion, restlessness, fever, abnormal muscle movements, hyperreflexia, sweating, diarrhea, and shivering.[31] It may result when a serotonergic agent is added to any other serotonergic agent, but the MAOIs are strongly associated with severe cases of serotonin syndrome.[31] Serotonin syndrome is complicated by (a) an unawareness by clinicians of the diagnosis and (b) the fact that many implicated drugs are not serotonergic in nature, such as dextromethorphan, meperidine, tramadol, linezolid, and methylene blue.[32]

Many antidepressants inhibit cytochrome P450 isoenzymes, elevating plasma levels of substrates for those isoenzymes and potentially leading to adverse effects or toxicity (see Table 38–5).[33]

Dosing

Antidepressant dosing is summarized in Table 38–6.[14,24,28] The extended release formulations of venlafaxine and bupropion allow for once daily dosing.[19] The delayed-release capsule of fluoxetine can be given weekly, which can be started 7 days after the last regular-release capsule or tablet.[24] Selegiline is available as a transdermal patch, and a dose of 6 mg/24 hours can be used without the usual dietary restrictions associated with MAOI use, although patients on the higher doses (9 and 12 mg/24 hours) should follow usual MAOI dietary restrictions.[14] Liquid dosage forms and disintegrating tablets of various antidepressants are ideal for patients who have difficulty swallowing tablets or capsules.

The starting dose is within usual therapeutic dosage range for most SSRIs, desvenlafaxine, duloxetine, and mirtazapine, but there is usually a need for at least some titration of venlafaxine, vilazodone, vortioxetine, bupropion, sertraline, levomilnacipran, nefazodone as well as TCAs.[14] A common first step in the management of partial response to an antidepressant is to optimize the dose even if the initial starting dose is within the therapeutic range.[14] An advantage of TCAs is that plasma levels may be used to help guide dosing, especially for those that have well-defined therapeutic plasma level ranges, including nortriptyline (50–150 ng/mL [190–570 nmol/L]).[28]

Efficacy of Pharmacotherapy

KEY CONCEPT Each antidepressant has a response rate of approximately 50% to 75%, and no antidepressant medication or class has been reliably shown to be more efficacious than another.[14] There is some evidence that dual-action antidepressants, such as TCAs and SNRIs, may be more effective in patients with severe depression than the single action drugs such as the SSRIs, but the more general assertion that multiple mechanisms of action confer efficacy advantages is controversial.[14]

Selection of Medication

LO 4

Figure 38–1 depicts an algorithm based on the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder and the Veterans Affairs/Department of Defense Clinical Practice Guideline for the Management of Major Depressive Disorder.[14,34] As depicted in the algorithm, the guidelines recommend the use of SSRI, SNRI, bupropion, or mirtazapine as a first-line treatment for patients with mild to severe depression.[14,34] Patients with mild depression may be managed with psychotherapy alone.[14,34]

Various factors must be taken into account when selecting antidepressant therapy for a particular patient. The most reliable predictor of response is the patient's history of response (eg, efficacy, side effects, and overall satisfaction) to antidepressants.[14] To a lesser extent, the history of a first-degree relative's response to antidepressants may be used to predict a patient's response.[14] Adverse effect profiles should be considered, because adherence is influenced by tolerability.[19] The patient is the best source of information regarding acceptability of adverse effects. Patients should be educated about how to manage side effects (eg, using sugarless chewing gum, hard candy, or ice chips for dry mouth). The clinician must anticipate and be vigilant for potential drug–drug interactions and drug–disease interactions. For instance, a patient with a seizure disorder would be an inappropriate candidate for bupropion therapy. The presence of comorbid psychiatric conditions can suggest the best antidepressant to choose. For example, an SSRI can treat both MDD and panic disorder, obviating the need for two separate medications. Likewise, a patient with MDD and a chronic pain condition may be treated with an SNRI with efficacy for both conditions. The potential for accidental or intentional overdose must be considered. Patients with a risk of accidental or intentional overdose should not be prescribed TCAs. Additionally, affordability of the medication influences drug selection.

Time Course of Response

LO 5

Antidepressants do not produce an immediate clinical response. Improvement in physical symptoms, such as sleep, appetite, and energy, can occur within the first or second week of treatment. KEY CONCEPT Although a meta-analysis suggests earlier effects of antidepressant treatment, it is widely accepted that approximately

Table 38–6

Dosing of Antidepressants in Adults[14,24,28]

Generic Name	Brand Name	Generic	Form	Initial Dose (mg/day)	Usual Dosing Range (mg/day)	Usual Dosage Schedule	Renal Dosing Adjustment	Hepatic Dosing Adjustment
MAOIs								
Phenelzine	Nardil	Yes	T	15	45–90	Three times daily	None	None
Selegiline	Emsam	No	TD	6	6–12	Once daily	None	None
Tranyl-cypromine	Parnate	Yes	T	10	30–60	Twice daily	None	None
Isocarboxazid	Marplan	No	T	20	40–60	Twice daily	None	None
TCAs								
Amitriptyline	Elavil	Yes	T	25–50	100–300	Once or twice daily	None	Use with caution
Desipramine	Norpramin	Yes	T	25–50	100–300	Once to four times daily	None	Use with caution
Doxepin	Sinequan[a]	Yes	C, Sol, T	25–50	100–300	Once to three times daily	Use with caution	Use a lower dose
Imipramine	Tofranil	Yes	C, T	25–50	100–300	Once daily or divided doses	Use with caution	Use a lower dose
Nortriptyline	Pamelor	Yes	C, Sol	25	50–150	Once or twice daily	Use with caution	Use a lower dose
SSRIs								
Citalopram	Celexa	Yes	Sol, T	20	20–40[b]	Once daily	No adjustment for CrCl > 20 mL/min (0.33 mL/s); for CrCl < 20 mL/min (0.33 mL/s), use with caution	20 mg/day maximum
Escitalopram	Lexapro	Yes	Sol, T	10	10–20	Once daily	No adjustment for CrCl > 20 mL/min (0.33 mL/s); for CrCl < 20 mL/min (0.33 mL/s), use with caution	10 mg/day
Fluoxetine	Prozac	Yes	C, T	10–20	20–80	Once daily	None	Use lower or less frequent dosing
	Prozac weekly	Yes	C	20	80	Once weekly	None	Use lower or less frequent dosing
Fluvoxamine	Luvox[a]	Yes	T	50	50–300	Twice daily	None	Reduce dose
	Luvox CR	Yes	C	100	100–300	Once daily	None	Reduce dose
Paroxetine	Paxil	Yes	T	10–20	20–50	Once daily	In CrCl < 30 mL/min (0.5 mL/s), initial dose 10 mg/day; increase weekly to a dose of 40 mg/day or less	Severe impairment, initial dose 10 mg daily; increase weekly to dose of 40 mg/day
	Paxil CR	Yes	Sus, T	12.5–25	25–62.5	Once daily	In CrCl < 30 mL/min (0.5 mL/s), initial dose 12.5 mg daily; may increase weekly to a dose of 50 mg/day or less	Severe impairment, initial dose 12.5 mg daily, increase weekly to dose of 50 mg/day or less
Sertraline	Zoloft	Yes	Sol, T	25–50	50–200	Once daily	None	Use a lower dose

(*Continued*)

Table 38–6

Dosing of Antidepressants in Adults[14,24,28] (*Continued*)

Generic Name	Brand Name	Generic	Form	Initial Dose (mg/day)	Usual Dosing Range (mg/day)	Usual Dosage Schedule	Renal Dosing Adjustment	Hepatic Dosing Adjustment
NDRI								
Bupropion	Wellbutrin	Yes	T	150	300–450[c] (max single dose is 150 mg)	Twice to three times daily (separated by 6 hours)	Consider lower dose	75 mg/day
	Wellbutrin SR	Yes	T	150	300–400[c] (max single dose is 200 mg)	Twice daily (separated by 8 hours)	Consider lower dose	100 mg/day or 150 mg every other day
	Wellbutrin XL	Yes	T	150	300–450[c]	Once daily	Consider lower dose	150 mg every other day
SNRIs								
Des-venlafaxine	Pristiq	Yes	XR T	50	50–100	Once daily	CrCl 30–50 mL/min (0.5–0.84 mL/s), 50 mg maximum daily dose; CrCl < 30 mL/min (0.5 mL/s), 50 mg every other day	100 mg/day maximum
Duloxetine	Cymbalta	Yes	DR C	40–60	60–120	Once to twice daily	Use lower dose; not recommended for CrCl < 30 mL/min (0.5 mL/s)	Not recommended for chronic liver disease or cirrhosis
Venlafaxine	Effexor[a]	Yes	T	37.5–75	75–375[c]	Once, twice or three times daily	Reduce dose 25%–50%	Reduce dose by 50% or more
	Effexor XR	Yes	C, T	37.5–75	75–225[c]	Once daily	Reduce dose 25%–50%	Reduce dose by 50%
Levo-milnacipran	Fetzima	No	XR C	20	40–120	Once daily	CrCl < 60 mL/min (1.0 mL/s), 80 mg/day maximum; CrCl < 30 mL/min (0.5 mL/s), 40 mg/day maximum	None
SARIs								
Nefazodone	Serzone[a]	Yes	T	100–200	300–600	Twice daily	Use with caution	Do not use; Discontinue if ALT/AST is more than three times normal
Trazodone	Desyrel[a]	Yes	T	50	150–300 (max 600)	Three times daily	Use with caution	Use with caution
NaSSA								
Mirtazapine	Remeron	Yes	ODT, T	15	15–45	Once daily	CrCl < 40 mL/min (0.67 mL/s), 30% decreased clearance CrCl < 10 mL/min (0.17 mL/s), 50% decreased clearance	Clearance decreased by 30%; monitor closely

(*Continued*)

Table 38–6

Dosing of Antidepressants in Adults[14,24,28] (*Continued*)

Generic Name	Brand Name	Generic	Form	Initial Dose (mg/day)	Usual Dosing Range (mg/day)	Usual Dosage Schedule	Renal Dosing Adjustment	Hepatic Dosing Adjustment
SRI/5-HT$_{1A}$								
Vilazodone	Viibryd	No	T	10	20–40[c]	Once daily with food	None	Use with caution
Vortioxetine	Trintellix	No	T	10	20[c]	Once daily	None	None

[a]Brand no longer available in the United States.

[b]Maximum dose is 40 mg/day.

[c]Upper limit of this range is the maximum dose.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, capsule; CrCl, creatinine clearance; DR, delayed release; MAOI, monoamine oxidase inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NDRI, norepinephrine and dopamine reuptake inhibitor; ODT, orally disintegrating tablet; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; Sol, solution; SRI/5-HT$_{1A}$, partial agonist-serotonin reuptake inhibitor/serotonin$_{1A}$ partial agonist; SSRI, selective serotonin reuptake inhibitor; Sus, suspension; T, tablet; TCA, tricyclic antidepressant; TD, transdermal; XR, extended release.

2 to 4 weeks of treatment is required before improvement is seen in emotional symptoms such as sadness and anhedonia. As long as 6 to 8 weeks may be required to see full antidepressant effects.[14,35]

Managing Partial or No Response

Approximately one-third of patients with MDD do not respond satisfactorily to their first antidepressant medication.[36] In such cases, the clinician must evaluate the adequacy of antidepressant

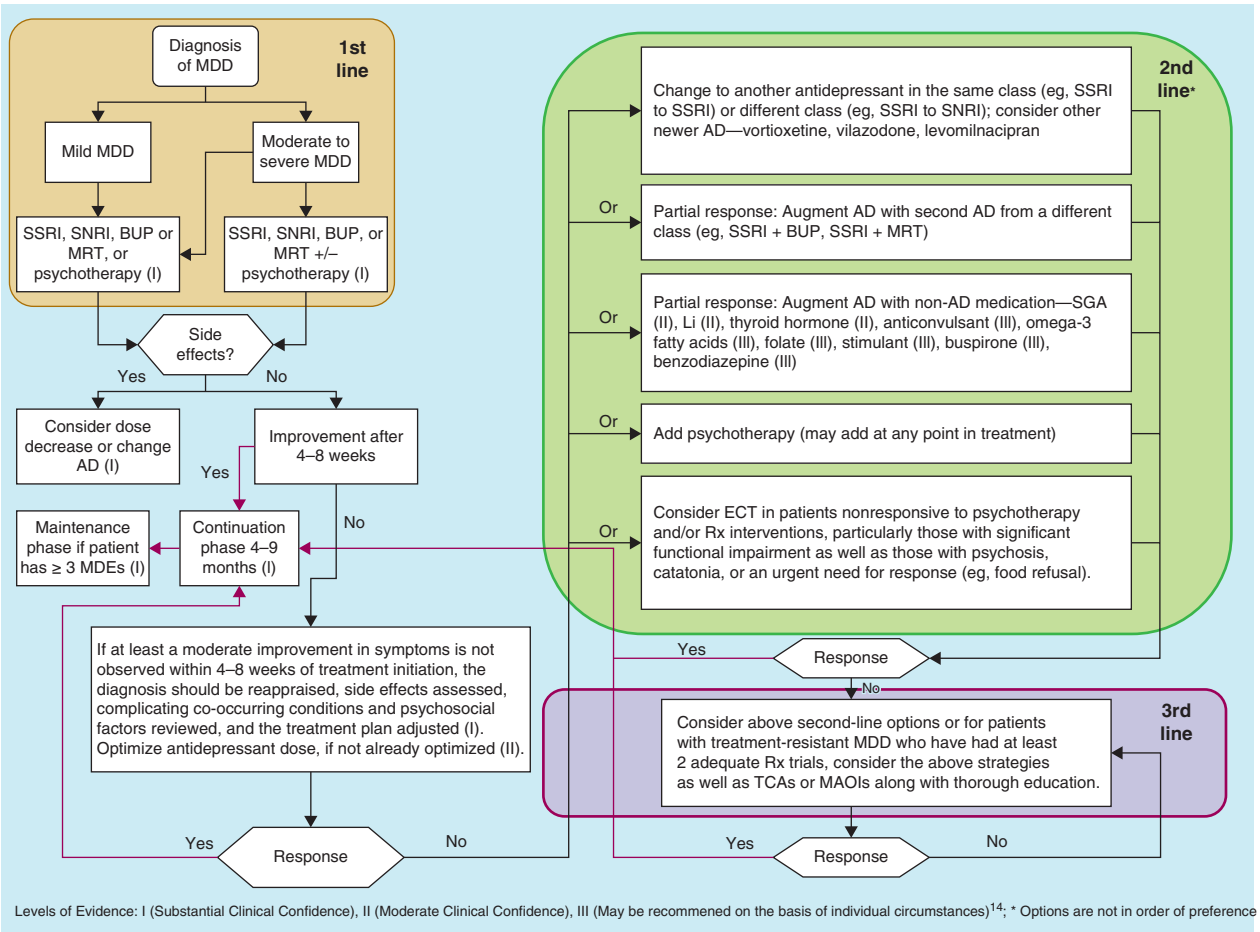

FIGURE 38–1. Algorithm based on the American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder[14] and VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder.[34] (AD, antidepressant; BUP, bupropion; ECT, electroconvulsive therapy; Li, lithium; MAOI, monoamine oxidase inhibitor; MDE, major depressive episode; MRT, mirtazapine; Rx, prescription; SGA, second-generation antipsychotic; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant).

therapy, including dosage, duration, patient adherence, verification of the patient's diagnosis, and reconsideration of clinical factors that could be impeding successful therapy, such as concurrent medical conditions (eg, thyroid disorder), comorbid psychiatric conditions or substance use disorders (eg, alcohol abuse), and psychosocial issues (eg, marital stress).[14]

A series of reports from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial revealed that remission is associated with a better overall prognosis than improvement alone.[3] STAR*D also established that in patients with a greater level of nonresponse to treatment, clinicians are less likely to push the patient to achieve remission, and in addition, those patients with the greatest levels of nonresponse had the highest rates of relapse.[3] STAR*D established some successful treatment recommendations. For patients experiencing a partial response, extending the medication trial and/or using higher doses within the recommended dosage range may be helpful.[3] Another option used in the STAR*D trials is augmentation therapy, that is adding a nonantidepressant such as lithium, buspirone, or triiodothyronine.[3]

Second-generation antipsychotics, aripiprazole, brexpiprazole, and the extended-release formulation of quetiapine are approved by the FDA for adjunctive treatment of MDD along with an antidepressant and are often added to an antidepressant in cases of partial or nonresponse.[18,37] Efficacy has been suggested for dopaminergic drugs (eg, pramipexole) psychostimulants (eg, methylphenidate), anticonvulsants (eg, lamotrigine), and modafinil although the evidence is less for these agents.[14,18] A third option is combination therapy, whereby another antidepressant, typically from a different pharmacologic class, is added to the first antidepressant.[18] Examples include combining bupropion or mirtazapine with SSRIs or SNRIs.[7] Switching to a different antidepressant is a common strategy for patients who have had no response to initial antidepressant therapy, but also is acceptable in cases of partial response.[14] Relative to augmentation or combination therapy, advantages of switching include improved adherence, decreased costs, and less concern over drug–drug interactions. Disadvantages include loss of time, exacerbation of illness, and loss of any improvement seen with the initial drug. When switching from one antidepressant to another, clinicians may choose to stay within the same class (eg, sertraline to fluoxetine) or go outside of the class (eg, paroxetine to venlafaxine). The olanzapine-fluoxetine combination, Symbyax, is also approved for treatment-resistant depression.[18,37]

Nonpharmacologic interventions in cases of treatment nonresponse include adding or changing to psychotherapy or initiating ECT.

Duration of Therapy

Treatment of MDD encompasses three phases: acute, continuation, and maintenance (Figure 38–2).[38] The goal of antidepressant therapy is remission of MDE symptoms.[14] This acute phase of treatment typically lasts 6 to 12 weeks.[14] KEY CONCEPT Because the typical MDE lasts 6 months or longer, if antidepressant therapy is interrupted after the acute phase, the patient may relapse into a depressive episode.[14] When treating the first depressive episode, antidepressants must be given for an additional 4 to 9 months in the continuation phase to prevent relapse.[14]

Maintenance treatment takes place after the normal course of an MDE to prevent recurrence, which is the development of future episodes.[14] This phase can last for years, or for a lifetime.[14] Although patients who have an MDE should receive acute and continuation treatment, not all of them require maintenance treatment, because not all patients experience multiple MDEs.[14] In some patients with multiple episodes, many years may separate the episodes.[14] Therefore, the clinician must consider various factors in determining whether an individual requires maintenance treatment. A major factor is the number of prior episodes experienced by the patient. The more prior episodes experienced, the higher the risk for future episodes. After three or more MDEs, patients are generally given lifelong maintenance treatment because of the high (ie, 90%) chance of experiencing additional episodes.[13,14] Other factors to consider are the severity of previous episodes, if suicide attempts were made, whether psychotic features were present, and patient preference.[14] The dose of the antidepressant required in the acute phase of treatment should be sustained during the continuation and maintenance phases.[14]

Discontinuing Therapy

When discontinuing therapy, it is best to gradually taper the antidepressant for two reasons. First, almost all antidepressants can produce withdrawal syndromes if discontinued abruptly or tapered too rapidly, especially antidepressants with shorter half-lives (eg, venlafaxine, paroxetine, and fluvoxamine).[39] Withdrawal syndromes can cause sleep disturbances, anxiety, fatigue, mood changes, malaise, GI disturbances, and a host of other symptoms

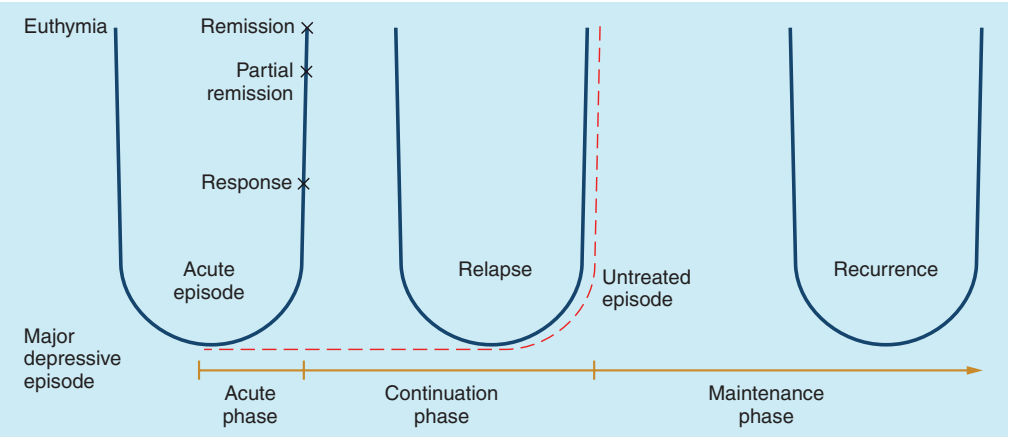

FIGURE 38–2. The course of depression and phases of treatment. Data from Refs. 7, 14.

which often are confused with depressive relapse or recurrence.[39] In general, the dose of the antidepressant should be tapered by no more than 25% per week to minimize the risk of withdrawal symptoms.[28] Tapering and discontinuation can be completed over 2 to 3 months.[28] Second, depressive symptoms may return upon taper or discontinuation of the antidepressant.[39] So, if the medication is gradually tapered, then early signs of depression can be countered with a return to the original dosage and a potentially quicker response.[39] Depending on the patient's illness and the clinical circumstances, tapering of the antidepressant can be extended for weeks or even months because of the concern over relapse or recurrence.

Special Considerations

▶ *Pregnant or Breastfeeding Patients*

Depression is quite common in pregnancy, especially for women with a history of recurrent depression.[14] Untreated depression carries risks for both the fetus and the mother. Likewise antidepressants have reported risks.[14] As such, both maternal and fetal well-being must be considered when weighing risks and benefits of antidepressant therapy during pregnancy.[14] Overall risk of teratogenicity with antidepressants after the first trimester appears to be low.[14] Paroxetine has been associated with an increased risk of cardiac malformations and should not be considered a first-line treatment in pregnant patients.[14] Fluoxetine has a long half-life and is more likely to be present at high levels in newborns after in utero exposure.[14] Antidepressant use late in pregnancy has been reported to occasionally cause perinatal sequelae, such as poor neonatal adaptation, feeding problems, and jitteriness.[14] Use of a single medication over multiple medications is favored in managing depression during pregnancy.[14] ECT may also be considered as a treatment option for pregnant patients.[14]

There is some drug exposure to the infant from nursing mothers who are taking antidepressants.[14] Although there have been rare anecdotal reports of adverse effects (ie, respiratory depression and seizure-like episodes) in infants exposed to antidepressants through breast milk, no rigorous study has confirmed this, and it is generally accepted that the benefits of breastfeeding outweigh the risks to the infant posed by antidepressant exposure.[14,40] However, the decision needs to be made on an individual basis.

▶ *Geriatric Patients*

Depression in older adults is underrecognized and undertreated.[14,41,42] Although not uncommon in community samples, MDD is prevalent among those living in long-term care facilities.[14] Barriers to recognition of geriatric depression include "masked" presentations, that is complaints of physical symptoms (eg, pain and GI problems) instead of mood symptoms, the frequent presence of medical illnesses, and the overlap of mood and cognitive symptoms with those of dementia.[41] Age-related pharmacokinetic and pharmacodynamic changes cause older patients to be more sensitive to antidepressant medications.[29] Thus, lower starting doses of antidepressants and slow upward titrations as tolerated are generally recommended for geriatric patients.[41] However, many older patients require the same dose as younger adult patients.[42] The SSRIs are chosen frequently for geriatric depression because of their overall favorable adverse effect profiles and low toxicity; most TCAs are avoided due to problematic anticholinergic, cardiovascular, and sedative properties.[42] The TCAs desipramine and nortriptyline are more tolerable in terms of these adverse effects and may be used in geriatric depression.[14] Other newer antidepressants, such as SNRIs, bupropion, vortioxetine, and mirtazapine, are alternatives for the treatment of geriatric patients.[42]

▶ *Pediatric Patients*

Antidepressant medications appear to be useful for certain children and adolescents, particularly those who have severe or psychotic depression, fail psychotherapy, or experience chronic or recurrent depression.[43] Fluoxetine and escitalopram are the only antidepressants FDA approved for depression in children younger than 18 years.[24] The SSRIs generally are considered the initial antidepressants of choice, but comorbid conditions may favor alternative agents.[43] "Behavioral activation" can occur with the SSRIs, including such symptoms as impulsivity, silliness, daring conduct, and agitation.[43]

All antidepressants have a black-box warning regarding the increase in the risk of suicidality (ie, suicidal thinking and behavior) in children and young adults.[44] A large analysis of clinical trials showed the risk of such events was 4% for antidepressants versus 2% for placebo, although no completed suicides occurred in the trials.[44] Following the addition of the black-box warning in 2003, prescriptions for antidepressants decreased among primary care providers by 58%.[45] The Centers for Disease Control and Prevention (CDC) estimated that suicide rates increased 8% in 2003 to 2004; however, a definite link between the black-box warning and increased suicide rates has not been conclusively determined.[45] Because antidepressants carry a black-box warning regarding suicidality, medication guides must be distributed with each prescription or refill of antidepressants.[44] KEY CONCEPT Patients 24 years and younger should be observed closely for suicidality, worsened depression, agitation, irritability, and unusual changes in behavior, especially during the initial few months of therapy and at times of dosage changes. Furthermore, families and caregivers should be advised to monitor patients for such symptoms.[44]

▶ *Suicidal Patients*

As previously discussed, patients younger than 24 have an increased risk of suicidal thoughts or behaviors with antidepressant medications. However, all patients receiving antidepressant medications should be monitored for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the first few months of drug therapy and at times of dosage changes.[44]

Whereas the TCAs and MAOIs have significant toxicity risk on overdose, most newer antidepressants are safer in overdose.[14]

Patient Counseling

LO 7

Major counseling points are outlined in Table 38–7. KEY CONCEPT Lack of patient understanding concerning optimal antidepressant

Patient Encounter Part 3

On the basis of information presented, create a care plan. Your plan should include: (a) a statement of the drug-related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

Table 38–7

Patient Counseling[14,49]

Counseling Point	Clinical Rationale
Mechanism of action—The medication works by affecting certain chemicals in the brain	Patient may feel that depression is a character weakness or personality flaw instead of a biological disorder
Lack of addiction potential—Although the medication affects certain chemicals in the brain, it is not addicting	Patient may worry that because the antidepressant is psychoactive, it must be addicting
Need for routine use—The medication will only work if it is taken as prescribed every day	Patient may try taking the medication on an as-needed basis
Delayed onset of action—It may take several weeks to see significant improvement in symptoms	Patient may prematurely discontinue therapy before the onset of beneficial effects
Prolonged duration of therapy—The medication should be taken for at least 6–12 months; do not discontinue it without consulting with the prescriber	Patient may prematurely discontinue therapy after symptoms have remitted, which could lead to relapse or recurrence
Adverse effects—Mention common and expected adverse effects as well as what to do if they occur	Patient may be more likely to discontinue therapy and distrust the prescriber if adverse effects occur without forewarning
Avoidance of alcohol and CNS depressants—Use of alcohol or other CNS depressants could cause worsened depression and additive adverse effects with the medicine	Patient may be unaware of the possible consequences of drinking alcohol or taking other drugs with antidepressants
Risk of suicidality—Be alert to symptoms of worsening depression and suicidality	Patient may become suicidal or have suicidal thinking while taking the antidepressant

CNS, central nervous system.

therapy frequently leads to partial or nonadherence with therapy; thus the primary purpose of antidepressant counseling is to enhance adherence and improve outcomes.[46] Patients should be educated that while they may see some improvement in some symptoms like sleep and appetite as early as the first week, generally at least 4 to 8 weeks is required for optimal mood changes to occur. Patients should also recognize common side effects including how long those side effects might last, and if there are any simple remedies for treatment (eg, using ice chips or sugarless gum for dry mouth).

OUTCOME EVALUATION

Symptom Assessment

LO 5

The patient interview should assess response of target symptoms. Rating scales are useful in this regard. The Hamilton Depression Scale (HAM-D) and the Montgomery Asberg Depression Rating Scale are clinician-rated scales often used in depression research studies to assess treatment efficacy.[14] The Patient Health Questionnaire (PHQ-9) is a 9-item depression scale that is patient-rated (Table 38–8).[14,47] A score of 4 or less would be considered normal

Table 38–8

Patient Health Questionnaire-9[47]

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not At All	Several Days	More Than Half the Days	Nearly Every Day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3
Trouble falling or staying asleep, or sleeping too much	0	1	2	3
Feeling tired or having little energy	0	1	2	3
Poor appetite or overeating	0	1	2	3
Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
Trouble concentrating on things, such as reading the newspaper or watching TV	0	1	2	3
Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Total Score = _____

Depression Severity, PHQ-9 Total Score: 1–4 minimal, 5–9 mild, 10–14 moderate, 15–19 moderately severe, 20–27 severe

If you checked any problems, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people?

	Not Difficult At All	Somewhat Difficult	Very Difficult	Extremely Difficult

Patient Care Process

Collect Information:

- Perform a medication history for antidepressant and other psychotropic drug use as well as nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the psychiatric history, medical history, physical assessment, laboratory findings, family history, and social history.
- Speak with the patient and review medical records to identify lifestyle habits, preferences, beliefs, health goals, and socioeconomic factors that may affect medication access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substances that could induce or worsen the depressive episode.
- Based on the psychiatric and medical history, determine whether the patient has any factors that would suggest the selection of certain antidepressants or adjunctive agents.
- Identify comorbidities associated with MDD.
- Evaluate relevant laboratory tests (eg, complete blood count [CBC], thyroid stimulating hormone [TSH], urine drug screen).
- Assess the efficacy, safety, and patient adherence with current pharmacotherapy.
- Identify any significant adverse drug effects or interactions.
- Determine whether the patient may benefit from nonpharmacologic therapy (ie psychotherapy, lifestyle modifications).

Develop a Care Plan:

- Based on discussions with the patient, determine whether a change in antidepressant therapy is warranted or if the addition of another antidepressant or nonantidepressant adjunctive agent is more appropriate.
- Select lifestyle modifications and depression nonpharmacologic and pharmacologic therapy that are likely to be effective and safe for the patient.
- Choose medications and doses that are optimal for the patient.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report any adverse effects that occur.
- Review the patient's practices for self-monitoring symptoms of depression as well as her support system.
- Address any patient concerns about depression and its management.
- Discuss importance of medication adherence and lifestyle modifications to manage symptoms of depression.
- Determine whether recommended agents are included on the institution's formulary and whether the patient has insurance coverage to continue medication as an outpatient.

Follow-up: Monitor and Evaluate:

- Follow-up every 2 to 4 weeks after changes in pharmacotherapy until the patient reaches remission then every 3 to 6 months.
- Review medication adherence as well rating scale assessment of patient's symptoms of depression and adverse effects.

mood and greater than 20 as severe depression.[14,47] The use of rating scales can improve treatment outcomes in the treatment of depression.[48]

Monitoring Adverse Effects

LO5 LO6

Adverse effects associated with the treatments for depression can often be predicted based on knowledge of pharmacologic profiles (Table 38–3) as well as familiarity with the most common adverse effects (Table 38–4). Evaluation for suicidal ideation should be a part of every patient visit. Patients can be taught to manage side effects such as sedation, constipation, and dry mouth. Potential side effects such as weight gain and sexual dysfunction should be discussed with the patient and monitored at each visit. SNRIs may increase blood pressure, and patients should have their blood pressure monitored regularly during treatment.[14] Patients with cardiovascular risk factors or over the age of 40 should have an electrocardiogram (ECG) completed prior to initiating a TCA.[14] Patients taking TCAs such as amitriptyline, imipramine, nortriptyline, or desipramine should have antidepressant serum levels checked if overdose, side effects, or nonadherence is an issue.[14] Patients should be monitored for serotonin syndrome if they are taking two or more serotonergic medications.[14,31]

Abbreviations Introduced in This Chapter

5-HT	Serotonin
BDNF	Brain-derived neurotrophic factor
CBC	Complete blood count
CNS	Central nervous system
DA	Dopamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
FDA	Food and Drug Administration
GI	Gastrointestinal
HAM-D	Hamilton Depression Rating Scale
HPA	Hypothalamic pituitary axis
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MDE	Major depressive episode
NaSSA	Noradrenergic and specific serotonergic antidepressant
NDRI	Norepinephrine and dopamine reuptake inhibitor
NE	Norepinephrine
NRI	Norepinephrine Reuptake Inhibitor
NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1

PHQ-9	Patient Health Questionnaire-9
SAM-e	S-adenosyl methionine
SARI	Serotonin antagonist and reuptake inhibitor
SNRI	Serotonin and norepinephrine reuptake inhibitor
SRI	Serotonin reuptake inhibition
SSRI	Selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TSH	Thyroid stimulating hormone
TCA	Tricyclic antidepressant
VEGF	Vascular endothelial growth factor
VNS	Vagus nerve stimulation
WHO	World Health Organization

REFERENCES

1. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet. 2009;374:609–619.
2. Bartholow M. Top 200 Drugs of 2012. Pharm Times. July 17, 2013.
3. Sinyor M, Schaffer A, Levitt A. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial: a review. Can J Psychiatry. 2010;55:126–135.
4. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095–3105.
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Association, 2013.
6. Depression. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed August 29, 2017.
7. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 4th ed. New York: Cambridge University Press; 2013.
8. Shyn SI, Hamilton SP. The genetics of major depression: moving beyond the monoamine hypothesis. Psychiatr Clin North Am. 2010;33:125–140.
9. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet. 2012;379:1045–1055.
10. Muscatell KA, Slavich GM, Monroe SM, Gotlib IH. Stressful life events, chronic difficulties, and the symptoms of clinical depression. J Nerv Ment Dis. 2009;197:154–160.
11. Goldberg D. The detection and treatment of depression in the physically ill. World Psychiatry. 2010;9:16–20.
12. Celano CM, Freudenreich O, Fernandez-Robles C, et al. Depressogenic effects of medications: a review. Dialogue Clin Neurosci. 2011;13:109–125.
13. Bulloch A, Williams J, Lavorato D, Patten S. Recurrence of major depressive episodes is strongly dependent on the number of previous episodes. Depress Anxiety. 2014;31:72–76.
14. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association, 2010.
15. Nussbaumer B, Kaminski-Hartenthaler A, Forneris CA, et al. Light therapy for preventing seasonal affective disorder. Cochrane Database Syst Rev. 2015;Nov 8(11): CD011269.
16. Blumberger DM, Mulsant BH, Daskalakis ZJ. What is the role of brain stimulation therapies in the treatment of depression? Curr Psychiatry Rep. 2013;15(7):368.
17. George MS, Post RM. Daily left prefrontal repetitive transcranial magnetic stimulation for acute treatment of medication-resistant depression. Am J Psychiatry. 2011;168:356–364.
18. McIntyre RS, Filteau M-J, Martin L, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. J Affect Disord. 2014;156:1–7.
19. Osuch E, Marais A. The pharmacological management of depression—update 2017. S Afr Fam Pract. 2017;59:6–16.
20. Citrome L. Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 2014;68:60–82.
21. Grasmäder K, Verwohlt PL, Kühn KU, et al. Relationship between mirtazapine dose, plasma concentration, response and side effects in clinical practice. Pharmacopsychiatry. 2005;30(30): 113–117.
22. Sarris J. St. John's wort for the teatment of psychiatric disorders. Psychiatr Clin North Am. 2013;36:65–72.
23. Carpenter DJ. St. John's wort and S-adenosyl methionine as "natural" alternatives to conventional antidepressants in the era of the suicidality boxed warning: what is the evidence for clinically relevant benefit? Altern Med Rev. 2011;16:17–39.
24. DRUGDEX® System [database online]. Greenwood Village, CO: Truven Health Analytics. Available from: http://www.micromedexsolutions.com/. Accessed August 28, 2017.
25. Appleton KM, Sallis HM, Perry R, et al. Omega-3 fatty acids for depression in adults. Cochrane Database Syst Rev. 2015;Nov 5(11):CD004692.
26. Baldwin DS, Manson C, Nowak M. Impact of antidepressant drugs on sexual function and satisfaction. CNS Drugs. 2015;29: 905–913.
27. Baghai TC, Zirngibl C, Heckel B, Sarubin N, Rupprecht R. Individualized pharmacological treatment of depressive disorders state of the art and recent developments. J Depress Anxiety. 2014;3:154.
28. Suehs B, Argo TR, Bendele SD, et al. Texas Medication Algorithm Project procedural manual: major depressive disorder algorithms. The Texas Department of State Health Services. 2008.
29. Boyce RD, Handler SM, Karp JF, Hanlon JT. Age-related changes in antidepressant pharmacokinetics and potential drug-drug interactions: a comparison of evidence-based literature and package insert information. Am J Geriatr Pharmacother. 2012;10:139–150.
30. Walker SE, Shulman KI, Tailor SA, Gardner D. Tyramine content of previously restricted foods in monoamine oxidase inhibitor diets. J Clin Psychopharmacol. 1996;16:383–388.
31. Boyer EW, Shannon M. The serotonin syndrome. New Engl J Med. 2005;352:1112–1120.
32. Tao R, Rudacille M, Zhang G, Ma Z. Changes in intensity of serotonin syndrome caused by adverse interaction between monoamine oxidase inhibitors and serotonin reuptake blockers. Neuropsychopharmacology. 2014;39:1996–2007.
33. Schellander R, Donnerer J. Antidepressants: clinically relevant drug interactions to be considered. Pharmacology. 2010;86: 203–215.
34. Department of Veterans Affairs and Department of Defense: The Management of MDD Working Group. VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder. 2016.
35. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry. 2005;66: 148–158.
36. Holtzheimer PE, Mayberg HS. Stuck in a rut: rethinking depression and its treatment. Trends Neurosci. 2011;34:1–9.
37. Thase ME. Adverse effects of second-generation antipsychotics as adjuncts to antidepressants. Psychiatr Clin North Am. 2016;39:477–486.
38. Bockting CLH, ten Doesschate MC, Spijker J, et al. Continuation and maintenance use of antidepressants in recurrent depression. Psychother Psychosom. 2008;77:17–26.

39. Fava GA, Gatti A, Belaise C, et al. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. Psychother Psychosom. 2015;84:72–81.
40. Boyce P, Galbally M, Snellen M, Buist A. Pharmacological management of major depression in pregnancy. In: Galbally M, Snellen M, Lewis A, eds. Psychopharmacology and Pregnancy. Berlin: Springer-Verlag Berlin Heidelberg; 2014:67–85.
41. Mukai Y, Tampi RR. Treatment of depression in the elderly: a review of the recent literature on the efficacy of single- versus dual-action antidepressants. Clin Ther. 2009;31:945–961.
42. Kok RM, Reynolds CF 3rd. Management of depression in older adults: a review. JAMA. 2017;317:2114–2122.
43. Birmaher B, Brent D. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. J Am Acad Child Adolesc Psychiatry. 2007;46:1503–1526.
44. Information by Drug Class—Antidepressant Use in Children, Adolescents, and Adults. U.S. Food and Drug Administration. Center for Drug Evaluation and Research; 2007. Available from: https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm161679.htm. Accessed May 18, 2018.
45. Morrison J, Schwartz TL. Adolescent angst or true intent? Suicidal behavior, risk, and neurobiological mechanisms in depressed children and teenagers taking antidepressants. Int J Emerg Ment Health. 2014;16:247–250.
46. Tursi MF, Baes C, Camacho FR, Tofoli SM, Juruena MF. Effectiveness of psychoeducation for depression: a systematic review. Aust N Z J Psychiatry. 2013;47:1019–1031.
47. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–613.
48. Morris DW, Trivedi MH. Measurement-based care for unipolar depression. Curr Psychiatry Rep. 2011;13:446–458.
49. Bollini P, Pampallona S, Kupelnick B, Tibaldi G, Munizza C. Improving compliance in depression: a systematic review of narrative reviews. J Clin Pharm Ther. 2006;31:253–260.

39 Bipolar Disorder

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LEARNING OBJECTIVES

LO

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

1. Explain the pathophysiologic mechanisms underlying bipolar disorder.
2. Recognize the symptoms of a manic episode and in patients with bipolar disorder.
3. Identify common psychiatric comorbidities of bipolar disorder.
4. Recognize the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*), criteria for bipolar disorder as well as the subtypes of bipolar I disorder, bipolar II disorder, and cyclothymic disorder.
5. List the desired therapeutic outcomes for patients with bipolar disorder.
6. Identify the optimal use of medications as first-line therapy in bipolar disorder, including appropriate dosing.
7. Recommend drug therapy for acute treatment of mania and depressive episodes.
8. Recommend baseline and routine monitoring for assessment of adverse effects of medications used in the treatment of bipolar disorder.
9. Identify general treatment differences for agents used to treat bipolar disorder in the pediatric population.
10. Explain why medication education is important for patients with bipolar disorder.

INTRODUCTION

Bipolar disorder is characterized by one or more episodes of mania or hypomania, often with a history of one or more major depressive episodes.[1] It is chronic, with recurrent episodes and remissions. Mood episodes can be manic, hypomanic, or depressed. Mood episodes can be further classified with features, like **mixed mood features**. They can be separated by periods of long stability or cycle rapidly. They occur with or without psychosis. Disability and other consequences (eg, increased risk of suicide) can be devastating to patients and families. Correct and early diagnosis and treatment are essential to prevent complications and maximize response to treatment.

EPIDEMIOLOGY

Bipolar disorders are categorized into bipolar I disorder, bipolar II disorder, and other specified and unspecified bipolar and related disorders. Bipolar I disorder is characterized by one or more manic episodes, whereas bipolar II disorder is characterized by at least one hypomanic episode. Both disorders also typically have major depressive episodes.

The lifetime prevalence of bipolar I disorder is estimated at 0.6% of US adults. The lifetime prevalence of bipolar II disorder is about 0.4%. When including the entire spectrum of bipolar disorders, the prevalence is approximately 3%.[2]

Bipolar I disorder affects men and women equally. Bipolar II, **rapid cycling** and mixed mood features are more common in women. In all, 78% to 85% of individuals with bipolar disorder report having another *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*), diagnosis during their lifetime. The most common comorbid conditions are anxiety, substance use disorder, and impulse control disorders. Medical comorbidities are also common.[2]

The mean age of onset is 20 years, although onset may occur in early childhood to the mid-40s.[1] If onset occurs after age 60, it is probably due to medical causes. An early onset is associated with greater comorbidities, more mood episodes, a greater proportion of days depressed, and greater lifetime risk of suicide attempts compared with later onset. Substance use and anxiety disorders are more common in patients with early onset. Patients with bipolar disorder have higher rates of suicidal thoughts, attempts, and completed suicides than the general population.

ETIOLOGY

The precise etiology is unknown. Thought to be genetically based, bipolar disorder is influenced by a variety of factors that may enhance gene expression. These include trauma, environmental factors, anatomical abnormalities, and exposure to chemicals or drugs.[3,4]

PATHOPHYSIOLOGY

Neurochemical

The pathophysiology of bipolar disorder remains incompletely understood. Imaging techniques such as positron emission tomography (PET) scans and functional magnetic resonance

Patient Encounter Part 1

Chief Complaint: "I went to my family physician after I wrecked my car. I told her I was fine but she insisted I see a psychiatrist."

HPI: Brad is a 34-year-old computer programmer who was evaluated by his primary care physician after running his car into a tree. Fortunately, he suffered no injuries and, since he had not had an annual physical for many years, examination and screening labs were obtained. Complete blood count, comprehensive metabolic profile, thyroid functions, chest X-ray, and electrocardiogram were normal with the exception of elevated creatinine at 2.3 mg/dL (203 µmol/L) and elevated blood urea nitrogen (BUN) at 40 mg/dL (14.3 mmol/L). Subsequent glomerular filtration rate (GFR) was decreased at 45 mL/min (0.75 mL/s). Brad does admit to increased nocturia, awakening him 3 to 4 times per night, as well as swelling of his hands and feet. Blood pressure on examination was elevated at 175/105 mm Hg.

Brad is a twice divorced, well-nourished, well-developed African American male appearing stated age. He is casually attired in jeans and shirt; however, his clothing is dirty and his shirt is untucked and wrinkled. His hair is long and uncombed and he is malodorous. He is unable to sit still and taps his foot and continually looks around the room during interview. Speech is pressured and loud, and patient frequently interrupts the examiner asking, "How much longer will this take? I'm going to Washington to meet the President and Buddha." He admits to increasing problems at work but states his boss does not appreciate his great talent. Although he has been an exemplary employee, over the past 2 weeks, he has made numerous mistakes on the job and has missed several days of work. He has spent his evenings going to various bars where he has been asked to leave due to getting into political arguments with patrons. He describes his mood as "spectacular" and states he is too busy to sleep. Brad recently attempted to buy an airplane "so I can get to Washington faster."

What diagnoses are suggested by this patient's presentation?

What additional information is needed to clarify the diagnosis (eg, differentiate between bipolar disorder and schizoaffective disorder)?

imaging (fMRI) are used to elucidate the cause. Historically, research focused on neurotransmitters such as norepinephrine (NE), dopamine (DA), and serotonin. One hypothesis is that bipolar disorder is caused by an imbalance of cholinergic and catecholaminergic activity. Serotonin is suggested to modulate catecholamines. Dysregulation of this relationship could cause mood disturbance. A variety of neurotransmitters are involved that interact with multiple neurochemical and neuroanatomic pathways.[3] The pathophysiology is also hypothesized based on the mechanisms of lithium and other drugs. Lithium, valproate, and carbamazepine all have similar effects on neuronal growth that are reversible by inositol, supporting a hypothesis that bipolar disorder may be related to inositol disturbance.[5] Brain-derived neurotrophic factor (BDNF) may play a role in bipolar disorder. Serum BDNF is low in mania and improves with treatment.[6]

LO 1

Genetic

Results of family studies suggest a genetic basis.[4] Lifetime risk of bipolar disorder in relatives of a bipolar patient is 40% to 70% for a monozygotic twin and 5% to 10% for other first-degree relatives.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis of Bipolar Disorder

KEY CONCEPT Patients presenting with depressive or elevated mood features and a history of abnormal or unusual mood swings should be assessed for bipolar disorder. Bipolar disorder is categorized into five subtypes: bipolar I (periods of major depressive, at least 1 manic episode, and/or hypomanic episodes); bipolar II (periods of major depressive and hypomanic episodes); cyclothymic disorder (periods of hypomanic episodes and depressive episodes that do not meet all criteria for diagnosis of a major depressive episode); other specified bipolar and related disorders; and unspecified bipolar and related disorders. The defining feature of bipolar disorder is one or more manic or hypomanic episodes in addition to depressive episodes that are not caused by a medical condition, substance use, or other psychiatric disorders.[1]

Initial and subsequent episodes are mostly depressive.[7] Studies show patients with bipolar I spend about 32% of weeks with depressive symptoms compared with 9% of weeks with manic or hypomanic symptoms.[8] Patients with bipolar II disorder spend 50% of weeks symptomatic for depression and only 1% with hypomania.[9] Because patients may present with depression and spend more time depressed than with mood elevation, bipolar disorder is often misdiagnosed or underdiagnosed. It is helpful to use a screening tool such as the mood disorder questionnaire.[10] *DSM-5* criteria for the diagnosis of major depressive, manic, and hypomanic episodes are summarized in Table 39–1.

LO 4

► *Bipolar I Disorder*

The diagnosis of bipolar I disorder requires at least one episode of mania for at least 1 week (or any duration if hospitalization due to symptoms is required). Mania is characterized by a persistently elevated, expansive, or irritable mood with related symptoms of increased goal-directed activity or energy including **grandiosity**, decreased need for sleep, excessive talkativeness, racing thoughts, **flight of ideas (FOI)**, distractibility, and a propensity to be involved in high-risk activities.[1] Bipolar I depression can be misdiagnosed as major depressive disorder (MDD); therefore, it is essential to rule out past episodes of hypomania or mania. If bipolar depression is mistaken for MDD and the patient is treated with antidepressants, it can precipitate a manic episode or induce rapid cycling.

LO 2

► *Bipolar II Disorder*

The distinguishing feature of bipolar II disorder is a current or past hypomanic episode and a current or past major depressive episode. Hypomanic symptoms last for at least 4 days, but fewer than 7 and include the same symptoms as mania without causing severe impairment or requiring hospitalization. Psychotic features are not present,[1] while irritability and anger are common. There cannot have been a prior full-manic episode.[1]

Table 39–1

Evaluation and Diagnosis of Mood Episodes

Diagnosis Episode	Impairment of Functioning or Need for Hospitalization[a]	*DSM-5* Criteria[b]
Major depressive	Yes	At least 2-week period of either depressed mood or loss of interest or pleasure in normal activities, associated with at least five of the following symptoms: • Depressed, sad mood (adults); can be irritable mood in children • Decreased interest and pleasure in normal activities • Decreased or increased appetite, weight loss or weight gain • Insomnia or hypersomnia • Psychomotor retardation or agitation • Decreased energy or fatigue • Feelings of excessive guilt or worthlessness • Impaired concentration or indecisiveness • Recurrent thoughts of death, suicidal thoughts or attempts
Manic	Yes	At least 1-week period of abnormally and persistently elevated mood (expansive or irritable) and energy, associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Distractibility (poor attention) • Increased goal-directed activity (socially, at work, or sexually) or psychomotor agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)
Hypomanic	No	At least 4 days of abnormally and persistently elevated mood (expansive or irritable) and energy, associated with at least three of the following symptoms (four if the mood is only irritable): • Inflated self-esteem (grandiosity) • Decreased need for sleep • Increased talking (pressure of speech) • Racing thoughts (flight of ideas) • Distractibility (poor attention) • Increased goal-directed activity (socially, at work, or sexually) or psychomotor agitation • Excessive involvement in activities that are pleasurable but have a high risk for serious consequences (buying sprees, sexual indiscretions, poor judgment in business ventures)

[a]Impairment in social or occupational functioning; may include need for hospitalization because of potential self-harm, harm to others, or psychotic symptoms.

[b]The disorder is not caused by a medical condition (eg, hypothyroidism) or substance-induced disorder (eg, antidepressant treatment, medications, drugs of abuse). Numerous specifiers are available to further characterize episodes (eg, with mixed features, with anxious distress, with rapid cycling, with melancholic features).

DSM, Diagnostic and Statistical Manual of Mental Disorders.

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▶ *Cyclothymic Disorder*

Cyclothymic disorder is a chronic mood disturbance lasting at least 2 years (1 year in children and adolescents) and is characterized by mood swings that include periods of hypomanic symptoms that do not meet the criteria for a hypomanic episode and depressive symptoms that do not meet the criteria for a major depressive episode.

Suicide

Patients with bipolar disorder have high risk of suicide. Factors that increase risk are early age at onset, high number and severity of depressive episodes, comorbid alcohol use disorder, comorbid personality disorder, history of antidepressant-induced mania, history of previous suicide attempt, and family history of suicidal behavior. About one-third of individuals with bipolar disorder report a previous suicide attempt.[11] Twenty percent of attempts are fatal, in contrast to 5 to 10 percent in the general population. Patients should be assessed for potential for violence and harm to themselves or others. Friends or family can be asked to remove from the home guns, caustic chemicals, medications, and objects that patients might use to harm themselves or others.[11]

Differential Diagnosis

Schizophrenia, schizoaffective disorder, and bipolar disorder share certain symptoms, including psychosis in some patients. Psychosis of schizophrenia occurs in the absence of mood symptoms in contrast to psychosis only occurring with mood symptoms in bipolar disorder. Schizoaffective disorder is characterized by major depressive episodes or manic episodes, concurrent with symptoms that meet criteria for schizophrenia and delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.[1]

Personality disorders are inflexible and maladaptive patterns of behavior that deviate markedly from expectations of society

Patient Encounter Part 2: Medical History, Physical Examination, and Laboratory Examination

Your interview reveals the following information:

PMH: No previous medical problems except recent finding of abnormal renal function and hypertension. Patient was recently started on furosemide (Lasix) 20 mg daily with improved blood pressure control and resolution of pedal edema.

PPH: Noncontributory

FH: Father deceased secondary to coronary artery disease and chronic renal failure. Patient's father previously on dialysis. Mother alive and well. The patient's paternal aunt was hospitalized multiple times at the state psychiatric hospital for "mood swings" prior to her death. No family history of suicide or substance use disorder. Patient denies prior suicide attempts. The patient has two brothers and one sister in good health.

SH: Brad has been married twice and states he is currently "playing the field." He admits to frequently "hooking up" with women at bars but is not currently in a relationship. He states his marriages were brief because his wives did not appreciate his intellect and complained about his mood swings. He has a master's degree in Computer Science but states his college grades were erratic. He admits to daily use of alcohol.

SUH: Brad smokes one-half pack of cigarettes per day × 10 years. He denies use of stimulants, opioids, benzodiazepines, hallucinogens, marijuana, or intravenous drugs. He does admit to drinking 4 to 6 beers each night and occasional shots of liquor. He drinks 3 to 4 cups of coffee each day.

Medications: Lasix 20 mg by mouth daily. Denies use of vitamins or herbal supplements.

ROS: Decreased need for sleep obtaining 2 to 3 hours per night. Increased energy, rapid speech, decreased appetite with 10 lb (4.5 kg) weight loss, hypersexuality, and distractibility with difficulty focusing on work tasks.

PE:

VS: BP 140/85 mm Hg, P 90 beats/min, RR 16 breaths/min, T 98.8°F (37.1°C)

HEENT: PERRLA. Extraocular movements intact. Nares patent. Ear canals patent and eardrums visualized. Neck supple without JVD, bruits, or lymphadenopathy. Thyroid midline, symmetric, and nontender.

CV: Heart reveals regular rate and rhythm without murmurs, gallops, or rubs.

ABDOMEN: Soft, nontender, without organomegaly or masses. Positive bowel sounds in all four quadrants.

EXTREMITIES: Without clubbing or cyanosis. Trace pedal edema. Peripheral pulses full and equal bilaterally.

CN: Cranial nerves II–XII intact.

LABS: Urine drug screen negative. HIV negative. Basic metabolic profile reveals Na^+ 138 mEq/L (mmol/L), K^+ 3.7 mEq/L (mmol/L), Cl^- 102 mEq/L (mmol/L), CO_2 29 mEq/L (mmol/L), BUN 42 mg/dL (15.0 mmol/L), creatinine 2.4 mg/dL (212 µmol/L), glucose 102 mg/dL (5.7 mmol/L). Urinalysis yellow, clear, negative for glucose, ketones, or protein.

Considering this additional information, what is the most likely diagnosis?

Identify your treatment goals for this patient.

What nonpharmacologic and pharmacologic alternatives are available for this patient?

beginning in adolescence or early adulthood.[1] Personality disorders and bipolar disorder may be comorbid, and patients with personality disorders may have mood symptoms. The two diagnoses are distinguished by the episodic course of bipolar disorder in contrast to the stability and persistence of the behavioral patterns of personality disorders.

Comorbid Psychiatric and Medical Conditions

Lifetime prevalence rates of comorbidity with bipolar disorder are as high as 58%.[2] Comorbidities, especially substance use disorders, make establishing a diagnosis more difficult and treatment complicated. Comorbidities also place the patient at risk for a poorer outcome, higher rates of suicidality, increased episodes of depression, and higher costs of treatment.[1]

Patient Encounter Part 3: Creating a Care Plan

Based on all information presented, create a care plan for this patient's bipolar disorder. Your plan should include (a) a statement of the drug-related needs or problems, (b) the goals of therapy, (c) a patient-specific therapeutic plan, and (d) a plan for follow-up to assess therapeutic response and adverse effects.

LO 3 Psychiatric comorbidities include personality disorders, alcohol and substance use or dependence, anxiety disorders, obsessive-compulsive disorder, eating disorders, and attention-deficit/hyperactivity disorder. Medical comorbidities include migraine, multiple sclerosis, type 2 diabetes mellitus, and obesity.

TREATMENT

Desired Outcomes

LO 5 KEY CONCEPT Goals of treatment are to reduce symptoms, induce remission, prevent relapse, improve patient functioning, and minimize adverse effects of drug therapy.

General Approach to Treatment

LO 7 General treatment guidelines for manic and depressive episodes of bipolar disorder are included in Table 39–2.

Although it is a goal of treatment, not all patients achieve remission. The mainstay of drug therapy has been mood-stabilizing drugs but research based on multiple treatments indicates antipsychotic drugs, both first-generation (FGAs) and second-generation (SGAs), may be more effective for acute mania.[12] Antipsychotic drugs may be used as monotherapy or adjunctively with mood-stabilizing drugs. A person entering treatment for a first mood episode in bipolar disorder must have a complete assessment and careful diagnosis to rule out nonpsychiatric causes. A variety of conditions can cause similar

Table 39–2

Guidelines for the Acute Treatment of Mood Episodes in Patients with Bipolar I Disorder

Acute Manic or Mixed Episode		Acute Depressive Episode	
General guidelines Assess for secondary causes of mania or mixed states (eg, alcohol or drug use) Taper off antidepressants, stimulants, and caffeine if possible Treat substance abuse Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy		General guidelines Assess for secondary causes of depression (eg, alcohol or drug use) Taper off antipsychotics, benzodiazepines, or sedative-hypnotic agents if possible Treat substance abuse Encourage good nutrition (with regular protein and essential fatty acid intake), exercise, adequate sleep, stress reduction, and psychosocial therapy	
Hypomania	**Mania**	**Mild to Moderate Depressive Episode**	**Severe Depressive Episode**
First, optimize current mood stabilizer or initiate mood-stabilizing medication: lithium,[a] valproate,[a] carbamazepine[a], or SGAs Consider adding a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia if needed Alternatives: carbamazepine[a]; if patient does not respond or tolerate, consider oxcarbazepine Second, if response is inadequate, consider a two-drug combination: • Lithium[a] plus an anticonvulsant or an SGA • Anticonvulsant plus an anticonvulsant or SGA	First, two- or three-drug combinations: lithium or valproate plus a benzodiazepine (lorazepam or clonazepam) for short-term adjunctive treatment of agitation or insomnia; lorazepam is recommended for catatonia. If psychosis is present, initiate SGA in combination with above Alternatives: carbamazepine[a]; if patient does not respond or tolerate, consider oxcarbazepine Second, if response is inadequate, consider a three-drug combination: • Lithium plus antipsychotic plus an antidepressant • Anticonvulsant plus an SGA Third, if response is inadequate, consider ECT for mania with psychosis or catatonia[a]; or add clozapine for treatment-refractory illness	First, initiate and/or optimize mood-stabilizing medication: lithium[a], lurasidone, quetiapine Alternatives: olanzapine/fluoxetine, valproate[a] or lamotrigine[b]	First, optimize current mood stabilizer or initiate mood-stabilizing medication: lithium,[a] lurasidone, or quetiapine If psychosis is present, initiate an antipsychotic in combination with above, do not combine antipsychotics Alternatives: olanzapine/fluoxetine, lamotrigine[b], valproate[a] Second if inadequate response carbamazepine[a] or add an antidepressant[c] Third, if response is inadequate, consider a three-drug combination: • Lithium plus lamotrigine[b] plus an antidepressant • Lithium[a] plus an anticonvulsant plus an SGA Fourth, if response is inadequate, consider ECT for treatment-refractory illness and depression with psychosis or catatonia[d]

[a]Use standard therapeutic serum concentration ranges if clinically indicated; if partial response or breakthrough episode, adjust dose to achieve higher serum concentrations without causing intolerable adverse effects; valproate is preferred over lithium for mixed episodes and rapid cycling; lithium and/or lamotrigine is preferred over valproate for bipolar depression.

[b]Lamotrigine is not approved for the acute treatment of depression, and the dose must be started low and slowly titrated to decrease adverse effects if used for maintenance therapy of bipolar I disorder. A drug interaction and a severe dermatologic rash can occur when lamotrigine is combined with valproate (ie, lamotrigine doses must be halved from standard dosing titration).

[c]Antidepressant monotherapy is not recommended for bipolar depression.

[d]ECT is used for severe mania or depression during pregnancy and for mixed episodes; prior to treatment, anticonvulsants, lithium, benzodiazepines should be tapered off to maximize therapy and minimize adverse effects.

ECT, electroconvulsive therapy; SGA, second-generation antipsychotic.

Data from Refs. 15 and 38.

symptoms (Table 39–3). Because early and accurate diagnosis is essential to maximizing response to treatment, pharmacologic and nonpharmacologic therapy should begin as soon as possible. Treatment is often lifelong. Comorbid conditions should also be addressed.

Nonpharmacologic Therapy

KEY CONCEPT Interpersonal, family, or group psychotherapy with a qualified therapist or clinician adjunctive to medication assists individuals with bipolar disorder to improve functional outcomes; they may also help treat or prevent mood episodes, establish a daily routine and sleep schedule, and improve interpersonal relationships.[13]

Cognitive-behavioral therapy (CBT) is a type of psychotherapy that stresses the importance of recognizing patterns of cognition (thought) and how thoughts influence subsequent feelings and behaviors. Other people, situations, and events external to the individual are not seen as the sources of thoughts and behaviors.

Table 39–3

Secondary Causes of Mania

Medical Conditions That Induce Mania
- CNS disorders (brain tumor, strokes, head injuries, subdural hematoma, multiple sclerosis, systemic lupus erythematosus, temporal lobe seizures, Huntington disease)
- Infections (encephalitis, neurosyphilis, sepsis, human immunodeficiency virus)
- Electrolyte or metabolic abnormalities (calcium or sodium fluctuations, hyperglycemia or hypoglycemia)
- Endocrine or hormonal dysregulation (Addison disease, Cushing disease, hyperthyroidism or hypothyroidism, menstrual-related or pregnancy-related or perimenopausal mood disorders)

Medications or Drugs That Induce Mania
- Alcohol intoxication
- Drug withdrawal states (alcohol, α_2-adrenergic agonists, antidepressants, barbiturates, benzodiazepines, opiates)
- Antidepressants (MAOIs, TCAs, 5-HT and/or NE and/or DA reuptake inhibitors, 5-HT antagonists)
- DA-augmenting agents (CNS stimulants: amphetamines, cocaine, sympathomimetics; DA agonists, releasers, and reuptake inhibitors)
- Hallucinogens (LSD, PCP)
- Marijuana intoxication precipitates psychosis, paranoid thoughts, anxiety, and restlessness
- NE-augmenting agents (α_2-adrenergic antagonists, β-agonists, NE reuptake inhibitors)
- Steroids (anabolic, adrenocorticotropic hormone, corticosteroids)
- Thyroid preparations
- Xanthines (caffeine, theophylline)
- Nonprescription weight loss agents and decongestants (ephedra, pseudoephedrine)
- Herbal products (St. John wort)

Somatic Therapies That Induce Mania
- Bright light therapy
- Deep brain stimulation
- Sleep deprivation

CNS, central nervous system; DA, dopamine; 5-HT, serotonin; LSD, lysergic acid diethylamide; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; PCP, phencyclidine; TCA, tricyclic antidepressant.

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With CBT, patients are taught self-management skills to change negative thoughts even if external circumstances do not change.

Electroconvulsive therapy (ECT) is the application of electrical impulses to the brain for the treatment of severe or treatment refractory depression, psychotic depression, and treatment refractory mania. It also may be used in pregnant women who cannot take carbamazepine, lithium, or divalproex.

Education for patients, families, and groups about chronicity of bipolar disorder and self-management through sleep hygiene, nutrition, exercise, stress reduction, and abstinence from alcohol or drugs is critical to success. The development of a crisis intervention plan is essential.

Pharmacologic Therapy

KEY CONCEPT The primary treatment modality for manic episodes is mood-stabilizing agents or antipsychotic drugs, often in combination.[14,15]

Mood-stabilizing drugs like lithium and divalproex are generally first-line treatments for acute mania. Many of the SGAs also have approvals for acute mania and are often used in combination with mood stabilizers especially if psychosis is present. Carbamazepine can be considered as second line therapy. Drugs used with less research support and without Food and Drug Administration (FDA) approvals include topiramate and oxcarbazepine. Benzodiazepines are used adjunctively for agitation and insomnia in acute manic episodes. Often the medications used for acute episodes are continued for maintenance therapy.

KEY CONCEPT The primary treatment for depressive episodes in bipolar disorder is mood-stabilizing agents or certain antipsychotics.

For treatment of bipolar depression episodes, quetiapine as monotherapy, lurasidone as monotherapy or adjunctive to lithium or divalproex, and olanzapine in combination with fluoxetine are approved. Antidepressants can be used but along with a mood stabilizer to reduce risk of a mood switch to mania and after the patient has failed to respond adequately to mood-stabilizing therapy. Evidence of efficacy of antidepressant drugs in bipolar depression is considered controversial.[12,14] Among antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) are possibly more likely than other antidepressants to cause a pharmacologic mood switch to mania or a mood episode with mixed mood features.[16] Combinations of two mood-stabilizing drugs or a mood-stabilizing drug and either an antipsychotic or antidepressant drug are common, especially in acute mood episodes.

KEY CONCEPT The primary treatment for relapse prevention is mood-stabilizing agents, often combined with antipsychotic drugs. Lamotrigine, lithium, aripiprazole (oral and long-acting injectable [LAI]), risperidone LAI, and quetiapine are approved for maintenance therapy.

LO 6 Table 39–4 includes a summary of current drug therapy for bipolar disorder. An algorithm for treatment of bipolar mania is shown in Table 39–2.

▶ *Mood-Stabilizing Drugs*

The optimal mood-stabilizing drug is effective in treatment of acute mania, hypomania, acute bipolar depression, and in prevention of mania relapse and bipolar depression relapse. All currently approved mood-stabilizing drugs have demonstrated efficacy over placebo for one or more of these types of episodes, but there are differences among them with regard to specific patient populations. The choice of treatment is dictated by patient characteristics and history. Few studies systematically compare mood stabilizers with each other. Efficacy of individual agents in placebo-controlled trials is similar. Lithium and divalproex are first-choice drugs for the most typical presentation of bipolar disorder.

Lithium Lithium, the first approved mood-stabilizing drug, remains a first-line agent and sets the standard for efficacy against which other drugs are measured. It is antimanic, prevents relapse, and has modest efficacy for acute bipolar depression. As one of the oldest drugs used for psychiatric illness, research continues to support its use.[12] In most studies, lithium's efficacy is equivalent to that of anticonvulsant mood stabilizers and SGAs. It is most effective for patients with few previous episodes, symptom-free interepisode remission, and a family history of bipolar disorder with good response to lithium. Evidence suggests genetic phenotypes that are more responsive to lithium.[17] However, patients with rapid cycling are less responsive to

Table 39–4

Product Formulation, Dose, and Clinical Use of Agents Used in Treatment of Bipolar Disorder

Generic Name	Brand Names	Formulations	Dosages	Clinical Use	Dosage Adjustment in Renal or Hepatic Impairment
Lithium Salts					
FDA approved in bipolar disorder					
Lithium carbonate	Lithobid Generic Generic Generic	ER tablets: 300 mg ER tablets: 450 mg ER tablets: 300 mg Tablet: 300 mg Capsules: 150, 300, 600 mg	900–2400 mg/day once daily or in two to four divided doses, preferably with meals. There is wide variation in the dosage needed to achieve therapeutic response and 12-hour serum lithium concentration (ie, 0.6–1.2 mEq/L [mmol/L] for maintenance therapy and 1.0–1.5 mEq/L [mmol/L] for acute mood episodes taken 12 hours after last dose). Single daily dosing is effective and causes fewer renal effects	Monotherapy or in combination with other drugs for the acute treatment of mania and for maintenance treatment	Reduce starting dosage by at least 50% in renal impairment
Lithium citrate	Generic	300 mg (8 mmol)/5 mL			
Anticonvulsants					
FDA approved for use in bipolar disorder					
Carbamazepine	Equetro (only the Equetro brand is FDA approved for bipolar disorder) Tegretol, generic Tegretol XR Carbatrol	Capsules: 100 mg, 200 mg, 300 mg SR; may open capsule but do not crush or chew beads; take with food Tablets: 200 mg Chewable tablet: 100 mg Suspension: 100 mg/5 mL ER tablets: 100, 200, 400 mg ER capsules: 100, 200, 300 mg	Start at 100–200 mg bid; increase by 200 mg every 3–4 days to 200–1800 mg/day in two to four divided doses Target serum concentration is 4–12 mcg/mL (mg/L; 17–51 µmol/L)	Monotherapy or in combination with other drugs for the acute treatment of mania or mixed episodes for bipolar I disorder	Reduce starting dosage by at least half or avoid in hepatic impairment
Divalproex sodium	Depakote, generic	Enteric-coated, delayed-release tablets: 125, 250, 500 mg	750–3000 mg/day (20–60 mg/kg/day) in two to three divided doses for delayed-release divalproex or valproic acid	Monotherapy or in combination with other drugs for the acute treatment of mania. Although commonly used for relapse prevention, maintenance treatment is not FDA approved	Reduce starting dosage by half or avoid in hepatic impairment
	Depakote ER	Sprinkles: 125 mg ER tablets: 250, 500 mg	ER divalproex may be given once daily A loading dose of 20–30 mg/kg/day can be given, then 20 mg/kg/day and titrated to a serum concentration of 50–125 mcg/mL (mg/L; 347–866 µmol/L)		

(*Continued*)

Table 39–4

Product Formulation, Dose, and Clinical Use of Agents Used in Treatment of Bipolar Disorder (*Continued*)

Generic Name	Brand Names	Formulations	Dosages	Clinical Use	Dosage Adjustment in Renal or Hepatic Impairment
Valproic acid	Depakene, generic	Capsules: 250 mg			
Valproic acid syrup	Depakene, generic	250 mg/5 mL			
Lamotrigine	Lamictal, generic	Tablets: 25, 100, 150, 200 mg Chewable tablets: 2, 5, 25 mg ODT: 25, 50, 100, 200 mg	50–400 mg/day in divided doses. Dosage should be slowly increased by following prescribing information. If divalproex is added to lamotrigine, the lamotrigine dosage should be reduced by half	Monotherapy or in combination with other drugs for maintenance treatment	
	Lamictal XR (not FDA approved for bipolar disorder)	ER tablets: 25, 50, 100, 200 mg			
Anticonvulsants and Other Drugs Not FDA Approved for Use in Bipolar Disorder					
Clonazepam	Klonopin, generic	Tablets: 0.5, 1, 2 mg Wafers: 0.125, 0.25, 0.5, 1, 2 mg	0.5–20 mg/day in divided doses or one dose at bedtime Dosage should be slowly adjusted up and down according to response and adverse effects	Use in combination with other drugs for the acute treatment of mania or mixed episodes	
Lorazepam	Ativan, generic	Tablets: 0.5, 1, 2 mg Oral solution: 2 mg/mL Injection: 2, 4 mg/mL	2–10 mg/day in divided doses or one dose at bedtime Dosage should be slowly adjusted up and down according to response and adverse effects		
Oxcarbazepine	Trileptal, generic	Tablets: 150, 300, 600 mg Suspension: 300 mg/5 mL	300–1200 mg/day in two divided doses Doses should be slowly adjusted up and down according to response and adverse effects (eg, 150–300 mg twice daily and increase by 300–600 mg/day at weekly intervals)	May cause fewer adverse drug–drug interactions than carbamazepine, but causes more gastrointestinal side effects and hyponatremia. Evidence is limited regarding efficacy	
Second Generation Antipsychotics					
FDA approved for bipolar disorder					
Aripiprazole	Abilify MyCite Abilify Abilify Discmelt Abilify Maintena	Tablets: 2, 5, 10, 15, 20, 30 mg Tablets: 2, 5, 10, 15, 20, 30 mg Oral solution: 5 mg/5 mL ODT: 10, 15 mg Long-acting injectable: 400 mg	10–30 mg once daily 10–30 mg/day once daily 400 mg IM once monthly	Use as monotherapy or in combination with lithium or valproate for the acute treatment of mania or mixed states for bipolar I disorder and prevention of manic relapse Use as monotherapy for maintenance treatment of bipolar I disorder	
Asenapine	Saphris	Sublingual tablets: 5, 10 mg	5–20 mg/day in two divided doses. Must be held under the tongue until dissolved completely, not chewed or swallowed, with no food or liquid for 10 minutes after administering	Use as monotherapy or in combination with lithium or valproate for the acute treatment of mania or mixed states of bipolar I disorder	

Lurasidone	Latuda	Tablets: 20, 40, 60, 80, 120 mg	20–120 mg once daily	Use as monotherapy or in combination with lithium or valproate for depression of bipolar I disorder
Olanzapine	Zyprexa, generic Zyprexa Zydis	Tablets: 2.5, 5, 7.5, 10, 15, 20 mg ODT: 5, 10, 15, 20 mg	5–20 mg/day in one or two doses	Used as monotherapy or in combination with lithium or valproate for acute treatment of mania or mixed states for bipolar I disorder and prevention of manic relapse. Used in combination with fluoxetine for treatment of bipolar depression
Olanzapine/Fluoxetine combination	Symbyax	Capsules: 3/25, 6/25, 6/50, 12/25, 12/50 mg		Approved for bipolar depression
Quetiapine	Seroquel Seroquel XR	Tablets: 25, 50, 100, 200, 300, 400 mg ER tablets: 50, 150, 200, 300, 400 mg	50–800 mg/day in divided doses or once daily when stabilized	Used as monotherapy or in combination with lithium or divalproex for acute treatment of mania, mixed states for bipolar I disorder, and depression of bipolar I and bipolar II disorder. Used adjunctively with lithium or divalproex for relapse prevention of bipolar mania and depression
Risperidone	Risperdal, generic	Tablets: 0.25, 0.5, 1, 2, 3, 4 mg	0.5–6 mg/day in one or two doses	Used as monotherapy or adjunctively with lithium or divalproex for acute mania or mixed episodes of bipolar I disorder
		Oral solution: 1 mg/mL		Used as monotherapy or adjunctively with lithium or divalproex for maintenance treatment of bipolar I disorder
	Risperdal M-Tabs	ODT: 0.5, 1, 2, 3, 4 mg	25–50 mg every 2 weeks	Used as monotherapy or adjunctively with lithium or divalproex for acute mania or mixed episodes of bipolar I disorder
	Risperdal Consta	Long-acting injectable: 12.5, 25, 37.5, 50 mg		Used as monotherapy or adjunctively with lithium or divalproex for maintenance treatment of bipolar I disorder
Ziprasidone	Geodon	Capsules: 20, 40, 60, 80 mg	40–160 mg/day in divided doses	Used as monotherapy or manic or mixed episodes of bipolar I disorder Used adjunctively with lithium or divalproex for maintenance treatment of bipolar I disorder

DIVALPROEX, divalproex; ER, extended release; FDA, Food and Drug Administration; ODT, oral disintegrating tablet; SR, sustained release; XR, extended release.

Data from Refs. 12, 14, 20, 21, 23, 24, 27–29, and 38.

lithium than to other mood-stabilizing drugs such as divalproex. Additionally, its efficacy for bipolar depression is less robust than for mania.[12] It may also be less effective in mood episodes with mixed mood features (symptoms of mania and depression occurring simultaneously).

Evidence shows lithium's effect on suicidal behavior is superior to that of other mood-stabilizing drugs.[18] Lithium reduces the risk of deliberate self-harm or suicide by 70%.

Lithium's mechanism of action is not well understood and is multimodal. Possibilities include altered ion transport, effects on neurotransmitter signaling, blocking adenyl cyclase, effects on inositol, neuroprotection or increased BDNF, and inhibition of second messenger systems.[19]

Lithium is usually initiated at a dosage of 600 to 900 mg/day. Although it is commonly given in a divided dosage, once-daily dosing is recommended, especially with sustained-release formulations. Once-daily dosing can improve adherence and reduce renal side effects. Lithium has a narrow therapeutic index, meaning the toxic dosage is not much greater than the therapeutic dosage. Lithium requires regular serum concentration monitoring as a guide to titration and to minimize adverse effects. At least weekly monitoring is recommended until stabilized; then the frequency can be decreased. Well-maintained patients who tolerate lithium without difficulty can be monitored by serum concentration as infrequently as twice yearly. The dosage is titrated to achieve a serum lithium concentration of 0.6 to 1.2 mEq/L (mmol/L). Higher serum concentrations are required to treat an acute episode than to prevent relapse. Serum lithium above 0.8 mEq/L (mmol/L) may be more effective at preventing relapse than lower serum concentrations. The suggested therapeutic serum concentration range is based on a 12-hour postdose sample collection, usually a morning trough in patients taking more than one dose per day. At least 2 weeks at a suggested therapeutic serum concentration is required for an adequate trial. Table 39–5 shows pharmacokinetic parameters and desired serum concentrations of mood-stabilizing drugs. It is common for lithium to be combined with other mood stabilizers or antipsychotics to achieve more complete remission.

The most common adverse effects are gastrointestinal (GI) upset, tremor, and polyuria, which are dose-related.[20] Nausea, dyspepsia, and diarrhea are minimized by coadministration with food, use of the sustained-release formulation, and giving smaller doses more frequently to reduce the amount of drug in the GI tract. Tremor is present in up to 50% of patients. In addition to these approaches, low-dose β-blockers, such as propranolol 20 to 60 mg/day, reduce tremor.

Lithium impairs the kidney's ability to concentrate urine because of its inhibitory effect on vasopressin. This causes an increase in urine volume and frequency of urination and an increase in thirst. Polyuria and polydipsia occur in up to 70% of patients. A severe form of polyuria, when urine volume exceeds 3 L/day, is termed lithium-induced nephrogenic **diabetes insipidus**. It can be treated with hydrochlorothiazide or amiloride. If the former is used, the lithium dosage should be reduced by 33% to 50% to account for the drug–drug interaction that increases serum lithium and causes toxicity. Long-term lithium has been associated with structural kidney changes, such as glomerular sclerosis or tubular atrophy. Once-daily dosing of lithium is less likely to cause renal adverse effects than divided-daily dosing.

Lithium is concentrated in the thyroid gland and can impair thyroid hormone synthesis. Although goiter is uncommon, as many as 30% of patients develop at least transiently elevated thyroid-stimulating hormone. Lithium-induced hypothyroidism is not usually an indication to discontinue the drug. Patients can be supplemented with levothyroxine.

Other common adverse effects include poor concentration, acneiform rash, alopecia, worsening of psoriasis, weight gain, metallic taste, impaired glucose regulation, and benign leukocytosis. Lithium causes a flattening of the T wave of the electrocardiogram (ECG), considered benign and not clinically significant. Less commonly, it can cause or worsen arrhythmias.[20]

Lithium and other mood-stabilizing drugs require baseline and routine laboratory monitoring to help determine medical appropriateness for initiation of therapy and monitoring of adverse effects. Guidelines for such monitoring are outlined in Table 39–6.

LO 8

Acute lithium toxicity, which usually occurs at serum concentrations over 2 mEq/L (mmol/L), can be severe and life threatening, necessitating emergency treatment. Milder toxicity can occur at concentration between 1.5 and 2 mEq/L (mmol/L). Symptoms include severe vomiting and diarrhea, deterioration in motor coordination, including coarse tremor, ataxia, and dysarthria, and impaired cognition. In its most severe form, seizures, cardiac arrhythmias, coma, and kidney damage are reported. Treatment includes discontinuation of lithium, IV fluids to correct fluid and electrolyte imbalance, and osmotic diuresis or hemodialysis. In case of overdose, gastric lavage is indicated. Clinical symptoms continue after the serum concentration is lowered because clearance from the central nervous system (CNS) is slower than from serum. Factors predisposing to lithium toxicity include fluid and sodium loss from hot weather or exercise or drug interactions that increase serum lithium.[20]

Drug interactions involving lithium are common. Because lithium is not metabolized or protein bound, it is not associated with metabolic drug interactions that occur with other mood-stabilizing drugs. Common and significant drug interactions involve thiazide diuretics, nonsteroidal anti-inflammatory drugs, and angiotensin-converting enzyme (ACE) inhibitor drugs. If a diuretic must be used with lithium and a thiazide is not required, loop diuretics such as furosemide are less likely to increase lithium retention. The ACE inhibitors and angiotensin receptor blockers (ARBs) can abruptly increase serum lithium with the potential for acute toxicity, including fatal toxicity, even after months of no change in serum lithium. This combination is strongly discouraged.[20] Any drug or condition that can cause hyponatremia may increase lithium toxicity.

Divalproex Sodium and Valproic Acid Divalproex sodium is composed of sodium valproate and valproic acid. The delayed-release and extended-release formulations are converted in the intestine into valproic acid (VPA), which is systemically absorbed. It is FDA approved for treatment of the manic phase of bipolar disorder. It is equal in efficacy to lithium and some other drugs for bipolar mania. It has utility in bipolar disorder with rapid cycling, mood episodes with mixed mood features, and substance use comorbidity. Although not FDA approved for relapse prevention, studies support its use, and it is widely prescribed for maintenance therapy. Divalproex can be used as monotherapy or in combination with lithium or an antipsychotic.[14]

The mechanism for bipolar disorder is not well understood. It is known to affect ion transport and enhance activity of γ-aminobutyric acid (GABA). Similar to lithium, it has possible neuroprotective effects through enhancement of BDNF.[19]

Divalproex is initiated at 500 to 1000 mg/day, but studies indicate a therapeutic serum VPA concentration can be reached more quickly through a loading dose approach of 20 to 30 mg/kg/day. Using this approach, patients may respond with a significant

Table 39–5

Pharmacokinetics and Therapeutic Serum Concentrations of Lithium and Anticonvulsants Used in the Treatment of Bipolar Disorder

	Lithium	Carbamazepine	Oxcarbazepine	Divalproex (DIVALPROEX) Sodium/ Valproic Acid (VPA)	Lamotrigine
Gastrointestinal Absorption					
Regular release	Rapid: 95%–100% within 1–6 hours	Slow and erratic: 85%–90%	Slow and complete: 100%	Rapid and complete (VPA)	Rapid: 98%
Syrup, suspension, solution	Faster rate of absorption: 100%	Faster rate of absorption	Unknown	Faster rate of absorption than tablets	NA
ER/enteric-coated tablets	Delayed absorption: 60%–90%	Delayed absorption: 89% of the suspension; and less than regular-release tablets	NA	Delayed absorption with delayed-release tablets; valproate is rapidly converted to VPA in the intestine and then is rapidly and almost completely absorbed from the GI tract ER bioavailability is approximately 15% less than delayed release	Delayed absorption but not significantly different from regular release
Delay in absorption by food	Yes	No; reports of increased rate of absorption with fatty meals (ER capsule)	No	Yes; food slows the rate of absorption but not the extent for DIVALPROEX	Bioavailability not affected by food
Time to reach peak serum concentrations	0.5–3 hours (regular-release) 4–12 hours (ER) 0.25–1 hour (oral solution)	4–5 hours (regular-release); 1.5 hours (suspension); 3–12 hours (ER tablets); 4.1–7.7 hours (ER capsules); higher peak concentrations with chewable tablets	4.5 hours (range of 3–13 hours)	1–4 hours (VPA) 3–5 hours (DIVALPROEX single dose) 7–14 hours (DIVALPROEX ER multiple dosing)	1–4 hours (regular release), 4–6 hours (ER)
Distribution					
Volume of distribution	Initial: 0.3–0.4 L/kg Steady state: 0.7–1 L/kg	0.6–2 L/kg (adults)	10-monohydroxy metabolite: 49 L/kg	11 L/1.73 m^2 (total valproate); 92 L/ 1.73 m^2 (free valproate)	0.9–1.3 L/kg
Crosses the placenta	Yes; pregnancy risk category: D Risk of cardiac defects: 0.1%–0.5%	Yes; pregnancy risk category: D	Yes; pregnancy risk category: C	Yes; pregnancy risk category: D Risk of neural tube defects: 1%–5%	Yes; pregnancy risk category: C
Crosses into breast milk	Yes; 35%–50% of mother's serum concentration; breastfeeding not recommended	Yes; ratio of concentration in breast milk to plasma is 0.4 for drug and 0.5 for epoxide metabolite; considered compatible with breastfeeding	Yes; both drug and active metabolite; breastfeeding not recommended	Yes; considered compatible with breastfeeding	Yes; breastfeeding not recommended
Protein binding	No	75%–90%	40% of active metabolite	80%–90% (dose dependent)	55%
Renal clearance	Yes; 10–40 mL/min with 90%–98% of dose excreted in urine; 80% of lithium that is filtered by the renal glomeruli is reabsorbed	Yes; 1%–3% excreted unchanged in urine	Yes; 95% excreted in the urine; < 1% excreted unchanged	Yes; 30%–50% excreted as glucuronide conjugate; < 3% excreted unchanged	Yes; 94% excreted as glucuronide conjugate

(*Continued*)

Table 39–5

Pharmacokinetics and Therapeutic Serum Concentrations of Lithium and Anticonvulsants Used in the Treatment of Bipolar Disorder (*Continued*)

	Lithium	Carbamazepine	Oxcarbazepine	Divalproex (DIVALPROEX) Sodium/ Valproic Acid (VPA)	Lamotrigine
Metabolism					
Hepatic metabolism	No	Yes; oxidation and hydroxylation; induces liver enzymes to increase its own metabolism and metabolism of other drugs	Yes; oxidation and conjugation	Yes; oxidation and glucuronide conjugation	Yes; glucuronic acid conjugation induces its own metabolism in normal volunteers
Metabolites	No	Yes; 10, 11–epoxide (active)	Yes; 10-monohydroxy metabolite (active)	Yes (not active)	No
Kinetics	First-order	First-order after initial enzyme induction phase	First-order	First-order	First-order
Half-life ($t_{½}$)	18–27 hours (adult); > 36 hours (elderly or patients with renal impairment)	Half-life decreases over time due to autoinduction: 25–65 hours (initial) 12–17 hours (adult multiple dosing) 8–14 hours (children multiple dosing)	2 hours (parent) 9 hours (metabolite)	5–20 hours (adults)	25 hours; increases to 59 hours with concomitant VPA therapy
Cytochrome P450 (CYP450) Isoenzyme					
CYP450 substrate	No	2C8 and 3A3/4	Unknown	2C19	Unknown
CYP450 inhibitor	No	No	2C19	2C9, 2D6, and 3A3/4	Unknown
CYP450 inducer	No	1A2, 2C9/10, and 3A3/4	3A3/4	No	Unknown
Therapeutic Serum/Plasma Concentrations					
	1–1.5 mEq/L (mmol/L): for adult, acute mania 0.4–0.6 mEq/L (mmol/L): for elderly or medically ill patients 0.6–1.2 mEq/L (mmol/L): for adult, maintenance; ranges based on 12-hour postdose sample collection	4–12 mcg/mL (mg/L; 17–51 µmol/L): for adult, acute mania and maintenance 4–8 mcg/mL (mg/L; 17–34 µmol/L): for elderly or medically ill	No established therapeutic range; 12–30 mcg/mL (mg/L; 47–118 µmol/L) for 10-hydroxy metabolite based on epilepsy trials	50–125 mcg/mL (mg/L; 347–866 µmol/L): adult, acute mania and maintenance 40–75 mcg/mL (mg/L; 277–520 µmol/L): elderly or medically ill	No established therapeutic range: 4–20 mcg/mL (mg/L; 16–78 µmol/L) based on epilepsy trials

ER, extended release; GI, gastrointestinal; NA, not applicable.

Data from Refs. 19–21, 23, and 24.

reduction in symptoms of acute mania within the first few days of treatment. The dosage is then titrated according to response, tolerability, and serum concentration. The most often referenced desired VPA serum concentration is 50 to 125 mcg/mL (mg/L; 347–866 µmoles/L), but it is not unusual for patients to require more than 100 mcg/mL (mg/L; 693 µmoles/L) for optimal efficacy. Some patients require high milligram dosages in order to reach a desired serum concentration. The suggested serum concentration range is based on trough values. Serum concentration monitoring is recommended at least every 2 weeks until stabilized, then less frequently. The extended-release formulation can be taken once daily (see Table 39–4). If the extended-release formulation is administered at night, a morning blood sampling is a peak, not a trough. The drug should be given in the morning so that blood sampling the following morning would be a trough value and more easily interpreted if the typical blood sampling time is in the morning. The systemic bioavailability of extended-release divalproex is about 15% less than that of the delayed-release formulation. Patients who have difficulty swallowing large tablets can use the sprinkle formulation. The immediate-release formulation, either capsules or syrup, is given three or four times per day.[21]

Table 39–6

Guidelines for Baseline and Routine Laboratory Tests and Monitoring for Agents Used in the Treatment of Bipolar Disorder

	Baseline: Physical Examination and General Chemistry[a]	Hematologic Tests[b]		Metabolic Tests[c]		Liver Function Tests[d]		Renal Function Tests[e]		Thyroid Function Tests[f]		Serum Electrolytes[g]		Dermatologic[h]	
	Baseline	Baseline	6–12 Months	Baseline	6–12 Months	Baseline	6–12 Months	Baseline	6–12 Months	Baseline	6–12 Months	Baseline	6–12 Months	Baseline	3–6 Months
SGAs[i]	X			X	X										
Carbamazepine[j]	X	X	X			X	X	X				X	X	X	X
Lamotrigine[k]	X													X	X
Lithium[l]	X	X	X	X	X			X	X	X	X	X	X	X	X
Oxcarbazepine[m]	X											X	X		
Valproate[n]	X	X	X	X	X	X	X							X	X

[a]Screen for drug abuse and serum pregnancy.

[b]Complete blood count (CBC) with differential and platelets.

[c]Fasting glucose, serum lipids, weight.

[d]Lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, alkaline phosphatase.

[e]Serum creatinine, blood urea nitrogen, urinalysis, urine osmolality, specific gravity.

[f]Triiodothyronine, total thyroxine, thyroxine uptake, and thyroid-stimulating hormone.

[g]Serum sodium.

[h]Rashes, hair thinning, alopecia.

[i]SGA, second generation antipsychotic: Monitor for increased appetite with weight gain (primarily in patients with initial low or normal body mass index); monitor closely if rapid or significant weight gain occurs during early therapy; cases of hyperlipidemia and diabetes reported.

[j]Carbamazepine: Manufacturer recommends CBC and platelets (and possibly reticulocyte counts and serum iron) at baseline, and that subsequent monitoring be individualized by the clinician (eg, CBC, platelet counts, and liver function tests every 2 weeks during the first 2 months of treatment, then every 3 months if normal). Monitor more closely if patient exhibits hematologic or hepatic abnormalities or if the patient is receiving a myelotoxic drug; discontinue if platelets are less than 100,000/mm^3 (100×10^9/L), if WBC is less than 3000/mm^3 (3×10^9/L) or if there is evidence of bone marrow suppression or liver dysfunction. Serum electrolyte levels should be monitored in the elderly or those at risk for hyponatremia. Carbamazepine interferes with some pregnancy tests.

[k]Lamotrigine: If renal or hepatic impairment, monitor closely and adjust dosage according to manufacturer's guidelines. Serious dermatologic reactions have occurred within 2 to 8 weeks of initiating treatment and are more likely to occur in patients receiving concomitant valproate, with rapid dose escalation, or using doses exceeding the recommended titration schedule.

[l]Lithium: Obtain baseline ECG for patients older than 40 years or if preexisting cardiac disease (benign, reversible T-wave depression can occur). Renal function tests should be obtained every 2 to 3 months during the first 6 months, then every 6 to 12 months; if impaired renal function, monitor 24-hour urine volume and creatinine every 3 months; if urine volume more than 3 L/day, monitor urinalysis, osmolality, and specific gravity every 3 months. Thyroid function tests should be obtained once or twice during the first 6 months, then every 6 to 12 months; monitor for signs and symptoms of hypothyroidism; if supplemental thyroid therapy is required, monitor thyroid function tests and adjust thyroid dose every 1 to 2 months until thyroid function indices are within normal range, then monitor every 3 to 6 months.

[m]Oxcarbazepine: Hyponatremia (serum sodium concentrations less than 125 mEq/L [mmol/L]) has been reported and occurs more frequently during the first 3 months of therapy; serum sodium concentrations should be monitored in patients receiving drugs that lower serum sodium concentrations (eg, diuretics or drugs that cause inappropriate antidiuretic hormone secretion) or in patients with symptoms of hyponatremia (eg, confusion, headache, lethargy, and malaise). Hypersensitivity reactions have occurred in approximately 25% to 30% of patients with a history of carbamazepine hypersensitivity and requires immediate discontinuation.

[n]Valproate: Weight gain reported in patients with low or normal body mass index. Monitor platelets and liver function during first 3 to 6 months if evidence of increased bruising or bleeding. Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin; discontinue if platelets are less than 100,000/mm^3/L (100×10^9/L) or if prolonged bleeding time. Pancreatitis, hyperammonemic encephalopathy, polycystic ovary syndrome, increased testosterone, and menstrual irregularities have been reported; not recommended during first trimester of pregnancy due to risk of neural tube defects.

Data from Refs. 15 and 38.

The most common adverse effects are GI (loss of appetite, nausea, dyspepsia, diarrhea), tremor, and drowsiness. GI distress can be reduced by coadministration with food. The delayed-release and extended-release formulations are less likely to cause gastric distress than immediate-release VPA. Dosage reduction can reduce all of the common side effects. As with lithium, a low-dose β-blocker may alleviate tremor. Weight gain is common, occurring in up to 50% of patients.[21]

Other less common adverse effects include alopecia or a change in hair color or texture. Hair loss can be minimized by supplementation with a vitamin containing selenium and zinc. Polycystic ovarian syndrome associated with increased androgen production is reported. Thrombocytopenia is common, and the platelet count should be monitored periodically. It is a dose-related, reversible adverse effect and usually asymptomatic, but the drug is usually stopped if the platelet count is less than $100 \times 10^3/mm^3$ ($100 \times 10^9/L$). Rarer are hepatic toxicity and pancreatitis, which are not always dose-related. Hyperammonemia has been reported. If patients develop unexplained lethargy and vomiting or changes in mental status, an ammonia level should be measured. Severe GI symptoms of hepatic or pancreatic toxicity include vomiting, pain, and loss of appetite. When these occur, the patient should be evaluated for possible hepatitis or pancreatitis. Divalproex has a wide therapeutic index. Acute toxicity for high dosages or over dosage is not life threatening.

Drug interactions involving divalproex are common. It is a weak inhibitor of some drug metabolizing liver enzymes and can affect metabolism of other drugs. These include other anticonvulsants and antidepressants. The interaction between divalproex and lamotrigine is significant. The risk of a dangerous rash caused by lamotrigine is increased when given concurrently with divalproex. Conversely, the metabolism of divalproex can be increased by enzyme-inducing drugs such as carbamazepine and phenytoin, but divalproex may simultaneously slow metabolism of the other agents.[21]

Carbamazepine Although used frequently as a mood-stabilizer, only the extended-release formulation is FDA approved for treatment of bipolar disorder. Carbamazepine has efficacy for mood stabilization; however, it is less desirable as a first-line agent because of safety and drug interactions. It is reserved for patients who fail to respond to lithium or for patients with rapid cycling or bipolar disorder with episodes of mixed mood features. Carbamazepine can be used as monotherapy or in combination with lithium or an antipsychotic drug.[22]

The mechanism of action of carbamazepine is not well understood. It blocks ion channels and inhibits sustained repetitive neuronal excitation, but whether this explains its efficacy as a mood stabilizer is not known.[22]

Carbamazepine is initiated at 400 to 600 mg/day. The sustained-release formulation can be given in two divided doses. An additional extended-release formulation contains a matrix of 25% immediate-release, 40% extended-release, and 35% enteric-release beads.[22] The suggested therapeutic serum concentration is 4 to 12 mcg/mL (mg/L; 17–51 μmol/L). As with divalproex, some patients require high dosages to achieve a desired serum concentration and therapeutic effect. The dosage can be increased by 200 to 400 mg/day as often as every 2 to 4 days. Serum concentration monitoring is suggested at least every 2 weeks until stabilized.[22]

The most common adverse effects are drowsiness, dizziness, ataxia, lethargy, and confusion. At mildly toxic levels, it causes diplopia and dysarthria. These can be minimized through dosage adjustments, use of sustained-release formulations, and giving more of the drug late in the day. GI upset is common. Carbamazepine has an antidiuretic effect similar to the syndrome of inappropriate antidiuretic hormone secretion and can cause hyponatremia. Mild elevations in liver enzymes can occur, but hepatitis is less common. Mild, dose-related leukopenia is not unusual and not an indication for discontinuation. More serious blood count abnormalities such as aplastic anemia and agranulocytosis are rare but life threatening.[22] Additionally, toxic epidermal necrolysis (TEN) and SJS have been reported. Higher risk of these serious dermatologic reactions is associated with the HLA-B*1502 allele found almost exclusively in Asian ancestry. Patients with ancestry from the at-risk population should have genetic testing done prior to initiation of carbamazepine.[23] See the epilepsy chapter for a full discussion. Suggested baseline and routine laboratory monitoring are reviewed in Table 39–6.

Carbamazepine induces hepatic metabolism of many drugs, including other anticonvulsants, antipsychotics, some antidepressants, oral contraceptives, and antiretroviral agents. Carbamazepine is an autoinducer (ie, it induces its own metabolism). The dosage may require an increase after 1 month or so of therapy because of this effect. Conversely, the metabolism of carbamazepine can be slowed by enzyme inhibiting drugs such as some antidepressants; macrolide antibiotics, including erythromycin and clarithromycin; azole antifungal drugs, including ketoconazole and itraconazole; and grapefruit juice.

Lamotrigine Lamotrigine is effective for maintenance treatment of bipolar disorder. It is more effective for depression relapse prevention than for mania relapse prevention. Its primary limitation as an acute treatment is the time required for titration to an effective dosage. In addition to maintenance monotherapy, it is sometimes used in combination with lithium or divalproex, although combination with divalproex increases the risk of rash, and lamotrigine dosage adjustment is required.[24]

The mechanism of action of lamotrigine appears to involve blockage of ion channels and effects on glutamate transmission, although the precise mechanism is not clear.[24]

Lamotrigine is initiated at 25 mg/day for 1 to 2 weeks, then increased in a dose-doubling manner every 1 to 2 weeks to a target of 200 to 400 mg/day. If lamotrigine therapy is interrupted for more than 5 half-lives, it should be restarted at the initial dosage and retitrated. Serum concentration monitoring is not recommended.[24]

The adverse effect of greatest significance is a maculopapular rash, occurring in up to 10% of patients.[24] Although usually benign and temporary, some rashes can progress to life-threatening Stevens-Johnson syndrome. The risk of rash is greater with a rapid dosage titration, when given concurrently with divalproex or other metabolic enzyme inhibitors, and in pediatric patients.[24] The risk is minimal in adults when the dosage titration schedule is slow. Other side effects include dizziness, drowsiness, headache, blurred vision, and nausea. In contrast to other mood-stabilizing drugs such as lithium and divalproex, lamotrigine does not significantly influence body weight.

The mechanisms of drug–drug interactions involving lamotrigine are unclear. Lamotrigine's primary route of metabolism is conjugative glucuronidation, although it is known to exhibit metabolic autoinduction. It is not significantly metabolized by CYP P450 enzymes. It does not affect drug metabolizing hepatic enzymes. Divalproex slows the rate of elimination of lamotrigine by about half. If lamotrigine is added to divalproex, the starting dosage is 25 mg every other day with a slower titration to reduce risk of rash. If divalproex is added to lamotrigine, the lamotrigine dosage should be reduced by 50% for the same reason. Conversely,

carbamazepine and estrogen-containing oral contraceptives increase the rate of lamotrigine metabolism. Upward adjustment in lamotrigine dosage may be needed.[24]

Oxcarbazepine Oxcarbazepine is an analogue of carbamazepine, developed as an anticonvulsant. An advantage over carbamazepine is that routine monitoring of hematology profiles and serum concentrations is not indicated because it is less likely to cause hematologic abnormalities.[25] Additionally, drug interactions are less significant, although it is a mild inducer of certain metabolic pathways. Vigilance for drug interactions is needed, especially with oral contraceptives. Oxcarbazepine appears in the most recent treatment algorithms for bipolar disorder,[14] but clinical trial data are limited.[26]

Adverse effects include drowsiness, dizziness, GI upset, and hyponatremia, the latter two of which may be more likely than with carbamazepine.[25]

Others High-potency benzodiazepine agents such as clonazepam and lorazepam are used as adjunctive therapy, especially during acute mania, to reduce anxiety and improve sleep.[27] As complementary or alternative medicines gain wider usage, omega-3 fatty acids have been used in mood disorders, but do not appear in treatment guidelines.

▶ *Antipsychotic Drugs*

First-generation antipsychotics (FGAs) such as chlorpromazine and haloperidol have long been used in the treatment of acute mania. SGA drugs, including aripiprazole, asenapine, cariprazine, olanzapine, quetiapine, risperidone, and ziprasidone, are approved for the treatment of bipolar mania or mixed mood features as monotherapy or in combination with mood stabilizers.[14] Among the LAI antipsychotic drugs, risperidone microspheres and aripiprazole monohydrate are approved for maintenance therapy in bipolar disorder. Aripiprazole LAI is approved as monotherapy and risperidone LAI is approved both as monotherapy and combined with lithium or valoprate.[14] Oral aripiprazole tablets with a sensor for tracking adherence is approved for maintenance as monotherapy or adjunctively to lithium or valproate. The combination of olanzapine and fluoxetine is approved for treatment of acute bipolar depression. Quetiapine is approved as monotherapy for acute bipolar depression and as adjunctive therapy with lithium or divalproex for prevention of bipolar depression relapse. Lurasidone is approved as monotherapy and as adjunctive therapy with lithium or divalproex for acute bipolar depression. Asenapine and olanzapine are approved as monotherapy for maintenance therapy. Approval of antipsychotic drugs in patients with bipolar disorder applies without regard to presence of psychosis. In comparative studies, SGAs are equivalent or superior in efficacy to lithium and divalproex for treatment of acute mania. Treatment guidelines include antipsychotic drugs as first-line therapy.[14] The combination of mood stabilizers and antipsychotics is more likely to achieve remission than monotherapy. Quetiapine data in relapse prevention of both manic and bipolar depression episodes favored combination therapy over mood-stabilizer monotherapy.[28]

The mechanisms of action, usual dosages, pharmacokinetics, adverse effects, and drug interactions involving antipsychotic drugs are discussed in detail in the chapter on schizophrenia. Dosages in bipolar disorder are similar to those used in schizophrenia. Higher dosages are often required to treat an acute episode. The recommended dosage of aripiprazole for bipolar disorder is 20 to 30 mg/day, somewhat higher than the average dosage used in schizophrenia.[29] The recommended dosage for quetiapine in treatment of acute bipolar depression is 300 mg/day, less than the 600 mg/day recommended in acute mania.[30]

SGAs are less likely than FGAs to cause neurologic side effects, especially movement abnormalities. SGAs are more likely to cause metabolic side effects, such as weight gain, glucose dysregulation, and dyslipidemia.[31] Among SGAs approved for treatment of bipolar disorder, olanzapine is most likely to cause metabolic side effects.

▶ *Antidepressants*

Treatment of depressive episodes in patients with bipolar disorder presents a particular challenge because of the risk of a drug-induced mood switch to mania. The FDA requires the product label of all antidepressants to contain language about the potential risk of inducing a mood switch to mania. Most research shows no advantage for adjunctive antidepressant use compared with mood-stabilizer therapy alone.[12,14] Treatment guidelines and current FDA approvals indicate lithium and quetiapine as first-line therapy.[14] Although lurasidone is FDA indicated for acute bipolar depression, its place in therapy relative to lithium and quetiapine is not established. When usual treatment fails, evidence supports use of antidepressants.[12,14]

Guidelines agree that when antidepressants are used, they should be combined with a mood stabilizer to reduce risk of mood switch. The question of which antidepressant drugs are less likely to cause a mood switch is not resolved, but TCAs and SNRI are thought to carry greater risk. A comparison of venlafaxine, sertraline, and bupropion as adjunctive therapy to a mood stabilizer showed venlafaxine with highest risk of a mood switch to mania or hypomania and bupropion with the least.[32]

Special Populations

Assessment and management by appropriate psychiatric specialists is important for special populations, such as pediatric, geriatric, and pregnant patients.

▶ *Pediatrics*

Evidence regarding treatment of bipolar disorder in children and adolescents is more limited than in adults. Children and adolescents are sensitive to medication side effects, including metabolic side effects of SGAs. With these caveats, evidence supports use of mood stabilizers and SGAs in children and adolescents with bipolar disorder. Lithium is FDA approved for treatment of bipolar disorder in children and adolescents as young as age 12. Aripiprazole, olanzapine/fluoxetine combination, quetiapine, and risperidone are FDA approved in children and adolescents as young as age 10.[14,33]

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Initial dosages in the pediatric population are lower than in adults. Metabolic elimination rates of many drugs are increased in children, so they may actually require higher dosages on a weight-adjusted basis. Dosages are titrated carefully according to response and tolerability.

Children and adolescents are especially likely to experience weight gain from SGAs.[34] Cognitive toxicity, manifested as confusion, memory or concentration impairment, or impaired learning, is difficult to detect and is a consideration in the pediatric population so that intellectual and educational development is not hindered.

For comorbid bipolar disorder and attention-deficit/hyperactivity disorder when stimulant therapy is indicated, treatment of mania is recommended before starting the stimulant to avoid exacerbation of mood symptoms.

▶ *Geriatrics*

Treatment of older adults with bipolar disorder requires care because of increased risks associated with medical conditions and drug–drug interactions.[35] General medical conditions, including endocrine, metabolic, or infectious diseases, can mimic mood disorders. Patients should be evaluated for such medical illnesses that cause or worsen mood symptoms. As physiologic systems change with aging, elimination of drugs is slowed. Examples are slowed renal elimination of lithium and slowed hepatic metabolism of VPA. As a result, dosages required for therapeutic effect are lower in geriatric patients. Also, changes in membrane permeability increase risk of CNS side effects. Increased frequency of patient monitoring is required, including serum drug concentration monitoring. As a result, older patients may respond at lower serum levels and may experience toxicity when serum levels are within the normal therapeutic range for younger adults.

Vigilance for drug–drug interactions is required because more medications tend to be prescribed to older adults and their enhanced sensitivity to adverse effects. Pharmacokinetic interactions include metabolic enzyme induction or inhibition and protein binding displacement interactions (eg, divalproex and warfarin). Pharmacodynamic interactions include additive sedation and cognitive toxicity, which increases risk of falls and other impairments.

▶ *Pregnancy and Postpartum*

Treatment of bipolar disorder during pregnancy is fraught with controversy and conflicting recommendations. The key issue is the relative risk of teratogenicity with drug use during pregnancy versus risk of bipolar relapse without treatment with consequent harm to both patient and fetus. Therapeutic judgments depend on the history of the patient and whether the pregnancy is planned or unplanned. Treatment is best managed when pregnancy is planned. Clinicians should discuss the issue with every patient with bipolar disorder who is of childbearing potential. A pregnancy test should be obtained before initiating therapy. For a patient with severe illness or a history of multiple mood episodes, rapid cycling, or suicide attempts, discontinuing treatment, even for a planned pregnancy, is unwise. For a patient with a remote history of a single mood episode with subsequent long-term stability and contemplating pregnancy, the answer is less clear. Patients should be provided clear and reliable information about risks versus benefits of stopping or continuing therapy so they can make an informed decision. Patients who decide to discontinue medication before pregnancy should taper medication slowly.[14,36]

Lithium administration during the first trimester is associated with Ebstein's anomaly, a downward displacement of the tricuspid valve. Although cardiac defects are more likely to occur in children of patients who took lithium during pregnancy, the absolute risk appears to be small.[37] Pharmacokinetic handling of lithium changes as pregnancy progresses. Renal lithium clearance increases, which requires a dosage increase to maintain a therapeutic serum concentration. It is advisable to decrease or discontinue lithium at term or onset of labor to avoid toxicity postpartum when there is a large reduction in fluid volume.[38]

Lithium can cause hypotonicity and cyanosis in the neonate, termed the "floppy baby" syndrome. Most data indicate normal neurobehavioral development when these symptoms resolve. Lithium is readily transferred via breast milk. Breastfeeding is not advised for patients taking lithium.[20]

VPA and carbamazepine are human teratogens. Neural tube defects such as spina bifida occur in up to 9% of infants exposed during the first trimester. The risk of neural tube defects is related to exposure during the third and fourth weeks of gestation. As such, women with unplanned pregnancies may not know they are pregnant until after the risk of exposure has occurred. Extreme caution is recommended when patients are taking VPA.[38]

Carbamazepine can cause fetal vitamin K deficiency. Vitamin K is important for facial growth and for clotting factors. The risk of facial abnormalities is increased with carbamazepine and VPA, and neonatal bleeding is increased in infants of mothers who are treated with carbamazepine during pregnancy.[39,40]

Fewer data are available on other anticonvulsant mood-stabilizing drugs. Lamotrigine may be associated with an increased risk of oral clefts but, overall, may be relatively safer in pregnancy than other anticonvulsants.[39,40]

The FGAs have been available for many years, and more data are available on their use in pregnancy compared with SGAs, but guidelines for bipolar disorder do not otherwise support FGAs as an initial choice.

Use of antidepressant drugs during pregnancy is discussed in the chapter on depression.

OUTCOME EVALUATION

Assessment of Therapeutic Effects

Effective interviewing skills and a therapeutic relationship with the patient are essential to assessing response. Understand the particular symptom profile and needs of individual patients. These are the primary therapeutic monitoring parameters. In

Patient Encounter Part 4: Outcome Evaluation

After an initial assessment, including evaluation of suicide risk, presence of support systems, and need for inpatient versus outpatient treatment, Brad was hospitalized for 5 days and subsequently followed in the community on a mood stabilizer. He was also enrolled in cognitive behavioral therapy to focus on maintaining healthy relationships and decreasing his use of alcohol. Brad has cut back his alcohol intake to one beer each night and his job performance has returned to normal although he is still on probation. He has stopped frequenting bars, preferring to stay home and watch TV. Due to Brad's abnormal renal function and family history of kidney disease, he was started on divalproex DR 500 mg by mouth three times daily. Current serum valproic acid level is 105 mcg/mL (mg/L; 728 µmol/L). He returns to the clinic for routine follow-up.

Brad initially complained of mild nausea and somnolence which have resolved, but he reports difficulty remembering to take his medication three times each day and asks if his medication can be changed. He also asks how much longer he will need to take the medication. He is switched to extended release divalproex 1750 mg by mouth daily and tolerates this well.

How would you assess therapeutic and adverse effects of treatment for this patient?

How would you educate the patient regarding the need for continued maintenance treatment?

Patient Care Process

Collect information:

- Assess the patient's symptoms.
- Review the family history, including the history of response to treatment by family members.
- Obtain an initial medical evaluation to rule out other causes of mood episodes.
- Evaluate physiologic parameters that may influence pharmacokinetics.
- Obtain a thorough medication use history, including present and past prescription and nonprescription drugs, the patient's self-assessment of response and side-effects, alcohol, tobacco, caffeine, illicit substances, herbal products, dietary supplements, allergies, and adherence.

Assess the Information:

- Assess potential drug–disease, drug–drug, and drug–food interactions.

Develop a Care Plan:

- Develop a plan for monitoring therapeutic outcomes, focusing on the individual symptom profile and level of function of the patient. Include a plan for dosage adjustments or alternate therapy if the patient fails to respond adequately. Include serum drug concentration monitoring as appropriate.
- Develop a monitoring plan for drug side effects. Include measures to prevent side effects as well as management if they occur. Include appropriate laboratory measures.
- Determine the role of nonpharmacological therapy and how it is to be integrated with drug therapy.

Implement the Care Plan:

- Educate the patient on the nature of bipolar disorder, its treatment, and what to expect with regard to response and side effects, and stress the need for adherence to treatment even when feeling well.
- Encourage a healthy lifestyle, including eliminating or stopping substance abuse, smoking cessation, and encouraging proper nutrition and exercise.

Follow-up: Monitor and Evaluate:

- See the patient daily if hospitalized or weekly if an outpatient to assess efficacy and safety until stabilized. Utilize the clinical interview, physical examination, and lab tests.
- Once stabilized, follow-up at decreased frequency, every 3 to 6 months. Use the same parameters and check for new drugs or drug–drug interactions.

addition to clinical interview, some clinicians use symptom rating scales such as the Young Mania Rating Scale (YMRS) for mania and the Hamilton Depression Rating Scale (Ham-D, discussed in the chapter on depression). The YMRS is composed of 11 items based on a patient's perception over the preceding 48 hours. Adjunctive information is obtained from clinical observations. The scale takes about 15 to 30 minutes to administer.[41] Check serum concentrations of mood-stabilizing drugs as a guide to dosage adjustment for optimal efficacy. The frequency of follow-up visits depends on response, tolerability, and adherence.

Assessment of Adverse Effects

Adverse effects cause more nonadherence than any other factor. Monitor patients regularly for adverse effects and health status, especially because mood stabilizers and antipsychotics commonly cause metabolic side effects such as weight gain. Repeat laboratory tests for renal and thyroid function for patients taking lithium and hematology and liver function for patients taking carbamazepine or divalproex. More specific discussion of metabolic side effect monitoring of patients taking SGAs is provided in the chapter on schizophrenia.

Patient Education

LO 10

KEY CONCEPT Education of the patient regarding benefits and risks of drug therapy and the importance of adherence to treatment must be integrated into pharmacologic management. This is important because responsiveness to treatment declines as the number of mood episodes increases. Discuss the nature and chronic course of bipolar disorder and risks of repeated relapses. Help patients understand treatment is not a cure but that many patients enjoy symptom-free or nearly symptom-free function. Make it clear that long-term recovery is dependent on adherence to pharmacologic and nonpharmacological treatment. Explain the purpose of medication, common side effects to expect, and how to respond to side effects. Provide the patient and family with written information about indications, benefits, and side effects. Discuss less frequent but more dangerous side effects of drugs, and give written instructions on seeking medical attention immediately should they occur.

Abbreviations Introduced in This Chapter

5-HT	5-hydroxytryptamine
Abd	Abdomen
ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
BDNF	Brain-derived neurotrophic factor
BP	Blood pressure
CBC	Complete blood count
CBT	Cognitive-behavioral therapy
CN	Cranial nerve
CNS	Central nervous system
DA	Dopamine
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
Exts	Extremities
FDA	Food and Drug Administration
FGA	First-generation antipsychotic
fMRI	Functional magnetic resonance imaging
FOI	Flight of ideas
GABA	γ-Aminobutyric acid

GI	Gastrointestinal
HAM-D	Hamilton Depression Rating Scale
β-HCG	Beta-human chorionic gonadotropin
HIV	Human immunodeficiency virus
JVD	Jugular venous distention
LMP	Last menstrual period
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
NE	Norepinephrine
P	Pulse
PERRLA	Pupils equal round and reactive to light and accommodation
PET	Positron emission tomography
RR	Respiration rate
SGA	Second-generation antipsychotic
T	Temperature
THC	Tetrahydrocannabinol, psychoactive substance in marijuana
VPA	Valproic acid
YMRS	Young Mania Rating Scale

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatric Press; 2013.
2. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011;68:241–251.
3. Thase ME. Mood disorders: neurobiology. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:1664–1674.
4. Kerner B. Genetics of bipolar disorder. Appl Clin Genet. 2014;7:33–42.
5. Serretti A, Drago A, De Ronchi D. Lithium pharmacodynamics and pharmacogenetics: focus on inositol mono phosphatase (IMPase), inositol poliphosphatase (IPPase) and glycogen sinthase kinase 3 beta (GSK-3 beta). Curr Med Chem. 2009;16:1917–1948.
6. Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: an historical overview and future directions. Psychiatry Clin Neurosci. 2010;64:341–357.
7. Bobo WV. The Diagnosis and Management of Bipolar I and II Disorders: Clinical Practice Update. Mayo Clin Proc. 2017;92(10):1532–1551.
8. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry. 2002;59:530–537.
9. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry. 2003;60:261–269.
10. Hirschfeld RM, Holzer C, Calabrese JR, et al. Validity of the mood disorder questionnaire: a general population study. Am J Psychiatry. 2003;160:178–180.
11. Novick DM, Swartz HA, Frank E. Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. Bipolar Disord. 2010;12:1–9.
12. Sidor MM, Macqueen GM. An update on antidepressant use in bipolar depression. Curr Psychiatry Rep. 2012;14:696–704.
13. McMahon K, Herr NR, Zerubavel N, Hoertel N, Neacsiu AD. Psychotherapeutic treatment of bipolar depression. Psychiatr Clin North Am. 2016;39(1):35–56.
14. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update on CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15:1–44.
15. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011;378:1306–1315.
16. Severino G, Squassina A, Costa M, et al. Pharmacogenomics of bipolar disorder. Pharmacogenomics. 2013;14:655–674.
17. Pacchiarotti I, Bond DJ, Baldessarini RJ, et al. The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry. 2013;170(11):1249–1262.
18. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ. 2013;346:f3646.
19. Meyer JM. Pharmacotherapy of psychosis and mania. In: Brunton LL, Chabner BA, Knollmann BC, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed. New York, NY: McGraw-Hill; 2011:417–456.
20. Lithium carbonate package insert. Columbus, OH: Roxane Laboratories; 2016.
21. Depakote (divalproex sodium) package insert. North Chicago, IL: Abbvie Inc; 2016.
22. Equetro (carbamazepine extended-release) package insert. Parsippany, NJ: Validus Pharmaceuticals LLC; 2016.
23. Grover S, Kukreti R. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. Pharmacogenet Genomics. 2014;24(2):94–112.
24. Lamictal (lamotrigine) package insert. Research Triangle Park, NC: GlaxoSmithKline; 2015.
25. Trileptal (oxcarbazepine) package insert. East Hanover, NJ: Novartis Pharmaceuticals; 2017.
26. Vasudev A, Macritchie K, Vasudev K, et al. Oxcarbazepine for acute affective episodes in bipolar disorder. Cochrane Database Syst Rev. 2011;(12):CD004857.
27. Nardi AE, Perna G. Clonazepam in the treatment of psychiatric disorders: an update. Int Clin Psychopharmacol. 2006;21:131–142.
28. Vieta E, Suppes T, Ekholm B, et al. Long-term efficacy of quetiapine in combination with lithium or divalproex on mixed symptoms in bipolar I disorder. J Affect Disord. 2012;142:36–44.
29. Aripiprazole package insert. Tokyo: Otsuka Pharmaceutical. Tokyo, Otsuka Pharmaceutical; 2017.
30. Seroquel XR package insert. Wilmington, DE: AstraZeneca Pharmaceuticals; 2017.
31. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. 2004;27:596–601.
32. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry. 2006;163:232–239.
33. Thomas T, Stansifer L, Findling RL. Psychopharmacology of pediatric bipolar disorders in children and adolescents. Pediatr Clin North Am. 2011;58:173–187.
34. Pringsheim T, Lam D, Ching H, et al. Metabolic and neurological complications of second-generation antipsychotic use in children: a systematic review and meta-analysis of randomized controlled trials. Drug Saf. 2011;34:651–668.

35. Lala SV, Sajatovic M. Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: a literature review. J Geriatr Psychiatry Neurol. 2012;25:20–25.
36. Yonkers KA, Vigod S, Ross LE. Diagnosis, pathophysiology, and management of mood disorders in pregnant and postpartum women. Obstet Gynecol. 2011;117:961–977.
37. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. N Engl J Med. 2017;376(23):2245–2254.
38. Deligiannidis KM, Byatt N, Freeman MP. Pharmacotherapy for mood disorders in pregnancy. A review of pharmacokinetic changes and clinical recommendations for therapeutic drug monitoring. J Clin Psychopharmacol. 2014;34:244–255.
39. Wlodarczyk BJ, Palacios AM, George TM, et al. Antiepileptic drugs and pregnancy outcomes. Am J Med Genet A. 2012;158A:2071–2090.
40. Drayton SJ, Fields CS. Bipolar disorder. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill.
41. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429–435.

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40 Generalized Anxiety Disorder, Panic Disorder, and Social Anxiety Disorder

Sheila R. Botts, Sallie H. Charles, and Douglas A. Newton

LEARNING OBJECTIVES

LO

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

1. Explain the pathophysiologic mechanisms underlying anxiety disorders.
2. Recognize common presenting symptoms of generalized anxiety, panic, and social anxiety disorder (SAD).
3. List treatment goals for patients with generalized anxiety, panic, and SAD.
4. Identify appropriate lifestyle modifications and over-the-counter medication use in these patients.
5. Compare the efficacy and tolerability profiles of psychotherapy and pharmacotherapy interventions for anxiety disorders.
6. Design a patient-specific pharmacotherapy treatment plan for patients with generalized anxiety, panic, and SAD.
7. Develop a monitoring plan for patients with anxiety placed on specific medications.
8. Formulate appropriate educational information to be provided to a patient receiving pharmacotherapy for generalized anxiety, panic, and SAD.

INTRODUCTION

Anxiety disorders are among the most frequent mental disorders encountered by clinicians.[1-3] All anxiety disorders are highly comorbid and share features of fear and anxiety that differ from developmentally normative fear or anxiety by being excessive, persistent, and resulting in behavioral disturbances.[1] Anxiety disorders are associated with significant patient and family burden, functional impairment, and increased risk of developing comorbid major depressive disorder (MDD).[1-4]

Initial detection and diagnosis generally falls to primary care clinicians, to whom most patients present in the context of other complaints.[4] Anxiety disorders are often missed or attributed incorrectly to other medical illnesses, and most patients are treated inadequately.[4] Untreated anxiety disorders are associated with increased health care utilization, morbidity and mortality, and a poorer quality of life.[1-4]

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

▶ *Prevalence*

The lifetime prevalence of anxiety disorders collectively is 28.8% with specific phobia (12.5%) and social anxiety disorder (SAD; 12.1%) being the most common.[2,3] Data from the National Comorbidity Survey, Revised (NCS-R) estimate the lifetime prevalence of generalized anxiety disorder (GAD) for those 18 years of age and older to be 5.7%, closely followed by panic disorder (PD) at 4.7%.[2,3]

Anxiety disorders are more prevalent among women than men (2:1).[2] Prevalence rates across the anxiety spectrum increase from the younger age group (18–29 years) to older age groups (30–44 and 45–59 years); however, rates are substantially lower for those older than age 59 years.[2]

▶ *Course of Illness*

PD and GAD have median ages of onset of 24 and 31 years, respectively, whereas SAD develops earlier (median age 13 years).[3] Although GAD and PD may not fully manifest until adulthood, as many as half of adult patients with anxiety report subthreshold symptoms during childhood.[5]

Anxiety disorders are chronic, and symptoms tend to wax and wane, with fewer than one-third of patients experiencing spontaneous symptom **remission**.[6] As such, the risk for relapse and recurrence of symptoms is high. In a 12-year follow-up study of anxiety disorder patients, recurrence rates ranged from 58% of PD and GAD patients to 39% of SAD patients.[7]

Remission, if achieved with treatment, is most likely to occur within the first 2 years of an index episode.[6] Similarly, the highest rates of relapse are within the same time frame. This suggests that many patients need ongoing maintenance treatment. Rates of remission and relapse do not appear to vary by sex.[6] Patients with anxiety disorders spend a significant portion of time "being ill" during a particular episode, ranging from 41% to 80% of the time.[7] Anxiety disorders are associated with impaired psychosocial functioning and a compromised quality of life.[8] Appropriate treatment improves overall quality of life and psychosocial functioning.[8]

▶ *Comorbidity*

More than 90% of individuals with an anxiety disorder have a lifetime history of one or more other psychiatric disorders.[9] Depression is the most common comorbidity, followed by alcohol and substance use disorders, as well as other co-occurring anxiety disorders, especially GAD and PD.[9] Generally, the onset of SAD and GAD symptoms precedes MDD, but there is an equal chance of PD onset before, during, or after MDD.

Etiology

Both genetic and psychosocial factors appear to play a role in the initiation and expression of anxiety disorders.[10,11] Moderate genetic risk has been identified for all anxiety disorders. Family and twin epidemiologic studies support familial aggregation of anxiety disorders (odds ratio [OR] 4–6) with heritability of 30% to 50%.[11] Twin studies further suggest that anxiety disorders share genetic risk factors which may help to explain the pattern of comorbidity. Candidate gene studies as well as genome wide association sequence (GWAS) studies seeking to identify genes contributing to risk have been inconclusive to date.[11]

Genetic factors may create a vulnerable phenotype for anxiety disorders, but environmental factors (eg, stressful life events, illness, parental relationships) contribute to the development and persistence of the disorder.[11] Marital status (single or divorced vs married), poor social support, low socioeconomic status, and education are associated with increased risk of developing an anxiety disorder.[1] Some researchers believe that stressful life events may have a strong role in the onset of anxiety disorders, especially in GAD and PD.[10] It has been reported that those experiencing one or more negative life events have a threefold increased chance of developing GAD.[1] Similar findings have been reported with PD.[12]

PATHOPHYSIOLOGY

LO 1

The thalamus, amygdala, nucleus accumbens, hippocampus, hypothalamus, and prefrontal cortex are key components of the neurocircuitry of fear response[13] and may play a central role in most anxiety disorders (Figure 40–1). Sensory data from environmental threats are first processed by the thalamus.

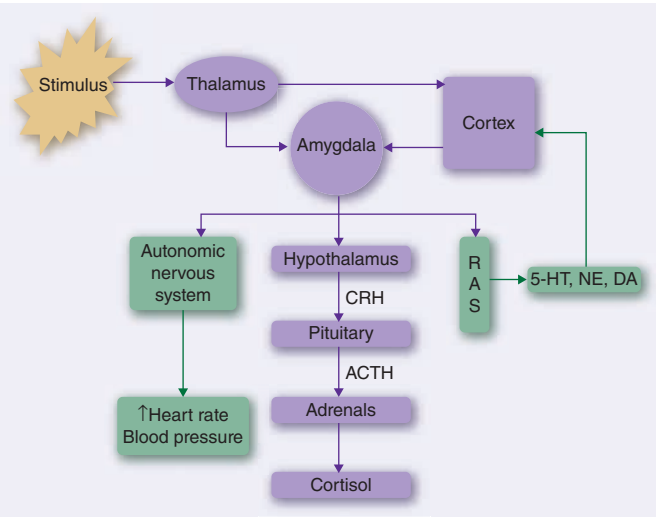

FIGURE 40–1. Neurocircuitry and key neurotransmitters involved in mediating anxiety disorders. (ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone; DA, dopamine; 5-HT, serotonin; NE, norepinephrine; RAS, reticular activating system.)

Information is simultaneously passed on to cortical centers for finer processing and to the amygdala for rapid assessment of highly charged emotional information. The amygdala provides emotional valence or importance of the information and enables quick action or response to an ambiguous but vital threat. The cortex performs a more detailed analysis and sends updates to the amygdala for comparison and any needed course corrections.

Anxiety disorders develop when the fear-response system leads to maladaptive behavior or distress. Anxiety occurs independent of stimuli (PD), is associated with benign stimuli (eg, phobias), or continues beyond the stimulus duration (eg, GAD). Direct and indirect connections to the reticular activating system (RAS), a region spanning the medulla, pons, and midbrain, help to regulate arousal, vigilance, and fear. These connections are modulated by serotonin (5-HT) and norepinephrine (NE), which have their primary origins in the RAS.[14] The amygdala sends projections to the hypothalamus, thus influencing the autonomic nervous system to affect heart rate, blood pressure, and stress-associated changes. It also influences the hypothalamic–pituitary–adrenal (HPA) axis, leading to a cascade of stress hormones.[14] Elevation of stress hormones, such as cortisol, for prolonged periods can damage the brain and other organs.[14]

Noradrenergic System

Norepinephrine-producing cells reside primarily in a region of the brain called the locus ceruleus (LC). Increased activity in this region is associated with an increase in arousal, anxiety, and panic. Drugs such as yohimbine that increase activity in the LC can be anxiogenic; drugs that decrease activity in the LC appear to improve anxiety. Furthermore, dysregulation of this region is implicated by elevated levels of NE or its metabolites in subjects with GAD, PD, and specific phobias.[15]

Serotonergic System

The raphe nuclei and the resident cell bodies of 5-HT-producing neurons have a complicated role related to anxiety symptoms. Activity of 5-HT cells in the raphe nuclei over time inhibits firing of noradrenergic cells in the LC. Other influences include their ability to regulate cells in the prefrontal cortex and amygdala. Perhaps the strongest evidence for the involvement of the serotonergic system is the success of serotonin reuptake inhibitors in treatment of anxiety disorders.[14]

γ-Aminobutyric Acid

γ-Aminobutyric acid (GABA) plays a complex role as an inhibitory neurotransmitter with nonspecific effects. GABAergic drugs reduce anxiety, but the lack of a specific target for their effect leads to multiple undesirable effects. Current research is focused on defining receptor subtypes that may allow for greater specificity in targeting anxiety symptoms.[14]

Hypothalamic–Pituitary–Adrenal Axis

The HPA axis provides a critical mechanism for regulation of the stress response and its effects on the brain and other organ systems. Several important hormones, including corticotropin-releasing hormone and cortisol, are involved in this pathway. These hormones regulate the effects of anxiety on the body and provide positive feedback to the brain.[13] A cycle of anxiety and sensitization by such feedback could, if unchecked, result in escalation of symptoms. Neuropeptides may provide one mechanism to balance positive and negative feedback, helping to minimize such escalation.

Patient Encounter 1, Part 1

A 32-year-old woman presents to her primary care team with complaints of fatigue, headaches, abdominal pain, and insomnia. She is tearful and reports "not feeling well" and is concerned she might have a serious illness. She has a family history of breast cancer and worries that she too will have cancer. She reports worrying about her health, her relationship with a significant other, her job, and finances. She is an elementary school teacher and likes her job, but worries she is not performing to expectations. She drinks wine daily, and smokes cannabis 1 to 2 times a month. She presented to the emergency department 2 weeks ago with a panic attack and was discharged with a prescription for diazepam. Her medical history is positive for depression.

Meds: Diazepam 5 mg po BID prn anxiety

What manifestations described above are suggestive of an anxiety disorder?

What additional information do you need to establish a diagnosis and develop a treatment plan?

What other diagnoses should be considered in your differential diagnosis?

Could her medication be contributing to her symptoms?

Neuropeptides

Several neuropeptides (eg, neuropeptide Y [NPY], substance P, and cholecystokinin) are under investigation for their role in anxiety disorders. NPY appears to reduce the effect of stress hormones and inhibit activity of the LC. Both mechanisms may contribute to the anxiolytic properties seen experimentally. Substance P may have anxiolytic and antidepressant properties partly because of its effects on corticotropin-releasing hormone.[16]

CLINICAL PRESENATION AND DIAGNOSIS

Anxiety disorders share common etiology and risk factors yet have distinct clinical presentation, diagnostic criteria, and treatment recommendations and thus will be discussed separately. Treatment guidelines recommend screening for the presence of anxiety symptoms using general questions such as "During the past 2 weeks how much have you been bothered by the following: (1) feeling nervous, anxious, frightened, worried, or on edge, (2) feeling panic or being frightened, (3) avoiding situations that make you anxious."[1,17] Positive **responses** should result in further assessment. Suicide risk assessment is recommended for all anxiety disorders as the risk of suicide attempts is increased irrespective of the presence of a comorbid mood disorder.[17,18]

TREATMENT: GENERALIZED ANXIETY DISORDER

Desired Outcomes

LO 3

The goals of therapy for GAD are to acutely reduce the severity and duration of anxiety symptoms and restore overall functioning. The long-term goal is to achieve and maintain remission. With a positive response to treatment, comorbid depressive symptoms should be minimized.

Clinical Presentation and Diagnosis of GAD

General

Onset is typically in early adulthood. Anxiety emerges and dissipates more gradually than in PD. The intensity and duration of anxiety is out of proportion to the likelihood or impact of the anticipated event. Laboratory evaluation usually is reserved for later onset, atypical presentation, or poor response to treatment.

Symptoms[1]

LO 2

- Essential feature is excessive anxiety or worry involving multiple events or activities occurring more days than not for at least 6 months
- Difficulty controlling worry
- Anxiety and worry associated with at least three of the following:
  - Restlessness
  - Easily fatigued
  - Poor concentration or mind going blank
  - Irritability
  - Muscle tension
  - Insomnia or unsatisfying sleep
- The anxiety or worry causes significant distress or functional impairment and is NOT attributable to another substance, medical, or psychiatric condition

Differential Diagnosis

Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (Tables 40–1 and 40–2)

Table 40–1

Medical Conditions That Can Cause Anxiety

Psychiatric Disorders
Mood disorders, hypochondriasis, personality disorders, alcohol or substance abuse, alcohol or substance withdrawal, other anxiety disorders

Neurologic Disorders
CVA, seizure disorders, dementia, stroke, migraine, encephalitis, vestibular dysfunction

Cardiovascular Disorders
Angina, arrhythmias, congestive heart failure, mitral valve prolapse, myocardial infarction

Endocrine and Metabolic Disorders
Hypothyroidism or hyperthyroidism, hypoglycemia, Cushing disease, Addison disease, pheochromocytoma, hyperadrenocorticism, hyponatremia, hyperkalemia, vitamin B_{12} deficiency

Respiratory Disorders
Asthma, COPD, pulmonary embolism, pneumonia, hyperventilation

Other
Carcinoid syndrome, anemias, SLE

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; SLE, systemic lupus erythematosus.

Data from Refs. 1 and 17.

Table 40–2

Medications Associated with Anxiety Symptoms

Category	Examples
Anticonvulsants	Carbamazepine, ethosuximide
Antidepressants	Bupropion, SSRIs, SNRIs, TCAs
Antihypertensives	Felodipine
Antimicrobials	Cephalosporins, ofloxacin, isoniazid
Antiparkinson drugs	Levodopa
Bronchodilators	Albuterol, isoproterenol, theophylline
Corticosteroids	Prednisone, methylprednisolone
Decongestants	Pseudoephedrine, phenylephrine
Herbals	Ma huang, St. John's wort, ginseng, guarana, belladonna
NSAIDs	Ibuprofen, indomethacin
Stimulants	Amphetamines, caffeine, cocaine, methylphenidate
Thyroid hormones	Levothyroxine
Toxicity	Anticholinergics, antihistamines, digoxin
Withdrawal of CNS depressants (abrupt)	Alcohol, barbiturates, benzodiazepines

CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Data from Refs. 1, 19, and 20.

General Approach to Treatment

KEY CONCEPT Patients with GAD may be managed with psychotherapy, pharmacotherapy, or both. Treatment should be individualized based on symptom severity, comorbid illnesses, medical status, age, access to care, cost, and patient preference. Patients with severe symptoms resulting in functional impairment should receive antianxiety medication.

Nonpharmacologic Therapy

LO 4 Nonpharmacologic therapy includes psychoeducation, exercise, stress management, and psychotherapy. Psychoeducation should provide information on GAD and its management. Patients should be instructed to avoid stimulating agents, for example, caffeine, decongestants, diet pills, and excessive alcohol use. Regular exercise is also recommended. Cognitive-behavioral therapy (CBT) is the most effective psychological therapy for GAD patients. It helps patients to recognize and alter patterns of distorted thinking and dysfunctional behavior. Treatment gains with CBT may be maintained for up to 1 year.[20] CBT may be delivered in individual or group settings.[17,21] Computerized CBT offered over the Internet is effective and may offer an alternative to face-to-face therapy for patients with access barriers.[22] LO 5 The effect sizes of trials with CBT are comparable to those of pharmacologic therapies.[17,20] CBT is effective for children with GAD and combined with medication may be superior to either treatment alone.[23]

Pharmacologic Therapy

Antidepressants, benzodiazepines, pregabalin, buspirone, hydroxyzine, and the second-generation antipsychotics (SGAs) have controlled clinical trial data supporting their use in GAD. KEY CONCEPT Antidepressants are the drugs of choice for chronic GAD because of a tolerable side-effect profile; no risk for dependency; and efficacy in common comorbid conditions, including depression, panic, obsessive-compulsive disorder (OCD), and SAD. Benzodiazepines remain the most effective and commonly used treatment for short-term management of anxiety when immediate relief of symptoms is desired. They are also recommended for intermittent or adjunctive use during GAD exacerbation or for sleep disturbance during the initiation of antidepressant treatment.[17,20] Buspirone and pregabalin are alternative agents for patients with GAD without depression. Hydroxyzine is usually adjunctive and is less desirable for long-term treatment because of side effects, for example, sedation and anticholinergic effects.

Patient Encounter 1, Part 2

After a medical workup, she was diagnosed with GAD, unspecified depressive disorder and alcohol use disorder.

PMH: Depression

FH: Mother treated for depression; father, alcohol dependence

SH: Two to three drinks per night; lives alone in apartment

Meds: Diazepam 5 mg po BID prn anxiety

What are first-line treatment options for this patient?

What factors should be considered in selecting the patient's treatment?

What is the role of benzodiazepines for this patient?

How should the patient be monitored when receiving an antidepressant?

LO 3 Patients with GAD should be treated to symptom remission. Continuation of antidepressant therapy after acute response significantly decreases the risk of relapse (OR 0.2 [0.15–0.26]).[24] Guidelines recommend continuing treatment for 6 months to 1 year.[17,20,21,25] An algorithm for the pharmacologic management of GAD is shown in Figure 40–2.

▶ *Antidepressants*

Antidepressants (Table 40–3) reduce the psychic symptoms (eg, worry and apprehension) of anxiety with a modest effect on autonomic or somatic symptoms (eg, tremor, rapid heart rate, and/or sweating). All antidepressants evaluated provide a similar degree of anxiety reduction. The onset of antianxiety effect is delayed 2 to 4 weeks. Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) are preferred over tricyclic antidepressants (TCAs) because of improved safety and tolerability. Selection of a specific antidepressant generally is based on history of prior response, side effect and drug interaction profile (see Chapter 38), cost, or formulary availability.

Antidepressants modulate synaptic 5-HT, NE, and/or dopamine (DA) reuptake and receptor-activated neuronal signal transduction. These intracellular changes modify the expression of genes and proteins important in stress response (eg, glucocorticoid receptors, brain-derived neurotrophic factor, corticotropin-releasing hormone).[26] Activation of these "stress-adapting" pathways may improve both somatic and psychic symptoms of anxiety.[26]

Selective Serotonin Reuptake Inhibitors The SSRIs paroxetine, escitalopram, and sertraline have been shown to be significantly more effective than placebo in reducing anxiety symptoms in adults with GAD. Response rates range from 56% to 68% during acute treatment, with remission achieved in

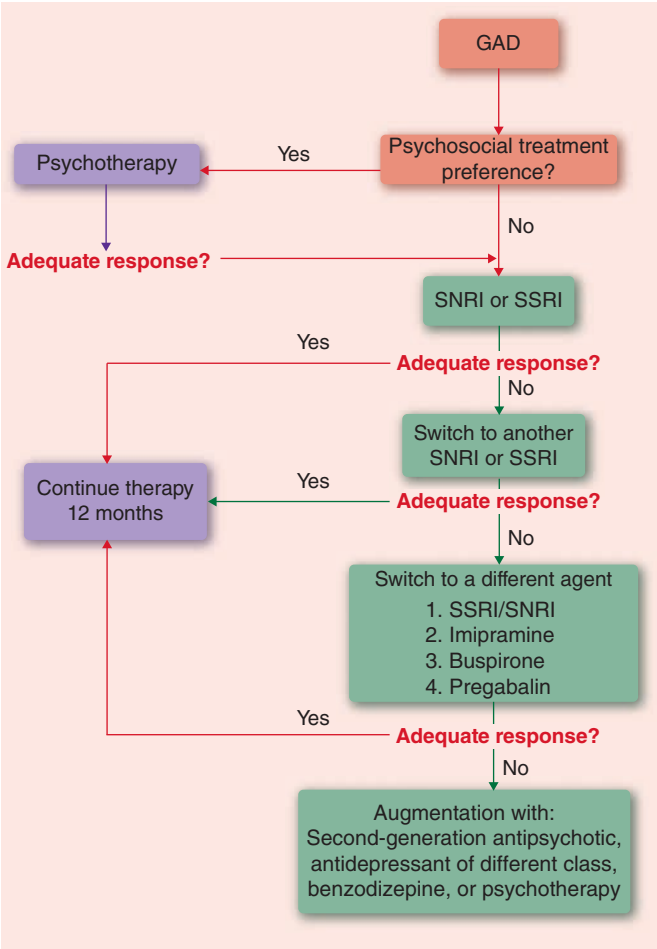

FIGURE 40–2. Treatment algorithm for generalized anxiety disorder. (SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.) (Data from Refs. 17, 19, 20, 25.)

approximately one-third of patients.[17,20,25,27] Common side effects include somnolence, headache, nausea, dry mouth (paroxetine), diarrhea (sertraline), sweating (sertraline), decreased libido, ejaculation disorder, anorgasmia, and asthenia.

SSRI therapy is better tolerated than TCAs, and tolerability is similar to that of SNRIs. The SSRIs, sertraline, fluoxetine, and fluvoxamine, have demonstrated benefits in children and adolescents with GAD and are the preferred pharmacologic treatment in this population.[21]

Serotonin Norepinephrine Reuptake Inhibitors Venlafaxine and duloxetine alleviate anxiety with or without comorbid depression, and maintain response with extended treatment.[17,20,25,27] Venlafaxine and duloxetine are effective for GAD in children and adolescents.[22] Common side effects reported in patients with GAD are nausea, somnolence, dry mouth, dizziness, sweating, constipation, and anorexia.

Vortioxetine has been evaluated in the treatment of GAD with conflicting results; however, a recent meta-analysis of four randomized controlled acute trials found vortioxetine more effective than placebo in reducing anxiety symptoms.[28]

Tricyclic Antidepressants Imipramine treatment of GAD results in a higher rate of remission of anxiety symptoms than treatment with trazodone or diazepam.[20] Both antidepressants were more effective than diazepam or placebo in reducing psychic symptoms of anxiety. TCA use is limited by bothersome adverse effects (eg, sedation, orthostatic hypotension, anticholinergic effects, and weight gain). TCAs have a narrow therapeutic index and are lethal in overdose because of atrioventricular block.

Novel Antidepressants Mirtazapine, an α-2 adrenergic antagonist and postsynaptic 5-HT_2 and 5-HT_3 receptor antagonist, is an effective antidepressant but has not been extensively evaluated in anxiety disorders. It is not associated with sexual dysfunction, but does have a propensity to cause sedation and weight gain. Bupropion, a DA and NE reuptake inhibitor, lacks the common antidepressant side effects of weight gain and sexual dysfunction. Bupropion has not been studied or used extensively in anxiety disorders. However, a small controlled trial comparing bupropion XL with escitalopram found bupropion to have comparable anxiolytic efficacy and tolerability.[17,20] Vilazodone, a SSRI and 5-HT1A receptor partial agonist, has shown benefit compared to placebo in several short-term randomized controlled trials in GAD, but does not appear to have advantages over generically available SSRIs/SNRIs.[29]

▶ *Benzodiazepines*

KEY CONCEPT Benzodiazepines are recommended for acute treatment of GAD when short-term relief is needed, as an adjunct during initiation of antidepressant therapy, or to improve sleep.[17,20,27] Benzodiazepine treatment results in a significant improvement in 65% to 75% of GAD patients, and most of the improvement occurs in the initial 2 weeks.[20] They are more effective for somatic symptoms than psychic symptoms. Major benzodiazepine disadvantages are lack of effectiveness for depression; risk for withdrawal and potential need for taper; risk for dependency and abuse; and potential interdose rebound anxiety, especially with short-acting benzodiazepines. They should be avoided in older adults and patients with current or past chemical dependency.

Benzodiazepines enhance transmission of the inhibitory neurotransmitter GABA through interaction with the $GABA_A$-receptor complex.[19,20] All benzodiazepines are expected to provide equivalent benefit when given in comparable doses. They differ substantially in their pharmacokinetic properties and potency for the $GABA_A$-receptor (Table 40–4).

Benzodiazepines are metabolized by hepatic oxidation (cytochrome P450 3A4) and glucuronide conjugation. Because lorazepam and oxazepam bypass hepatic oxidation and are conjugated only, they are preferred agents for patients with reduced hepatic function secondary to aging or disease (eg, cirrhosis; hepatitis B or C from intravenous drug use). Many benzodiazepines are metabolized to long-acting metabolites (Table 40–4) that provide long-lasting anxiety relief. Drugs that either inhibit or induce CYP450 isozymes or glucuronidation can cause drug interactions (Table 40–5).

The most common side effects of benzodiazepine therapy include central nervous system (CNS) depressive effects (eg, drowsiness, sedation, psychomotor impairment, and ataxia) and cognitive effects (eg, poor recall and anterograde amnesia). Anterograde amnesia is more likely with high-potency benzodiazepines such as alprazolam.[33] Some patients also may be disinhibited and experience confusion, irritability, aggression, and excitement.[19,20] Discontinuation of benzodiazepines may be associated with withdrawal, rebound anxiety, and a high rate of relapse. Higher doses of benzodiazepines and a longer duration of therapy increase the severity of withdrawal and risk of seizures after abrupt or rapid discontinuation. Patients should be tapered rather than discontinued abruptly from benzodiazepine therapy

Table 40–3

Pharmacotherapy for the Treatment of Generalized Anxiety Disorder

Medication Class	Recommended Starting Dose (mg/day)	Usual Therapeutic Dosage Range (mg/day)	Hepatic Insufficiency	Renal Insufficiency
Antidepressants				
SSRIs				
Citalopram[a] (Celexa)	20	20–40	Maximum, 20 mg/day	
Escitalopram[b] (Lexapro)	10	10–20	Maximum, 10 mg/day	
Fluoxetine (Prozac)	20	20–80	Titrate with caution	
Fluvoxamine (Luvox)	50	100–300	Titrate with caution	
Paroxetine (Paxil)[b]	20	20–50	Titrate with caution	
Paroxetine CR (Paxil CR)	25	25–62.5	Maximum, 50 mg/day	Maximum, 50 mg/day
Sertraline (Zoloft)	50–100	50–200	Reduce dose	
SNRIs				
Venlafaxine XR[b] (Effexor XR)	75	75–225	Reduce dose by 50%	Reduce dose 25%–50%
Desvenlafaxine (Pristiq)	50	50–100	Maximum, 100 mg/day	Maximun, 50 mg/day; CrCl < 30 mL/min (0.50 mL/s), dose once every other day
Duloxetine[b,c] (Cymbalta)	30	60–120	Use not recommended	CrCl < 30 mL/min (0.50 mL/s) Use not recommended[b]
TCAs				
Imipramine (Tofranil)	50–75	75–200	Titrate with caution	
Other Agents				
Hydroxyzine (Atarax)	25–50	50–100		Reduce dose by 50% GFR < 50 mL/min (0.83 mL/s)
Azapirones				
Buspirone (Buspar)	5–15	20–30	Not recommended in severe hepatic impairment	Not recommended in severe renal impairment
Anticonvulsants				
Pregabalin (Lyrica)	150	150–600		Reduce dose[d]
Second-Generation Antipsychotic				
Quetiapine XR (Seroquel XR)	50	50–300		

[a]Maximum daily dose of citalopram is 20 mg/day when used in the elderly or when given concomitantly with CYP2C19 inhibitors.

[b]Food and Drug Administration approved for use in generalized anxiety disorder.

[c]Duloxetine use is not recommended in severe renal impairment (creatinine clearance < 30 mL/min [0.50 mL/s]).

[d]Dose reduction recommended for CrCl < 60 mL/min (1.0 mL/s) and again for CrCl, 30 mL/min (0.50 mL/s) and 15 mL/min (0.25 mL/s).

CR, controlled-release; CrCl, creatinine clearance; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; XR, extended release.

Data from Refs. 19 and 30.

to avoid withdrawal symptoms. The duration of the taper should increase with extended duration of benzodiazepine therapy.[19,20] A general approach to the taper is to reduce the dose by 25% every 5 to 7 days until reaching half the original dose and then decreasing by 10% to 12% per week until discontinued. Patients should expect minor withdrawal symptoms and discomfort even when tapering. Rebound symptoms (eg, return of original symptoms at increased intensity) are transient. The patient should be educated that rebound anxiety is not a relapse. Relapse or recurrence of anxiety may occur in as many as 50% of patients discontinuing benzodiazepine treatment.[19,20] It is unclear if this relapse rate represents an inferiority of benzodiazepines or supports the chronic nature of GAD.

► *Pregabalin*

Pregabalin is a calcium channel modulator, and its anxiolytic properties are attributed to its selective binding to the α-2-delta subunit of voltage-gated calcium channels. Pregabalin reduces anxiety with a similar onset to alprazolam.[17,27,29] Compared with venlafaxine and placebo, pregabalin was safe, well tolerated, and efficacious in GAD, and results were seen one week sooner than with venlafaxine.[17] Pregabalin reduces the risk of relapse during maintenance treatment.[17,27,29] It has a short elimination half-life and must be dosed two to three times daily. It is excreted renally with a low risk of drug–drug interactions. Pregabalin is a schedule V controlled substance owing to a propensity to cause euphoria, and may cause withdrawal symptoms if discontinued abruptly. It should be used cautiously in patients with a current or past history of substance abuse. It is not beneficial for depression or other anxiety disorders.

► *Alternative Agents*

Hydroxyzine, buspirone, and SGAs are alternative agents. Hydroxyzine may be effective for acute reduction of somatic symptoms of anxiety[20] but not for psychic features of anxiety, depression, or other common comorbid anxiety disorders. Buspirone, a 5-HT_{1A} partial agonist, is thought to exert its anxiolytic effects by reducing presynaptic 5-HT firing.[34]

Table 40–4

Comparison of Benzodiazepines

Drug Name (Brand Name)	Metabolite	Time to Peak Concentration (hours)	Half-Life Range (hours)	Approved Dosage Range (mg/day)	Dose Equivalent (mg)
Alprazolam[a,b] (Xanax)		1–2	12–15	1–4 (GAD) 1–10 (PD)	0.5
Lorazepam[a] (Ativan)		2–4	10–20	0.5–10	0.75–1
Oxazepam[a] (Serax)		2–4	5–15	30–120	15
Clonazepam[b] (Klonopin)		1–4	18–50	1–4	0.25
Chlordiazepoxide[a] (Librium)		1–4	5–30	25–100	10
	Desmethyldiazepam		40–120		
	Desmethlychlordiazepoxide		18		
	Demoxepam		14–95		
	Oxazepam		5–15		
Clorazepate[a] (Tranxene)		1–2		7.5–60	7.5
	Desmethyldiazepam		40–120		
	Oxazepam		5–15		
Diazepam[a] (Valium)		0.5–2	20–80	2–40	5
	Desmethyldiazepam		40–120		
	Oxazepam		5–15		
	Temazepam		8–15		

[a]Food and Drug Administration (FDA) approved for use in generalized anxiety disorder.

[b]FDA approved for use in panic disorder.

[c]CYP2C19 genetic polymorphisms resulting in little or no enzyme activity are present in 15% to 20% of Asians and 3% to 5% of blacks and whites, resulting in reduced clearance of desmethyldiazepam.[34]

GAD, generalized anxiety disorder; PD, panic disorder.

Data from Refs. 30 and 31.

Table 40–5

Pharmacokinetic Drug Interactions with Benzodiazepines

Drug	Effect
Alcohol (chronic)	Increased CL of BZs
Carbamazepine	Increased CL of alprazolam
Cimetidine	Decreased CL of alprazolam, diazepam, chlordiazepoxide, and clorazepate and increased $t_{1/2}$
Disulfiram	Decreased CL of alprazolam and diazepam
Erythromycin	Decreased CL of alprazolam
Fluoxetine	Decreased CL of alprazolam and diazepam
Fluvoxamine	Decreased CL of alprazolam and prolonged $t_{1/2}$
Itraconazole	Potentially decreased CL of alprazolam and diazepam
Ketoconazole	Potentially decreased CL of alprazolam
Nefazodone	Decreased CL of alprazolam, AUC doubled, and $t_{1/2}$ prolonged
Omeprazole	Decreased CL of diazepam
Oral contraceptives	Increased free concentration of chlordiazepoxide and slightly decreased CL; decreased CL and increased $t_{1/2}$ of diazepam and alprazolam
Paroxetine	Decreased CL of alprazolam
Phenobarbital	Increased CL of clonazepam and reduced $t_{1/2}$
Phenytoin	Increased CL of clonazepam and reduced $t_{1/2}$
Probenecid	Decreased CL of lorazepam and prolonged $t_{1/2}$
Propranolol	Decreased CL of diazepam and prolonged $t_{1/2}$
Ranitidine	Decreased absorption of diazepam
Rifampin	Increased metabolism of diazepam
Theophylline	Decreased alprazolam concentrations
Valproate	Decreased CL of lorazepam

AUC, area under the plasma concentration time curve; BZ, benzodiazepine; CL, clearance; $t_{1/2}$, elimination half-life.

Adapted from Melton ST, Kirkwood CK. Anxiety disorders: I. Generalized anxiety, panic and social anxiety disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017:1079, with permission.

Unlike benzodiazepines, it does not have abuse potential, cause withdrawal reactions, or potentiate alcohol and sedative-hypnotic effects. It has a gradual onset of action (ie, 2 weeks) and does not provide immediate anxiety relief. Data are inconsistent regarding its efficacy in chronic GAD or GAD with comorbid depression.[17,20,27,29] It may be less effective in patients who have been treated previously (4 weeks–5 years) with benzodiazepines.[20]

Buspirone is well tolerated and most common side effects include dizziness, nausea, and headaches. Buspirone elimination is affected significantly by drugs that inhibit (eg, verapamil, diltiazem, itraconazole, fluvoxamine) or induce (eg, rifampin) CYP3A4.[32] Buspirone may increase blood pressure when coadministered with a monoamine oxidase inhibitor (MAOI).

The SGAs, quetiapine, olanzapine, and risperidone have demonstrated benefit in GAD. In three large placebo-controlled trials, quetiapine in daily doses of 50 to 300 mg resulted in 26% greater likelihood of treatment response (effect size, ~0.3).[35] Quetiapine had similar outcomes to paroxetine 20 mg/day and escitalopram 10 mg/day.[35] Low dose risperidone (0.5–1.5 mg/day) and olanzapine (2.5–15 mg/day) may improve treatment outcomes in patients with inadequate response to initial pharmacotherapy.[17,20,27] SGAs are associated with a risk of weight gain, glucose intolerance, sedation, fatigue, and extrapyramidal symptoms which limit their use.

Outcome Evaluation

Assess patients for improvement of anxiety symptoms and return to baseline of occupational, social, and interpersonal functioning. Brief questionnaires like the Generalized Anxiety Disorder 7-Item (GAD-7) may be used to monitor changes in symptoms and measure response to treatment.[36] With effective treatment, patients should have no or minimal symptoms of anxiety or depression. With initiation of drug therapy, evaluate patients frequently for tolerability and response. Monitor for suicidal ideation and behaviors for children, adolescents, and young adults (24 years of age or less) initiated on antidepressants.[21,37,38] Increase the dose in patients exhibiting a partial response after 2 to 4 weeks on an antidepressant or 2 weeks on a benzodiazepine. Individualize the duration of treatment as some patients require up to 1 year of treatment.[17,20,27]

LO 7

TREATMENT: PANIC DISORDER

Desired Outcomes

LO 3

The main objectives of treatment are to reduce the severity and frequency of panic attacks, reduce anticipatory anxiety and avoidant behavior, and minimize symptoms of depression or other comorbid disorders.[39] The long-term goal is to achieve and sustain remission and restore overall functioning.

General Approach to Treatment

LO 5

Treatment options include medication, psychotherapy, or a combination of both. In some cases, pharmacotherapy will follow psychotherapy treatments when full response is not realized. Patients with panic symptoms without comorbid agoraphobia may respond to pharmacotherapy alone. Agoraphobic symptoms generally take longer to respond than panic symptoms. KEY CONCEPT The acute phase of PD treatment lasts about 12 weeks and should markedly reduce or eliminate panic attacks and minimize anticipatory anxiety and phobic avoidance. Treatment should be continued to prevent relapse for an additional 12 to 18 months before attempting discontinuation.[17,20,39] For patients who relapse after discontinuation, therapy should be resumed.[39]

Clinical Presentation and Diagnosis of PD

General

Typically presents in late adolescence or early adulthood. Onset in older adults raises suspicion of a relationship to medical disorders or substance use. Laboratory evaluation must be driven by history and physical examination.

Symptoms[1]

LO 2

Recurrent, unexpected panic attacks. A panic attack is an abrupt surge of intense fear or discomfort peaking within minutes, and with four or more of the following symptoms:

- Palpitations or rapid heart rate
- Sweating
- Trembling or shaking
- Sensation of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy or lightheaded
- Chills or hot flushes
- Paresthesias
- Derealization or depersonalization
- Fear of dying
- Fear of losing control or "going crazy"

At least one of the attacks has been followed by 1 month or more of one or both:

- Persistent concern or worry about additional attacks
- Significant maladaptive change in behavior related to the attacks (eg, avoidance)

Differential Diagnosis

Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (see Tables 40–1 and 40–2).

Laboratory Evaluation

- Urine drug screen
- Basic metabolic panel (HbA_{1C})
- Thyroid-stimulating hormone
- Electrocardiogram

Patient Encounter 2

A 15-year-old male presents to the pediatric clinic for his annual examination. He reports having difficulty with his grades and feels very anxious when taking an examination at school or presenting to his class. He did not try out for the high school soccer team as he was afraid he would embarrass himself and would not make the team. He avoids study groups after school as it makes him "nervous". He has one close friend and avoids going to parties or hanging out with large groups of his peers. He denies substance use.

His medical history is positive for ADHD.

Meds: None

His medical workup is noncontributory, and he is diagnosed with SAD.

What treatment options should be considered?

What are the benefits of using pharmacotherapy versus psychotherapy versus both?

Nonpharmacologic Therapy

LO 4 Patients with PD should avoid stimulant agents (eg, decongestants, diet pills, and caffeine) that may precipitate a panic attack. CBT generally includes psychoeducation, self-monitoring, countering anxious beliefs, exposure to fear cues, and modification of anxiety-maintaining behaviors.[20,39] Exposure therapy is useful for patients with phobic avoidance.[20,39]

LO 5 CBT is considered a first-line treatment of PD, with efficacy similar to that of pharmacotherapy. Some studies suggest lower risk of relapse after CBT versus drug therapy.[39] CBT in combination with antidepressant treatment is more effective than either treatment alone.[40]

Pharmacologic Therapy

LO 6 Patients with PD may be treated with TCAs, SSRIs, SNRIs, or MAOIs, as well as benzodiazepines[17,20,39] (Table 40–6) with similar effectiveness, but SSRIs are the treatment of choice. Benzodiazepines often are used concomitantly with antidepressants, especially early in treatment, or as monotherapy to acutely reduce panic symptoms. Benzodiazepines are not preferred for long-term treatment but may be used when patients fail several antidepressant trials.[17,20,39] PD patients with comorbid depression should be treated with an antidepressant. An algorithm for pharmacologic management of PD appears in Figure 40–3.

▶ *Antidepressants*

Antidepressants typically require 4 weeks for onset of antipanic effect, with optimal response at 6 to 12 weeks. Reduction of anticipatory anxiety and phobic avoidance generally follows improvement in panic symptoms. KEY CONCEPT PD patients are more likely to experience stimulant-like side effects of antidepressants than patients with major depression. Antidepressants should be initiated at lower doses (see Table 40–6) in PD patients than in depressed patients. Target doses are similar to those used for depression. KEY CONCEPT Antidepressants should be tapered when treatment is discontinued to avoid withdrawal symptoms, including irritability, dizziness, headache, and dysphoria.

Table 40–6

Antidepressants Used in the Treatment of Panic and Social Anxiety Disorder[18,23,42]

Medication Class	Recommended Starting Dose (mg/day)	Usual Therapeutic Dosage Range (mg/day)	Advantages	Disadvantages
SSRIs/SNRIs			**SSRIs (in General)** Antidepressant activity; antianxiety activity; single daily dosing (all but fluvoxamine); low toxicity; available in generic	**SSRIs (in General)** Activation; delayed onset of action; may precipitate mania; sexual side effects; GI side effects
Citalopram	10	20–40		
Escitalopram[b]	5–10	10–20		
Fluoxetine[a]	5–10	20–60		
Fluvoxamine	25	100–300		
Paroxetine[a,b]	10	20–60		
Sertraline[a,b]	25	50–200		
Venlafaxine XR[a,b]	37.5	75–225		
TCAs			**TCAs (in General)** Established efficacy; available in generic	**TCAs (in General)** Activation; sedation; anticholinergic effects; cardiovascular effects; delayed onset of action; may precipitate mania; sexual side effects; toxic in overdose; weight gain
Clomipramine	25 mg (twice a day)	75–250		
Imipramine[a]	10–25	75–250		
MAOI				
Phenelzine	15	45–90	Antidepressant effects; available in generic	Dietary restrictions; drug interactions; weight gain; orthostasis; may precipitate mania

[a]Food and Drug Administration approved for use in panic disorder.

[b]Food and Drug Administration approved for use in social anxiety disorder.

GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Data from Refs. 20, 25, and 39.

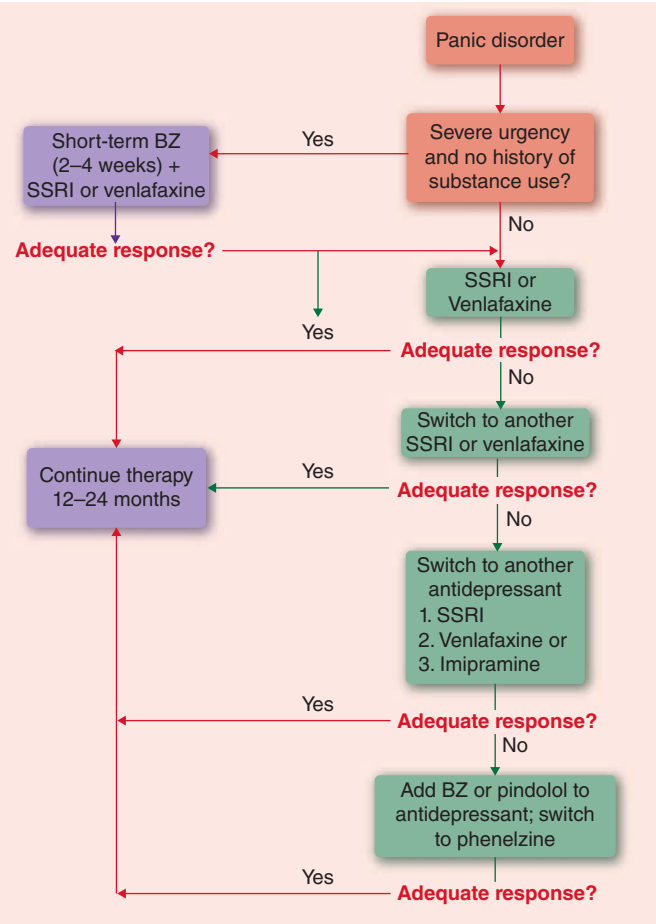

FIGURE 40–3. Algorithm for the pharmacotherapy of panic disorder. (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor.) (Adapted from Young AS, Klap R, Sherbourne CD, Wells KB. The quality of care for depressive and anxiety disorders in the United States. Arch Gen Psychiatry. 2001;58:55–61 and Bruce SE, Yonkers SE, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry. 2005;162:1179–1187, with permission.)

Selective Serotonin and Serotonin-Norepinephrine Reuptake Inhibitors SSRI and SNRIs are the medications of choice for patients with PD. All SSRIs have demonstrated effectiveness in controlled trials, with 60% to 80% of patients achieving a panic-free state.[17,20,39] Similarly, venlafaxine, in dosages of 75 to 225 mg/day, reduced panic and anticipatory anxiety in short-term controlled trials and prevented relapse with extended treatment over 6 months.[17,39] Given lack of head-to-head trials and similar efficacy between agents, drug selection is generally based on pharmacokinetics, drug interactions, side effects, and cost differences (see Chapter 38).

Tricyclic Antidepressants Treatment with imipramine has resulted in 45% to 70% of patients achieving a panic free state. Desipramine and clomipramine have also demonstrated effectiveness in PD. TCAs are considered second- or third-line therapeutic options because of poorer tolerability and toxicity upon overdose which may be fatal.[20,39] Owing to their side-effect profile, TCAs are associated with a higher rate of treatment discontinuation than SSRIs.[39] PD patients taking TCAs may experience anticholinergic effects, orthostatic hypotension, sweating, sleep disturbances, dizziness, fatigue, sexual dysfunction, and weight gain. In addition, stimulant-like side effects occur in up to 40% of patients.[39]

Monoamine Oxidase Inhibitors MAOIs have not been evaluated systematically for treatment of PD under the current diagnostic classification. In general, they are reserved for patients who are refractory to other treatments.[39] They have significant side effects that limit adherence coupled with restrictions to avoid tyramine-containing foods and sympathomimetic drugs to prevent hypertensive crisis (see Chapter 38). The reversible inhibitors of monoamine oxidase (RIMAs) (brofaromine and meclobemide [unavailable in the United States]) have been studied with mixed results.[17,20,39]

Other Antidepressants There is insufficient evidence to support the use of bupropion, trazodone, nefazodone, or mirtazapine for treatment of PD.[17,20,39]

► *Benzodiazepines*

Benzodiazepines are effective antipanic agents with significant effects on anticipatory anxiety and phobic behaviors. Alprazolam, the benzodiazepine most studied, is associated with significant panic reduction after 1 week of therapy (eg, 55%–75% panic free).[39,41] Benzodiazepines achieve outcomes similar to antidepressants over extended treatment, but benzodiazepine-treated patients are more likely to relapse when the drugs are discontinued.[39] The risk for dependence and withdrawal and lack of efficacy for depression are significant concerns for long-term treatment of patients with PD. There is no evidence that tolerance to therapeutic effect occurs. Patients with PD experience greater rebound anxiety and relapse when discontinuing benzodiazepines than do patients with GAD.[20,39] Tapering should be done at a slower rate and over a more extended period of time than with other anxiety disorders.[20,39]

KEY CONCEPT The dose of benzodiazepine required for improvement generally is higher than that used in other anxiety disorders, and this may explain why high-potency agents such as alprazolam and clonazepam generally are preferred. Lorazepam and diazepam, when given in equivalent doses, produce similar treatment benefits.[20,39] Doses should be titrated to response (see Table 40–4). The use of extended-release alprazolam or clonazepam may minimize breakthrough panic symptoms that are sometimes observed with immediate-release alprazolam.[41]

► *Adjunctive Treatment*

LO 6 Pindolol, a mixed beta-adrenergic/serotonergic medication, at a dose of 25 mg three times a day is effective as adjunctive treatment with an SSRI for treatment resistant PD.[39] Propranolol, a nonselective β-blocker, is not effective for PD and is not recommended.[39]

Outcome Evaluation

LO 8 Assess patients for symptom improvement frequently (eg, weekly) during the first 4 weeks of therapy. With effective therapy, patients should experience significant reductions in the frequency and intensity of panic attacks, anticipatory anxiety, and phobic avoidance with resumption of normal activities.

Clinical Presentation and Diagnosis of SAD

General

Individuals have marked fear or anxiety about one or more social situations where they are exposed to possible scrutiny or negative evaluation (eg, common social interactions, conversation, eating, drinking, or performing). SAD differs from specific phobia, in which the fear and anxiety are limited to a particular object or situation (eg, insects, heights, public transportation). In children, the anxiety must be present in peer settings, not just in interactions with adults.

Symptoms[1]

LO 2

- The individual fears acting in a way or showing anxiety that will be negatively evaluated (ie, humiliating or embarrassing or lead to rejection or offend others)
- Social situations almost always provoke fear or anxiety and are avoided or endured with intense fear or anxiety. Children may express fear or anxiety by crying, tantrums, freezing, clinging, or failing to speak in social situations.
- The fear or anxiety is
  - out of proportion to the actual threat posed by the social situation;
  - persistent, typically lasting for 6 months or more;
  - causes clinically significant distress or impairment in social, occupational, or other areas of functioning;
  - not attributable to physiological effects of a substance or another medical condition; and
  - not better explained by the symptoms of another mental disorder (eg, panic disorder, body dysmorphic disorder, or autism spectrum disorder)

Differential Diagnosis

Rule out underlying medical or psychiatric disorders and medications that may cause anxiety (see Tables 40–1 and 40–2).

Laboratory Evaluation

Laboratory investigation is of limited value and should be pursued only in context of other history or physical examination findings.

LO 7 Rating scales, such as the Panic Disorder Symptom Scale (PDSS), can be useful in measuring symptom change over time. Assess patients for comorbidities (eg, depression) as well as suicidal ideation. Alter the therapy of patients who do not achieve a significant reduction in panic symptoms after 6 to 8 weeks on an adequate dose of antidepressant or 3 weeks on a benzodiazepine.

LO 8 Regularly evaluate patients for adverse effects and medication adherence, and educate them about appropriate expectations of drug therapy.

When significant response to drug therapy is achieved, continue treatment for at least 1 year. Evaluate for symptom relapse and adverse effects that may emerge with continued treatment (eg, weight gain and sexual dysfunction). During drug discontinuation, monitor frequently for withdrawal, rebound anxiety, and relapse.

TREATMENT: SOCIAL ANXIETY DISORDER

Desired Outcomes

LO 3 SAD is a chronic disorder that begins in adolescence and occurs with significant functional impairment and high rates of comorbidity. The goal of acute treatment is to reduce physiologic symptoms of anxiety, fear of social situations, and phobic behaviors. Patients with comorbid depression should have a significant reduction in depressive symptoms. The long-term goal is to restore social functioning and improve the patient's quality of life.

General Approach to Treatment

LO 5 Patients with SAD may be managed with pharmacotherapy or psychotherapy. There is insufficient evidence to recommend one treatment over the other, and data are lacking on the benefits of combining treatment modalities. Children with SAD should be offered psychotherapy first.[17,42,43] Pharmacotherapy often is the first choice of treatment owing to relative greater access and reduced cost compared with psychotherapy.[42,43] Many patients will not achieve a full response.

Nonpharmacologic Therapy

LO 8 Patient education on disease course, treatment options, and expectations is essential. Support groups may be beneficial for some patients. CBT targets avoidance-learning and negative-thinking patterns associated with social anxiety. CBT is effective for reducing anxiety and phobic avoidance with response in 50% to 65% of patients, and leads to a greater likelihood of maintaining response after treatment discontinuation than does pharmacotherapy.[17,42] Web-based CBT is an alternative when access to face-to-face CBT is a barrier.[17,43]

Pharmacologic Therapy

Several pharmacologic agents have demonstrated effectiveness in SAD, including the SSRIs, venlafaxine, phenelzine, RIMAs, benzodiazepines, gabapentin, and pregabalin (Table 40–6). KEY CONCEPT SSRIs are considered the drugs of choice based on their tolerability and efficacy for SAD and comorbid depression if present. The onset of response for antidepressants may be as long as 8 to 12 weeks.[20,44] Patients responding to medication should be continued on treatment for at least 1 year.[17,20,43] Many patients relapse when medication is discontinued, and there are no clear predictive factors for who will maintain response.[44] Some patients may elect more long-term treatment owing to fear of relapse. A suggested treatment algorithm is shown in Figure 40–4.

▶ *Selective Serotonin Reuptake Inhibitors and Venlafaxine*

The efficacy of paroxetine, sertraline, escitalopram, fluvoxamine, and venlafaxine was established in large controlled trials.[20,44,45] SSRIs and SNRIs improve social anxiety and phobic avoidance and reduce overall disability. Approximately 50% of patients achieve response during acute treatment. SSRIs reduce the risk of relapse with extended treatment.[46] Limited data support the effectiveness of citalopram and fluoxetine in SAD.[46,47]

The initial dose of SSRI and venlafaxine is similar to that used in depression. Patients should be titrated as tolerated to response. Patients with comorbid PD should be started on lower doses (see Table 40–6). When discontinuing SSRI/SNRIs, the dose should be tapered slowly to avoid withdrawal symptoms. Relapse rates

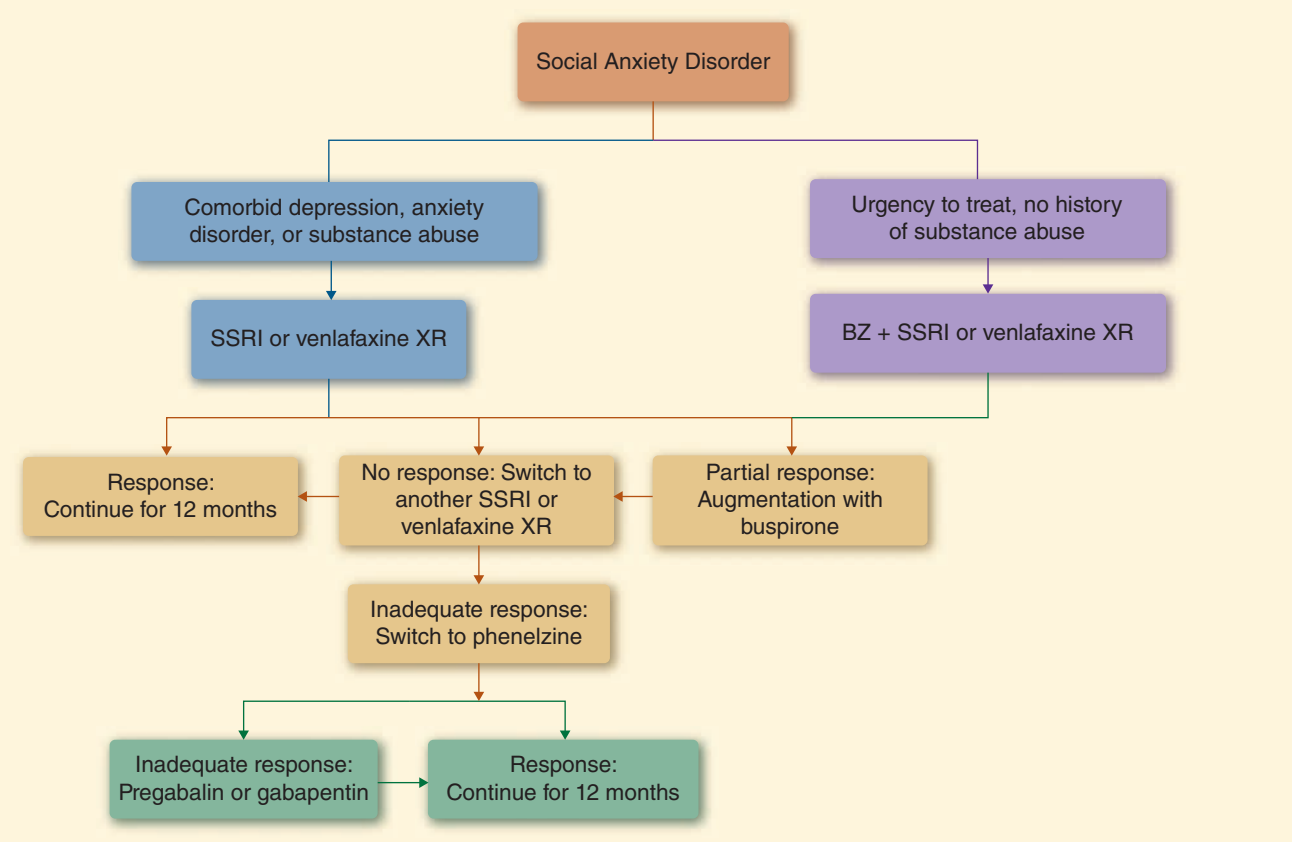

FIGURE 40–4. Algorithm for the pharmacotherapy of social anxiety disorder. (BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; XR, extended release.) (Adapted from Melton ST, Kirkwood CK. Anxiety disorders I: generalized anxiety, panic and social anxiety disorders. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York, NY: McGraw-Hill; 2011:1209–1227, with permission.)

may be as high as 50%, and patients should be monitored closely for several weeks.[43,44] Side effects of SSRI/SNRIs in SAD are similar to those seen in depression.

▶ *Monoamine Oxidase Inhibitors and Reversible Inhibitors of Monoamine Oxidase*

Phenelzine, effective in 64% to 69% of SAD patients,[44] is generally reserved for treatment-refractory patients owing to dietary restrictions,[47] drug interactions, and side effects. The RIMAs brofaromine and meclobemide are also effective.

▶ *Alternative Agents*

Benzodiazepines Benzodiazepines are used commonly in SAD; however, limited data support their use. Clonazepam was shown effective for social anxiety, fear, and phobic avoidance, and it reduced social and work disability during acute treatment.[44] Long-term treatment is not desirable for many SAD patients because of the risk of withdrawal and difficulty with discontinuation, cognitive side effects, and lack of effect on depressive symptoms. Benzodiazepines may be useful for acute relief of physiologic symptoms of anxiety when used concomitantly with antidepressants or psychotherapy.

Anticonvulsants Gabapentin and pregabalin, structurally similar anticonvulsants, have each demonstrated modest benefit in a randomized, placebo-controlled trial.[17,20,46] Gabapentin was titrated to a maximum dose of 3600 mg/day and pregabalin to 600 mg/day. While both medications have good tolerability, they should be considered for patients with inadequate response to SSRI/SNRIs.

β-Blockers β-Blockers decrease the physiologic symptoms of anxiety and are useful for reducing performance anxiety (eg, speech, interview). Propranolol or atenolol should be administered 1 hour before a performance situation. β-Blockers are not useful for management of SAD.[44,46]

Outcome Evaluation

KEY CONCEPT Pharmacotherapy for patients with SAD should lead to improvement in anxiety and fear, functionality, and overall well-being.[20,43] Many patients will experience significant improvement in symptoms but may not achieve full remission. Monitor patients weekly during acute treatment (eg, initiation and titration of pharmacotherapy) and monthly once stabilized. Inquire about adverse effects, SAD symptoms, suicidal ideation, and symptoms of comorbid psychiatric conditions at each visit. Ask patients to keep a diary to record fears, anxiety levels, and behaviors in social situations.[20] Administer the Liebowitz Social Anxiety Scale (LSAS) to rate SAD severity and change, and the Social Phobia Inventory can be used as a "self-assessment" tool.[43,48] Counsel patients on appropriate expectations of pharmacotherapy in SAD, including gradual onset of effect and the need for extended treatment of at least 6 months following response.

LO 7

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications.
- Review medical history and physical examination findings.
- Review mental status examination and screen for depression, anxiety, and substance use.
- Interview the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect treatment access or preference.

Assess the Information:

- Determine whether the patient is taking any medication or substance that could cause or worsen anxiety (Table 40–2).
- Review relevant laboratory tests (eg, urine toxicology, thyroid stimulating hormone).
- Document pertinent family medical and mental health history (eg, depression, anxiety, substance use, suicide).
- Based on clinical presentation, mental status examination, and screening tools (eg, GAD-7), determine whether the patient is experiencing symptoms of sufficient intensity and duration to warrant treatment.
- Document current symptom severity using a valid measurement-based tool (eg, GAD-7, LSAS).
- Identify comorbidities that will affect treatment choice (eg, depression, substance use).
- Assess the efficacy, safety, and adherence of current pharmacotherapy, if applicable.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- Select lifestyle modifications and antianxiety therapy that are likely to be effective and safe.
- Use shared decision making for selection of behavioral and pharmacotherapy treatment intervention(s).
- Choose medications and doses that are optimal for the patient based on age, anxiety disorder, and comorbid conditions (see Tables 40–3, 40–4, and 40–6).

Implement the Care Plan:

- Educate the patient about antianxiety medication effectiveness, onset and expected time to benefit, administration, and common adverse effects.
- Address any patient concerns about anxiety and its management.
- Discuss the importance of lifestyle modifications to reduce anxiety (eg, social support, substance use, exercise).
- Determine whether the patient has access to recommended medication or behavioral treatment (eg, insurance, medication on formulary, CBT provider nearby).

Follow-up: Monitor and Evaluate:

- Follow-up at monthly intervals or more frequently during acute treatment to assess effectiveness and tolerability until treatment goal achieved.
- Review medication adherence and anxiety symptom control.
- Use appropriate rating scales to assess symptom change over time.
- Once anxiety is controlled and baseline function restored, determine the appropriateness of treatment beyond 1 year based on the patient's previous treatment and comorbid conditions.

Abbreviations Introduced in This Chapter

CBT	Cognitive-behavioral therapy
CNS	Central nervous system
DA	Dopamine
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
GAD	Generalized anxiety disorder
HPA	Hypothalamic–pituitary–adrenal
5-HT	Serotonin
LC	Locus ceruleus
LSAS	Liebowitz Social Anxiety Scale
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
NCS-R	National Comorbidity Survey, Revised
NE	Norepinephrine
NPY	Neuropeptide Y
OCD	Obsessive-compulsive disorder
OTC	Over-the-counter
PD	Panic disorder
PDSS	Panic Disorder Symptom Scale
RAS	Reticular activating system
RIMA	Reversible inhibitors of monoamine oxidase A
SAD	Social anxiety disorder
SGA	Second-generation antipsychotic
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: American Psychiatric Association; 2013. Available from: https://psychiatryonline.org/. Accessed August 8, 2018.
2. Kessler RC, Angermeyer M, Anthony JC, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007;6(3):168–176.
3. Kessler RC, Chiu TW, Demler O, Walters E. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:590–592.
4. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Lowe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007;146:317–325.

5. Pollack MH. The pharmacotherapy of panic disorder. J Clin Psychiatry. 2005;66(suppl 4):23–27.
6. Yonkers KA, Bruce SE, Dyck IR, Keller MB. Chronicity, relapse, and illness-course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. Depress Anxiety. 2003;17:173–179.
7. Bruce SE, Yonkers SE, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry. 2005;162:1179–1187.
8. Cramer V, Torgersen S, Kringlen E. Quality of life and anxiety disorders: a population study. J Nerv Ment Dis. 2005;193:196–202.
9. Kaufman J, Charney D. Comorbidity of mood and anxiety disorders. Depress Anxiety. 2000;12(suppl 1):69–76.
10. Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch Gen Psychiatry. 2005;62:182–189.
11. Shimada-Sugimoto M, Otowa T, Hettema JM. Genetics of anxiety disorders: genetic epidemiological and molecular studies in humans. Psychiatry Clin Neurosci. 2015;69:388–401.
12. Ninan PT, Dunlop BW. Neurobiology and etiology of panic disorder. J Clin Psychiatry. 2005;66(suppl 4):3–7.
13. Shin LN, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. Neuropsychopharmacology Rev. 2010;35:169–191.
14. Gould TD, Gray NA, Manji HK. Cellular neurobiology of severe mood and anxiety disorders: implications for development of novel therapeutics. In: Charney DS, ed. Molecular Neurobiology for the Clinician (Review of Psychiatry Series. Vol. 22. No. 3; Oldham JM, Riba MB, series, eds). Washington, DC: American Psychiatric Publishing; 2003:123–200.
15. Plata-Salaman CR, Shank RP, Smith-Swintosky VL. Amino acids as neurotransmitters. In: Sadock BJ, Sadock VA, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:60–72.
16. Brothers SP, Young LJ, Nemeroff CB. Neuropeptides: biology, regulation, and role in neuropsychiatric disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017:84–96.
17. Katzman MA, Bleu P, Blier P, et al. Canadian Clinical Practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14(suppl 1):S1.
18. Suicide Assessment Five-step Evaluation and Triage for Mental Health Professionals. https://www.integration.samhsa.gov/images/res/SAFE_T.pdf. Accessed August 4, 2018.
19. Melton ST, Kirkwood CK. Anxiety disorders I: generalized anxiety, panic, and social anxiety disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014:717–732.
20. Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and posttraumatic stress disorders—first revision. World J Biol Psychiatry. 2008;9:248–312.
21. Practice Parameter for the Assessment and treatment of children and adolescents with anxiety disorders. J Am Acad Child Adolesc Psychiatry. 2007;46(2):267–283.
22. Andrews G, Cuijpers P, Craske MG, McEvoy P, Titov N. Computer therapy for anxiety and depressive disorders is effective, acceptable, and practical health care: a meta-analysis. PLoS One. 2010;5(10):e13196.
23. Wang Z, Whiteside SPH, Sim L, et al. Comparative effectiveness and safety of cognitive behavioral therapy and pharmacotherapy for childhood anxiety disorders: a systematic review and meta-analysis. JAMA Pediatr. 2017;171(11):1049–1056.
24. Donovan MR, Glue P, Kolluri S, Emir B. Comparative efficacy of antidepressants in preventing relapse in anxiety disorders: a meta-analysis. J Affective Disord. 2010;123:9–16.
25. Davidson JR, Zhang W, Connor KM, et al. Review: a psychopharmacological treatment algorithm for generalised anxiety disorder (GAD). J Psychopharmacol. 2010;24:3–26.
26. Shelton RC, Brown LL. Mechanisms of action in the treatment of anxiety. J Clin Psychiatry. 2001;62(suppl 12):10–15.
27. Bandelow B, Sher L, Bunevicius R, et al. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Practice. 2012;16:77–84.
28. Fu J, Peng L, Li X. The efficacy and safety of multiple doses of vortioxetine for generalized anxiety disorder: a meta-analysis. Neuropsychiatr Dis Treat. 2016;12:951–959.
29. Stein MB, Sareen J. Generalized anxiety disorder. N Engl J Med. 2015;373:2059–68.
30. Micromedex Healthcare Series. Drugdex Evaluations. © 1974–2012 Thomson Reuters.
31. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. J Clin Psychiatry. 2004;65(suppl 5):7–12.
32. Table of Pharmacogenomic Biomarkers in Drug Labeling. U.S. Food and Drug Administration. Available from: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. Accessed August 4, 2018.
33. Longo LP, Johnson B. Benzodiazepines: side effects, abuse risk and alternatives (addiction part 1). Am Fam Physician. 2000;61:2121–2128.
34. Chessick CA, Allen MH, Thase M, Batista Miralha de Cunha AB, Kapczinski FF de Lima MS, dosSantos Souza JJ. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev. 2006;(3):CD006115.
35. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA. 2011;306(12):1359–1369.
36. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166:1092–1097.
37. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007;297:1683–1696.
38. Rynn MA, Walkup JT, Compton SN, et al. Child/adolescent anxiety multimodal study: evaluating safety. Journal of the American Academy of Child & Adolescent Psychiatry. 2015;54(3):180–190.
39. Stein MB, Goin MK, Pollack MH, et al. Practice Guideline for the Treatment of Patients with Panic Disorder, 2nd ed. Washington, DC: American Psychiatric Association; 2009. Available from: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/panicdisorder.pdf. Accessed August 4, 2018.
40. van Apeldoorn FJ, van Hout WJ, Mersch PP, et al. Is a combined therapy more effective than either CBT or SSRI alone? Results of a multicenter trial on panic disorder with or without agoraphobia. Acta Psychiatr Scand. 2008;117(4):260–270.
41. Rickels K. Alprazolam extended release in panic disorder. Expert Opin Pharmacother. 2004;5(7):1599–1611.
42. Social anxiety disorder: recognition, assessment and treatment. National Institute for Health and Care Excellence, NICE Clinical Guideline 159, May 2013. Available from: http://guidance.nice.org.uk/CG159. Accessed August 4, 2018.

43. Leichsenring F, Leweke F. Social anxiety disorder. N Engl J Med. 2017;376:2255–2264.
44. Blanc C, Bragdon LB, Schneier R, Liebowitz MR. The evidence-based pharmacotherapy of social anxiety disorder. Int J Neuropsychopharmacol. 2013;16(1):235–249.
45. deMenezes GB, Coutinho ESF, Fontenelle LF, Vigne P, Fiqueira I, Versiani M. Second-generation antidepressants in social anxiety disorder: meta-analysis of controlled clinical trials. Psychopharmacology. 2011;215:1–11.
46. Williams T, Hattingh CJ, Kariuki CM, et al. Pharmacotherapy for social anxiety disorder (SAnD). Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD001206.
47. Gardner DM, Shulman KI, Walker SE, Tailor SA. The making of a user friendly MAOI diet. J Clin Psychiatry. 1996;57(3):99–104.
48. Liebowitz MR. Social phobia. Mod Probl Pharmacopsychiatry. 1987;22:141–173.

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41 Sleep Disorders

John M. Dopp and Bradley G. Phillips

LEARNING OBJECTIVES

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

LO

1. List the sequelae of undiagnosed or untreated sleep disorders and appreciate the importance of successful treatment of sleep disorders.
2. State the incidence and prevalence of sleep disorders.
3. Describe the pathophysiology and characteristic features of the sleep disorders covered in this chapter, including insomnia, narcolepsy, restless legs syndrome (RLS), obstructive sleep apnea (OSA), and parasomnias.
4. Assess patient sleep complaints, conduct sleep histories, and evaluate sleep studies to recognize daytime and nighttime symptoms and characteristics of common sleep disorders.
5. Recommend and optimize appropriate sleep hygiene and nonpharmacologic therapies for the management and prevention of sleep disorders.
6. Recommend and optimize appropriate pharmacotherapy for sleep disorders.
7. Describe the components of the patient care process to implement and assess safety and efficacy of pharmacotherapy for common sleep disorders.
8. Educate patients about preventive behavior, appropriate lifestyle modifications, and drug therapy required for effective treatment and control of sleep disorders.

INTRODUCTION

Individuals with normal sleep patterns sleep up to one-third of their lives and spend more time sleeping than in any other single activity. Despite this, our understanding of the full purpose of sleep and the mechanisms regulating sleep homeostasis remains incomplete. Sleep is necessary to enable one to maintain wakefulness and good health. Disruption of normal sleep is a major cause of societal morbidity, lost productivity, and reduced quality of life.[1] Sleep disturbances may contribute to the development and progression of comorbid medical conditions.[1]

LO 1

Sleep is governed and paced by the suprachiasmic nucleus in the brain that regulates circadian rhythm. Environmental cues and amount of previous sleep also influence sleep on a daily basis. There are two main types of sleep: **rapid eye movement (REM) sleep**, during which eye movements and dreaming occur but the body is mostly paralyzed, and **non–rapid eye movement (NREM) sleep**, which consists of four substages (stages 1–4). Stage 1 serves as a transition between wake and sleep. Most of the time being asleep is spent in stage 2 NREM sleep. Stage 3 sleep is referred to as *deep sleep*, or *delta sleep*, because prominent delta waves are seen on the electroencephalogram (EEG) during this stage of sleep.

EPIDEMIOLOGY AND ETIOLOGY

Approximately 50% of adults will report a sleep complaint over the course of their lives.[2] In general, sleep disturbances increase with age, and each disorder may have gender differences. The full extent and impact of disordered sleep on our society are not known because many patients' sleep disorders remain undiagnosed. Normal sleep, by definition, is "a reversible behavioral state of perceptual disengagement from and unresponsiveness to the environment."[3] Individuals with sleep disorders exhibit or complain about consequent symptoms (eg, daytime sleepiness) or a bed partner often observes hallmark characteristics of the sleep disorder. Insomnia, restless legs syndrome (RLS), and sleep-related breathing disorders are the most common sleep disorders.

Insomnia

LO 2

The prevalence of insomnia increases with age and is nearly 1.5 times greater in women than in men. Approximately one-third of patients older than age 65 years have persistent insomnia.[4,5] About 10% of adults experience chronic insomnia, and slightly more experience short-term insomnia. KEY CONCEPT Diagnostic criteria for insomnia specify difficulty initiating sleep, maintaining sleep or early morning awakenings occur at least three times per week for a minimum duration of at least 3 months. Forty percent of patients with psychiatric conditions have accompanying insomnia.[6] Insomnia is frequently triggered by acute stress and resolves when the stress resolves. Numerous coexisting medical conditions, such as pain, thyroid abnormalities, asthma, and gastroesophageal reflux, and medications, including selective serotonin reuptake inhibitors (SSRIs), steroids, stimulants, and β-agonists, can cause insomnia.

Narcolepsy

LO 2

Although difficult to estimate, the prevalence of narcolepsy is between 0.03% and 0.06%.[7] Significant differences have been reported for various ethnic groups. Narcolepsy has a higher prevalence in Japanese and a lower prevalence in Israeli

populations.[8,9] The new classification system reclassifies the disorder into narcolepsy type 1 (narcolepsy with cataplexy), and narcolepsy type 2 (narcolepsy without cataplexy). Between 50% and 80% of patients with narcolepsy have accompanying **cataplexy**.[10]

Restless Legs Syndrome (Willis-Ekbom Disease) and Periodic Limb Movement Disorder

LO 2

RLS occurs in 6% to 12% of the population.[11,12] Prevalence increases with age and in various medical conditions, such as end-stage renal disease, pregnancy, and iron deficiency.[13] RLS appears to be more common in women than in men and has a genetic link in a majority of patients.[14]

Obstructive Sleep Apnea

LO 2

Obstructive sleep apnea (OSA) affects 4% of middle-aged white men and 2% of middle-aged white women.[15] In women, the frequency increases after menopause. Prevalence is the same or higher in African Americans and lower in Asian populations. The risk for OSA increases with age and obesity. Individuals with OSA experience repetitive upper airway collapse during sleep, which decreases or stops airflow, with subsequent arousal from sleep to resume breathing. Severity is determined by **nocturnal polysomnography** (NPSG) or home sleep study and is graded by the number of episodes of apnea (total cessation of airflow) and hypopnea (partial airway closure with blood oxygen desaturation) experienced during sleep. Severity is expressed as the **respiratory disturbance index** (RDI), quantified in events per hour.

Parasomnias

NREM **parasomnias** have variable prevalence rates depending on patient age and comorbid diagnoses. Sleep talking, bruxism, sleepwalking, sleep terrors, and enuresis occur more frequently in childhood than in adulthood. Nightmares appear to occur with similar frequency in adults and children. REM-sleep behavior disorder (RBD), an REM-sleep parasomnia, has a reported prevalence of 0.5%, is more common in elderly men, and frequently is associated with concomitant neurologic conditions.[16]

PATHOPHYSIOLOGY

Although the neurophysiology of sleep is complex, certain neurotransmitters promote sleep and wakefulness in different areas of the central nervous system (CNS). Whereas serotonin is thought to control NREM sleep, cholinergic and adrenergic transmitters mediate REM sleep. Dopamine, norepinephrine, **hypocretin**, substance P, and histamine all play a role in wakefulness. Perturbations of various neurotransmitters are responsible for some sleep disorders and explain why various treatments are beneficial.

Insomnia

LO 3

There is no single pathophysiologic explanation for the manifestations of insomnia. Current hypotheses focus on a combination of possible models that incorporate physiologic, cognitive, and cortical arousal. Most models focus on hyperarousal and its interference with the initiation or maintenance of sleep.

Narcolepsy

LO 3

The onset of narcolepsy–cataplexy is typically in adolescence, suggesting that the disease may require environmental influence to develop. Currently, it is believed that narcolepsy results from autoimmune insult to the CNS because it is associated with human leukocyte antigen (major histocompatibility complex) DQB10602 and DQ1A1*0102.[17,18] Concentrations of hypocretin (a wake-promoting neuropeptide) in the cerebrospinal fluid of patients with narcolepsy and cataplexy are reduced significantly (< 110 pg/mL [ng/L; 31 pmol/L]), suggesting that the autoimmune attack is against hypocretin-producing cells in the hypothalamus.[19]

RESTLESS LEGS SYNDROME (WILLIS-EKBOM DISEASE) AND PERIODIC LIMB MOVEMENTS DISORDER (PLMD)

LO 3

RLS is a neurologic medical condition characterized by an irresistible desire to move the limbs. It is thought that these abnormal sensations are a result of iron deficiency in the brain and iron-handling abnormalities in the CNS. Iron and H-ferritin concentrations, along with transferrin receptor and iron transporter numbers, are reduced in the substantia nigra of patients with RLS.[20] These iron abnormalities lead to dysfunction of dopaminergic transmission in the substantia nigra. Recently, it has been suggested that local hypoxia in the legs may contribute to pathophysiology of RLS.[21]

OBSTRUCTIVE SLEEP APNEA

LO 3

At least 20 muscles and soft tissue structures control patency of the upper airway. Patients with OSA may have differences in upper airway muscle activity during sleep and may have smaller airways, predisposing them to upper airway collapse and consequent apneic episodes during sleep. The inability of the upper airway to contend with factors that promote collapse, including fat deposition in the neck, negative pressure in the airway during inspiration, and a smaller lower jawbone, also may play a role in the pathogenesis of OSA. Patients with sleep apnea often are obese and may be predisposed to weight gain.

Poor sleep architecture and fragmented sleep secondary to OSA can cause excessive daytime sleepiness (EDS) and neurocognitive deficits. These sequelae can affect quality of life and work performance and may be linked to occupational and motor vehicle accidents. OSA is also associated with systemic disease such as hypertension, heart failure, and stroke.[22,23] OSA is likely an independent risk factor for the development of hypertension.[24] Furthermore, when hypertension is present, it is often resistant to antihypertensive therapy. Breathing against a closed upper airway during sleep causes intermittent and repetitive episodes of hypoxemia and hypercapnia, dramatic changes in intrathoracic pressure, and activation of the sympathetic nervous system. These responses can produce acute hemodynamic and humoral responses.[25]

PARASOMNIAS

LO 3

The pathogenesis of parasomnias (eg, sleepwalking, enuresis, sleep talking) is variable, poorly described, and involves state dissociation, whereby two states of being overlap simultaneously. For example, abnormal activation of the central pattern generator of the spinal cord that produces motor movements is hypothesized to underlie sleepwalking behavior. In RBD, active inhibition of motor activity in the perilocus coeruleus region is lost, resulting in loss of paralysis and dream enactment.

Clinical Presentation and Diagnosis

KEY CONCEPT Patients with sleep complaints should have a careful sleep history performed to assess their possible sleep disorder in order to guide diagnostic and therapeutic decisions.

Daytime Symptoms and Associated Characteristics

EDS is the primary symptom described by patients with sleep disorders. It is usually described as not waking up refreshed in the morning or falling asleep or fighting the urge to sleep during the day despite a night of sleep. Other daytime characteristics of sleep disorders include:

- Irritability, fatigue, or depression
- Confusion or impaired performance at work or school
- Cataplexy
- Hypertension

Nighttime Sleep Complaints

Depending on the sleep disorder, patients may exhibit or experience various nocturnal complaints during sleep. Some complaints can be uncovered by clinical history alone (eg, hallucinations, RLS, snoring), but others can be diagnosed during sleep studies (eg, OSA, nighttime awakenings, somnambulism, PLMS [Periodic limb movements of sleep], etc). Frequent complaints include:

- Inability to fall asleep, nighttime awakenings
- Sleep walking (somnambulism), sleep talking (somniloquy)
- Cessation of breathing (apnea), snoring
- Sleep paralysis or hallucinations when waking or falling asleep
- Restlessness (PLMS or RLS)

CLINICAL PRESENTATION AND DIAGNOSIS

LO 4

KEY CONCEPT Although the clinical history guides diagnosis and therapy, only NPSG, home sleep studies, and/or multiple sleep latency tests (MSLTs) can definitively diagnose and guide therapy for OSA, narcolepsy, and periodic limb movement disorder. All patients presenting with sleep complaints should have a thorough interview and history to inventory their sleep habits and sleep hygiene.

Insomnia

Insomnia is often characterized by difficulty falling asleep, frequent nocturnal awakenings, and early morning awakenings, which may result in daytime impairments in concentration and school or work performance. In some situations, social factors (eg, family difficulties, bereavement), medications (eg, antidepressants, β-agonists, corticosteroids, decongestants), and coexisting medical or psychiatric conditions (eg, depression, bipolar disorder) may help to explain difficulties in initiating and maintaining sleep.

Narcolepsy

The hallmark of narcolepsy is EDS, and may also include disrupted nighttime sleep. Patients with narcolepsy experience the tetrad of EDS, cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations (dream-like images that appear at sleep-wake transitions). Cataplexy is a weakness or loss of skeletal muscle tone in the jaw, legs, or arms that is elicited by emotion (eg, anger, surprise, laughter, or sadness).

Restless Legs Syndrome and Periodic Limb Movement Disorder

Although RLS symptoms can vary, patients commonly report creepy-crawly, burning, tingling, or achy feelings in the legs or arms. These sensations create a desire to move the limbs and may produce motor restlessness. Symptoms are worse in the evening and are worse or exclusively present at rest, with temporary relief with movement. Symptoms also can occur during sleep and often lead to semi-rhythmic PLMS. PLMS are objective findings during NPSG recorded by leg electrodes. PLMS are present in most patients with RLS but can occur independently.

Obstructive Sleep Apnea

Common characteristics of OSA include snoring, choking, gasping for air, nocturnal reflux symptoms, and morning headaches. A bed partner or roommate may observe these symptoms and witness apneic episodes where the patient stops breathing. Patients with large neck sizes (> 45 cm [~18 in] neck circumference) and a body mass index (BMI) of 30 kg/m^2 or greater are at higher risk for OSA.

Parasomnias

Parasomnias are characterized by undesirable physical or behavioral phenomena that occur during sleep (eg, sleepwalking, sleep eating, sleep talking, bruxism [grinding of teeth], enuresis, night terrors, and RBD). People with RBD act out their dreams during sleep, often in a violent manner.

Circadian Rhythm Disorders

The most common circadian rhythm disorders (CRDs) include jet lag, shift-work sleep disruption, delayed sleep-phase disorder, and advanced sleep-phase disorder. Jet lag occurs when a person travels across time zones, and the external environmental time is mismatched with the internal circadian clock. Delayed and advanced sleep-phase disorders occur when bed and wake times are delayed or advanced (by 3 or more hours) compared with socially prescribed bed and wake times.

Sleep Diagnostics

Complete NPSG is the "gold standard" for diagnosing and identifying sleep-disordered breathing, PLMS, parasomnias, and nocturnal sleep irregularities related to narcolepsy. Sleep is observed and monitored in a controlled setting using an EEG, electrooculography, electromyography, electrocardiography, air thermistors, abdominal and thoracic strain belts, and an oxygen saturation monitor. This setup records sleep onset, arousals, sleep stages, eye movements, leg and jaw movements, heart rhythm, airflow, respiratory effort, and oxygen desaturations. Home sleep studies are increasingly used to diagnose sleep apnea due to their reduced cost and increased patient convenience. These devices typically measure nasal airflow, respiratory effort, oxygen saturation, and heart rate to determine if a patient experiences apnea/hypopnea episodes.

The MSLT is a commonly performed test to assess daytime sleepiness. During the MSLT, the patient attempts to take a 20-minute nap every 2 hours during the day beginning 2 hours

after morning awakening (after a normal night's sleep) to evaluate physiologic sleepiness. The patient is instructed not to resist the urge to fall asleep. Sleep latency of less than 5 to 6 minutes is considered pathologically sleepy. The occurrence of a REM onset period during two naps with short sleep latency is indicative of a diagnosis of narcolepsy.

TREATMENT

Desired Outcomes

KEY CONCEPT Treatment goals vary among different sleep disorders but generally include restoration of normal sleep patterns, elimination of daytime sequelae, improved quality of life, and prevention of complications and adverse effects from therapy.

General Approach to Treatment

LO 5 LO 6 LO 8

Nonpharmacologic interventions for insomnia are outlined in Table 41–1. Sleep hygiene should be reinforced in all patients, and behavioral, cognitive, and stimulus-control interventions are used mainly for patients with insomnia-type complaints. Both pharmacologic and nonpharmacologic therapies are effective at improving sleep and reducing insomnia complaints. An algorithm for the initial assessment and first treatment step of EDS is provided in Figure 41–1.

Insomnia

KEY CONCEPT Early treatment of insomnia may prevent the development of persistent psychophysiologic insomnia. The ideal hypnotic drug would be effective at reducing sleep latency, increasing total sleep time, and would be free of unwanted side effects. KEY CONCEPT Benzodiazepine receptor agonists (BZDRAs) (including traditional benzodiazepines, zolpidem, zaleplon, and eszopiclone) and ramelteon are approved by the Food and Drug Administration (FDA) for the treatment of insomnia and are first-line therapies.[2,26,27] Pharmacologic treatment of insomnia is recommended for transient and acute insomnia. Long-term use of hypnotics is not contraindicated unless the patient has another contraindication to their use. Eszopiclone is the only sedative hypnotic approved by the FDA for chronic use up to 6 months.[28] Although not first-line agents for insomnia, sedating antidepressants are also commonly prescribed.

Table 41–1

Nonpharmacologic Therapies for Insomnia

Sleep Hygiene
- Keep a regular sleep schedule.
- Exercise frequently but not immediately before bedtime.
- Avoid alcohol and stimulants (caffeine, nicotine) in the late afternoon and evening.
- Maintain a comfortable sleeping environment that is dark, quiet, and free of intrusions.
- Avoid consuming large quantities of food or liquids immediately before bedtime.

Stimulus Control
- Go to bed only when sleepy.
- Avoid daytime naps.
- If you cannot sleep, get out of bed and go to another room—only return to your bed when you feel the need to sleep.
- Bed is for sleep and intimacy only (no eating or watching TV in bed).
- Always wake up at the same time each day.

Relaxation Training
- Reduce somatic arousal (muscle relaxation).
- Reduce mental arousal (eg, attention-focusing procedures, imagery training, meditation).
- Use biofeedback (visual or auditory feedback to reduce tension).

Cognitive Therapy
- Alter beliefs, attitudes, and expectations about sleep.

▶ *Benzodiazepine Receptor Agonists*

Pharmacokinetic differences between the eight BZDRAs help to guide selection, depending on patient considerations and specific sleep complaints (Table 41–2). These agents occupy the benzodiazepine site on the γ-aminobutyric acid (GABA) type A receptor complex, resulting in opening of chloride channels that facilitate GABA inhibition and promote sleepiness.[33] BZDRAs are the first-line agents for treating insomnia and sleep-maintenance problems. They are all efficacious, have wide therapeutic indices, and have a low incidence of abuse.[26,28,29]

Patients should be instructed to take BZDRAs at bedtime and avoid activities requiring alertness after ingestion. Although BZDRAs generally are well-tolerated and have good safety profiles, mild to moderate side effects can occur, and precautions are warranted.

Precautions and Safety The most common side effects associated with BZDRAs include residual sedation into the waking hours after sleep, grogginess, and psychomotor impairment.[30] Selection of a hypnotic with a duration of action matching the patient's budgeted sleep time can help minimize the risk of residual sedation. BZDRAs should be initiated at low doses, and agents with active metabolites (see Table 41–2) should be avoided in elderly patients. BZDRAs may cause anterograde amnesia, defined as memory loss of activities and interactions after ingestion of the drug. All sedatives can cause anterograde amnesia, and higher doses increase the extent of amnesia.[31,32]

On discontinuation of hypnotic BZDRAs, patients may experience rebound insomnia that may last for a few nights. Rebound insomnia occurs more frequently after discontinuation of shorter duration BZDRAs compared with longer duration BZDRAs. Intermittent hypnotic therapy with the lowest dose possible reduces the likelihood of tolerance, dependence, and withdrawal when therapy is stopped. Patients should be counseled that rebound insomnia is not necessarily a return of their original symptoms, and it may take a few nights for rebound symptoms to subside. In general, eszopiclone, zaleplon, and zolpidem appear to be associated with lower risk of tolerance, rebound insomnia, and withdrawal than traditional benzodiazepines. Zolpidem, however, is associated with increased reports of complex sleep behaviors (sleep eating, sleep driving, etc). Female patients have reduced zolpidem clearance compared to males, and the maximum dose of zolpidem is 5 mg for female patients.

▶ *Sedating Antidepressants*

Sedating antidepressants (eg, trazodone, amitriptyline, mirtazapine, doxepin) are commonly used for insomnia and may be an appealing option in patients with concomitant depression. However, at the doses frequently used for sleep, only mirtazapine exhibits significant antidepressant activity. Furthermore, quality clinical studies demonstrating efficacy for insomnia are lacking. Side effects from antidepressants can be frequent, including carryover sedation, grogginess, anticholinergic effects, and weight gain. Tricyclic antidepressants (TCAs; eg, amitriptyline) should be used with caution in the elderly and patients with cardiovascular and hepatic impairment. The TCA doxepin

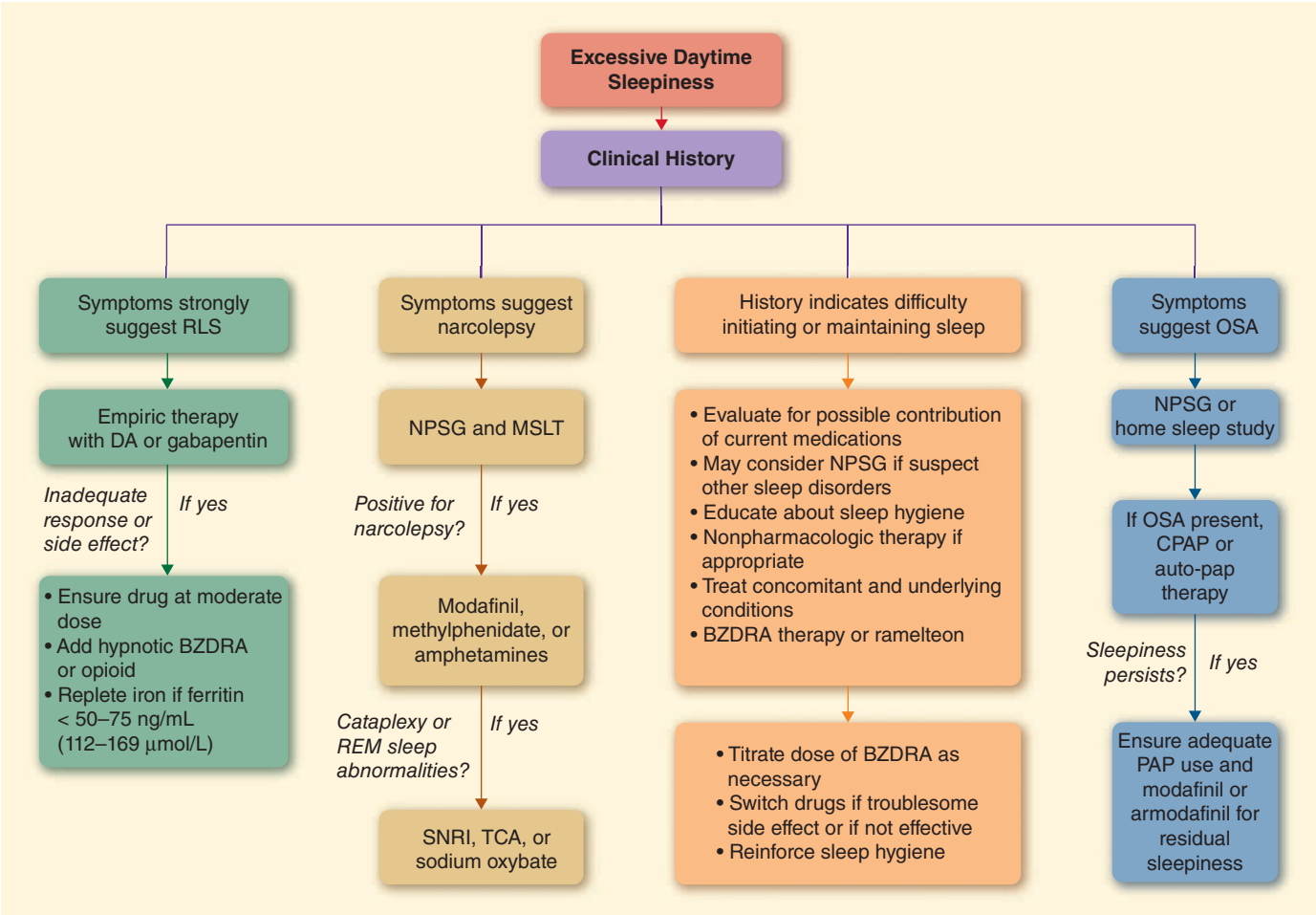

FIGURE 41–1. Primary assessment and initial treatment for complaint of excessive daytime sleepiness. (BZDRA, benzodiazepine receptor agonist; CPAP, continuous positive airway pressure; DA, dopamine agonist; MSLT, multiple sleep latency test; NPSG, nocturnal polysomnography; OSA, obstructive sleep apnea; PAP, positive airway pressure; REM, rapid eye movement; RLS, restless legs syndrome; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.)

is approved for treatment of sleep maintenance insomnia at low doses (3–6 mg). Mirtazapine can cause daytime sedation, dizziness, and weight gain; trazodone can cause orthostatic hypotension and dizziness and should be used with caution in patients with heart disease or hypertension and those taking cardiovascular agents.[33,34]

▶ *Over-the-Counter Agents*

Over-the-counter antihistamines such as diphenhydramine are frequently used (usual doses, 25–50 mg) for difficulty sleeping. Diphenhydramine is FDA-approved for the treatment of insomnia and can be effective at reducing sleep latency and increasing sleep time.[35] However, diphenhydramine produces undesirable anticholinergic effects and carryover sedation that limit its use, especially in the elderly. Valerian root is an herb that has inconsistent effects on sleep but may reduce sleep latency and increase efficiency at commonly used doses of 400 to 900 mg valerian extract.

▶ *Miscellaneous Agents*

Ramelteon, a melatonin receptor agonist, is indicated for insomnia characterized by difficulty with sleep onset. Ramelteon is not a controlled substance and can be a viable option for patients with a history of substance abuse. Suvorexant, an orexin receptor antagonist, is the first medication that turns off wakefulness mechanisms instead of stimulating pathways that induce sleepiness. Suvorexant is indicated for both difficulty initiating and maintaining sleep, and like BZDRAs, it is classified as a Schedule IV controlled substance.[36] Both suvorexant and ramelteon have documented safety in those with chronic obstructive pulmonary disease and OSA.[36-39]

Narcolepsy

Therapy for narcolepsy involves two key principles: (a) treatment of EDS with scheduled naps and CNS stimulants and (b) suppression of cataplexy and REM-sleep abnormalities with aminergic signaling drugs. Modafinil, armodafinil, methylphenidate, and amphetamines are effective FDA-approved drugs for the treatment of EDS with narcolepsy.[40] Modafinil and armodafinil (the active R-isomer of modafinil) are Schedule IV medications, and these drugs may have fewer peripheral and cardiovascular effects than traditional stimulants. Selegiline, a selective monoamine oxidase B enzyme inhibitor, is metabolized to amphetamines and can reduce daytime sleepiness. In an individual patient, one wake-promoting agent may work better than another, and if the first drug selected is not successful at

Table 41–2

Pharmacokinetics and Dosing of Prescription Medications[a] Approved to Treat Insomnia

Generic Name	Parent $t_{½}$ (hours)	Duration of Action (hours)	Daily Dose Range (mg)	Recommended Daily Dose in Elderly (mg)[b]	Dose or Action in Hepatic Impairment	Comments
Doxepin (Silenor)	15.3	Unpublished[c]	3–6	3	3 mg	Effective for sleep maintenance difficulties only
Estazolam (Prosom)	2	12–15	1–2	0.5	Dose ↓ may be needed	Moderate duration
Eszopiclone (Lunesta)	6	8	2–3	1–2	1 mg in severe impairment	Can be used up to 6 months for chronic insomnia
Flurazepam (Dalmane)	8	10–30	15–30	15	No change necessary	High risk of hangover and residual effects
Quazepam (Doral)	2	25–41	7.5–15	7.5–15	Dose ↓ may be needed	High risk of hangover and residual effects
Ramelteon (Rozerem)	1–2.6	Unpublished[c]	8	No specific recommendations	Do not use in severe hepatic impairment	Noncontrolled substance; may be useful in patients with a history of substance abuse
Suvorexant (Belsomra)	12	Unpublished	10–20	No specific recommendations	No change necessary	Novel mechanism of action—little documented rebound upon discontinuation
Temazepam (Restoril)	10–15	7	7.5–30	7.5	No change necessary	Moderate duration, well tolerated, inexpensive
Triazolam (Halcion)	2	6–7	0.125–0.25	0.125	0.125 mg	Short acting; little residual hangover
Zaleplon (Sonata)	1	6	5–10	5	5 mg	Short acting; only for difficulty falling asleep
Zolpidem (Ambien)	2–2.6	6–8	5–10[d]	5	5 mg	Short to moderate duration; no effects on sleep architecture
Zolpidem CR (Ambien CR)	2.8	7–8	6.25–12.5[d]	6.25	6.25 mg	Longer duration of action than regular release zolpidem
Zolpidem sublingual (Intermezzo)	2.5	Less than 4	1.75–3.5[d]	1.75	1.75 mg	Approved for middle-of-the-night insomnia taken more than 4 hours before awakening

[a]In 2007, the Food and Drug Administration required additional information added to the safety labeling of sedative–hypnotic drugs concerning potential risks, including severe allergic reactions and complex sleep-related behaviors, which may include sleep driving. Sleep driving is defined as driving while not fully awake after ingestion of a sedative–hypnotic product with no memory of the event.

[b]If a dosing range is displayed, the first dose listed should be the starting dose.

[c]Data not available.

[d]For zolpidem, recommended dose for women is 5 mg, 6.25 mg for zolpidem CR, and 1.75 mg for sublingual zolpidem.

CR, controlled release.

Adapted, with permission, from DiPiro JT, Talbert RL, Yee GC, et al (eds). Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014:1244.

adequate doses, a trial with another agent should be attempted. KEY CONCEPT Treatment of EDS in narcolepsy and other sleep disorders may require sustained- and immediate-release stimulants to promote wakefulness throughout the day and at key times that require alertness. One potential treatment regimen includes a sustained-release stimulant preparation first thing in the morning and again at noon followed by an immediate-release stimulant preparation as needed in the late afternoon or before driving to maintain wakefulness. One advantage of traditional CNS stimulants over modafinil is their ability to help control cataplexy and REM-sleep abnormalities.

Traditional CNS stimulants have the potential to increase blood pressure and heart rate when used long term. In addition, excessive CNS stimulation can cause tremors and tics and can carry over into evening hours, disrupting normal nighttime sleep. Caution should be used in patients with underlying cardiovascular or cerebrovascular disease and in patients with a history of seizures because stimulants may lower the seizure threshold.

► *Cataplexy*

Traditionally, aminergic signaling antidepressants have been used effectively to control symptoms of cataplexy, sleep paralysis, and other REM-sleep manifestations of narcolepsy.[40] These include TCAs and certain selective serotonin and serotonin/norepinephrine reuptake inhibitors (SSRIs and SNRIs). Clomipramine, protriptyline, imipramine, venlafaxine, and fluoxetine are the agents used most frequently. In addition,

Patient Encounter Part 1

A 48-year-old woman with a history of RLS complains of worsened RLS symptoms, excessive daytime sleepiness, disrupted nighttime sleep, and change of her RLS symptoms. She states her symptoms now appear in her arms and legs and start to appear in the late afternoon. Additionally, her husband tells you that now she has begun snoring quite loudly over the past year. She takes pramipexole 0.75 mg two hours before bedtime and sertraline 100 mg daily.

What sleep problems do her symptoms suggest?

What additional information do you need to know in your assessment of this patient?

low-dose selegiline may be effective at reducing cataplexy. Although not approved by the FDA for treatment of cataplexy, these drugs suppress REM sleep and have been the mainstay of anticataplectic therapy for years. Sodium oxybate, a potent sedative with a very short duration of action, is FDA approved for the treatment of narcolepsy with cataplexy. Its mechanism of action is not entirely known. Two doses per night are taken, one at bedtime and one follow-up dose taken 2½ to 4 hours later. Sodium oxybate is tightly regulated and is available from only one central pharmacy because of its high abuse potential.

Restless Legs Syndrome and Periodic Limb Movement Disorder

KEY CONCEPT RLS treatment involves suppression of abnormal sensations and leg movements and consolidation of sleep. Dopaminergic and sedative–hypnotic medications are prescribed commonly. Dopamine agonists (DAs) successfully treat RLS symptoms and offer many advantages over levodopa–carbidopa, including longer half-lives to cover overnight symptoms, flexible dosing, and a reduced incidence of symptom augmentation. Up to 80% of patients who take levodopa–carbidopa eventually will experience symptom augmentation: RLS symptoms appear earlier in the day, previously unaffected body parts become involved, duration of relief gets shorter, and higher doses of medication are required to control symptoms.[41] Augmentation should be managed by tapering and discontinuing dopaminergic medications, repleting body iron stores (if low) and switching to alternative medications such as gabapentin. Additionally, use of longer-duration DAs may reduce symptom augmentation.[42] Ropinirole, pramipexole, and rotigotine are FDA approved for the treatment of RLS and are available in sustained-release products.[43]

Gabapentin is an effective treatment for RLS, particularly in patients with painful symptoms.[44] The gabapentin prodrug (gabapentin enacarbil) is FDA approved for RLS at a recommended dose of 600 mg taken with food at about 5 pm.[45] Although not FDA approved for RLS, pregabalin has demonstrated similar or greater efficacy compared to DAs for RLS treatment.[46] BZDs (eg, temazepam, clonazepam) and GABA-agonists (eg, zolpidem, zaleplon) reduce arousals in patients with RLS.[47] Their main benefit is derived from improving sleep continuity in patients with RLS, particularly as adjunct treatment with other pharmacologic therapies. Opioids are effective in some patients with RLS symptoms, with oxycodone, hydrocodone, and methadone being used most frequently. For both BZDRAs and opioids, caution should be used in the elderly, in patients who are at risk for sleep apnea, and in patients with a history of substance abuse. Low iron levels frequently exacerbate RLS symptoms. Iron supplementation should be prescribed in patients who are iron deficient. Iron supplementation in patients with serum ferritin concentrations of less than 50 to 75 mcg/L (ng/mL; 112–169 pmol/L) improves RLS symptoms. Medications frequently used for RLS are shown in Table 41–3.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Test

The patient undergoes further workup for her sleep complaint, which includes an overnight sleep study (in-lab).

PMH: Restless legs syndrome × 4 years, depression × 10 years

FH: Noncontributory

SH: Married, no children. No tobacco or alcohol intake.

Meds: Pramipexole 0.75 mg taken at 8:00 PM

Sertraline 100 mg daily

ROS: (+) daytime sleepiness (Epworth sleepiness score: 16 out of 24); (+) symptoms of RLS

PE:

VS: BP 122/68 mm Hg, P 72 beats/min, RR 16 breaths/min, T 37°C (98.6°F); BMI 21 kg/m^2

Labs: TSH 1.6 μIU/mL (mIU/L), Ferritin 31 ng/mL (mcg/L; 70 pmol/L)

Overnight Polysomnogram: Bedtime at 10 PM; awake at 7 AM. Significant snoring but no significant apneas observed, with accompanying frequent awakenings.

- RDI 4.6 events/hour
- 230 limb movements, 124 caused arousal

Given this additional information, summarize what is occurring with this patient.

Identify your treatment goals and therapy recommendations for the patient.

What nonpharmacologic and pharmacologic alternatives are available for this patient if the prescribed therapy is not successful or not tolerated?

Patient Encounter Part 3: Modifying the Treatment Plan

The patient returns to the clinic 3 months later. The physician previously tapered pramipexole due to RLS symptom augmentation and initiated gabapentin and oral iron therapy. The patient was instructed to gradually reduce her pramipexole dose by 0.25 mg per week and then discontinue it. She reports today that the gabapentin has helped improve her RLS symptoms but she still feels like she awakens frequently during the night and her sleep is still disrupted. She still is somewhat sleepy during the day. Her Epworth sleepiness scale (ESS) score today is 13 out of 24.

Based on the information presented, recommend therapy and a plan for the patient.

Table 41–3

Frequently Used Medications for Restless Legs Syndrome

Generic Name (Brand Name)	Half-Life (hours)	Dose Range (mg/day)[a]	Potential Side Effect or Disadvantage
Dopaminergic Agents[b]			
Levodopa–carbidopa (Sinemet)	1.5–2	100–200 of levodopa	Nausea or vomiting; high incidence of symptom augmentation
Pramipexole (Mirapex)	8–12[c]	0.125–0.5	Nausea or vomiting; risk of compulsive behaviors[d]
Ropinirole (Requip)	6[e]	0.25–3	Nausea or vomiting; risk of compulsive behaviors[d]
Rotigotine (Neupro)	5–7	1–3	Application site reactions with patch
Anticonvulsants			
Gabapentin (Neurontin, Horizant)	5–7[c]	300–3600	Dizziness, ataxia
Pregabalin (Lyrica)	5–6.5	50–300	Weight gain, daytime sedation
Hypnotic Agents			
Clonazepam (Klonopin)	30–40	0.5–2	Tolerance, carryover sedation
Temazepam (Restoril)	10–15	7.5–30	Tolerance, carryover sedation
Zolpidem (Ambien)	2–2.6[e]	5–10	Tolerance
Zaleplon (Sonata)	1[e]	5–10	Tolerance; may not last entire night
Opioids			
Hydrocodone	3.8–4.5[e]	5–10	Constipation, nausea, sedation
Codeine	2.5–3.5[e]	30–60	Constipation, nausea, sedation
Methadone	22[e]	5–20	Constipation, nausea, sedation
Oxycodone	3.2–12[c,e]	5–30	Constipation, nausea, sedation

[a]Usual range; all medications (other than dopaminergic agents) are dosed at bedtime.

[b]Dopaminergic agents are frequently given at bedtime or 2 hours before bedtime or the anticipated onset of RLS symptoms.

[c]May be longer in patients with renal dysfunction.

[d]Compulsive behaviors such as gambling, shopping, sexual behaviors, and eating have been reported in patients taking dopamine agonists.

[e]May be longer in patients with hepatic dysfunction.

Data from Earley CJ. Restless legs syndrome. N Engl J Med. 2003;348:2103–2109.

Obstructive Sleep Apnea

KEY CONCEPT The main therapy for OSA is nasal **continuous positive airway pressure (CPAP)** therapy, which alleviates sleep-disordered breathing by producing a positive pressure column in the upper airway using room air. A flexible tube connects the CPAP machine to a mask that covers the nose. CPAP therapy has a favorable impact on blood pressure and attenuates some of the potential hemodynamic and neurohumoral responses that may link OSA to systemic disease.

Not all individuals tolerate CPAP therapy, in part because it requires wearing a mask during sleep, and therapy can dry and irritate the upper airway. In some individuals, these barriers for adherence may be reduced by properly fitting the mask, adding humidity to therapy, or using bilevel positive airway pressure (BiPAP) or auto-titrating continuous positive airway pressure (AutoPAP) therapy. BiPAP therapy applies a variable pressure into the airway during the inspiratory phase of respiration but, unlike CPAP, reduces the applied pressure during the expiratory phase. AutoPAP machines are set for a pressure range and individualize the pressure based on breath-to-breath analysis of the necessary pressure to keep the airway open.

Obesity can worsen sleep apnea, and weight management should be implemented for all overweight patients with OSA. In obese patients with mild OSA, weight loss alone can be effective, and studies have reported reduced severity of OSA following bariatric surgery. For patients who cannot tolerate CPAP, oral appliances can be used to advance the lower jawbone and to keep the tongue forward to enlarge the upper airway. For individuals who have OSA only when on their backs during sleep, positional therapies may be effective. Surgical therapy (uvulopalatopharyngoplasty) is not a first-line option because of its invasiveness and relatively low long-term effectiveness.

There is no drug therapy for OSA. Drug therapy for symptoms of OSA may be considered in selected patients. Modafinil and armodafinil are wake-promoting medications that are approved by the FDA to treat residual daytime sleepiness despite CPAP therapy. Initiation of these medications should be attempted only after patients are using optimal CPAP therapy to alleviate sleep-disordered breathing. The need for treating residual sleepiness in this population is not clear because it may not be related to the OSA and is similar to sleepiness in the general population.[48] OSA should always be considered and evaluated in hypertensive patients who are resistant to therapy.

Parasomnias

NREM parasomnias usually do not require treatment. If needed, low-dose BZDRAs such as clonazepam can be prescribed for bothersome episodes. Clonazepam reduces the amount of sleep time spent in stages 3 and 4 of NREM sleep, when most NREM parasomnias occur. For treating RBD, clonazepam 0.5 to 2 mg at bedtime is the drug of choice, although melatonin 3 to 12 mg at bedtime also may be effective. Patients with RBD also should have dangerous objects removed from the bedroom and environmental accommodations made to reduce the chance of injury from breakthrough episodes.

Circadian Rhythm Disorders

Melatonin, 0.5 to 5 mg taken at appropriate target bedtimes for east or west travel, is the drug of choice for jet lag. Melatonin significantly reduces jet lag and shortens sleep latency in travelers.[49] Hypnotic agents with relatively short durations of action (3–5 hours) may also be used to sustain sleep during the initial adaptation to the new time zone.

Drug–Disease and Drug–Drug Interactions

KEY CONCEPT It is important to review medication profiles for drugs that may aggravate sleep disorders. Patients should be monitored for adverse drug reactions and potential drug–drug interactions and assessed for treatment adherence. Pharmacotherapy for sleep disorders should be individualized. Often medications can treat several concomitant sleep disorders. Conversely, drug therapy may be effective for one sleep disorder and exacerbate another. For example, antidepressants may alleviate depressive symptoms but exacerbate symptoms of RLS. Medications that block dopaminergic transmission may worsen RLS symptoms. Alcohol and CNS depressants, including opiates, sedatives, and muscle relaxants, can worsen OSA, even in small doses, by reducing respiratory drive and relaxing the upper airway muscles responsible for maintaining patency. CNS depressants should be avoided, and if they are necessary, they should not be administered before sleep. Drug therapy for sleep disorders should be patient specific, and careful consideration should be given to coexisting diseases, concomitant medications, and potential drug–drug and drug–disease interactions to optimize patient care and treatment.

OUTCOME EVALUATION

Evaluate whether the treatment plan restored normal sleep patterns, reduced daytime sequelae, and improved quality of life without causing adverse effects. Schedule patients for follow-up within 3 weeks for insomnia and within 3 months for other sleep disorders. Perform a detailed clinical history to determine the patient's perception of treatment progress and symptoms along with medication effectiveness and side effects.

Instruct patients to keep sleep diaries (number of hours, number of awakenings, and worsening or improved sleep) and daytime symptoms, along with documentation of episodes such as cataplexy or RBD. Increase medication to effective doses, and if necessary, start additional therapy to control symptoms. Patients with sleep disorders should experience relief of symptoms the first night of drug therapy but may not receive maximal benefit (effect on daytime symptoms) for a few weeks. Perform a detailed history of prescription, nonprescription, and complementary or alternative medications and review the patient's sleep diary, daytime symptoms, and nonpharmacologic therapies on a regular basis.

LO 7

Patient Care Process

Collect Information:

- Perform a detailed history of prescription, nonprescription, and complementary or alternative medication use.
- Based on patient nighttime and daytime complaints and bed partner report, determine the suspected sleep problem and its consequences.
- Review objective and subjective data regarding sleepiness, nighttime sleep quality, and limb movements, sleep disordered breathing, and parasomnias.
- Evaluate concomitant sleep and medical conditions that influence therapy decisions.

Assess the Information:

- Evaluate effectiveness, safety, adherence, and side effects of therapy.
- Assess whether patient is taking any medications that may contribute to sleep complaint and/or daytime complaints.
- Determine whether the patient has insurance coverage for prescribed medications.
- Review relevant laboratory parameters for sleep (eg, serum TSH, ferritin).

Develop a Care Plan:

- If patient requires sedative-hypnotic therapy, determine best agent based on timing of sleep complaint (difficulty initiating and/or maintaining sleep).
- For treatment of insomnia, try to ensure the lowest possible doses are prescribed and used for the shortest possible time period.
- If patient complaints are not entirely improved, consider increasing dose or adding a complementary agent.
- Ensure sleep hygiene (see **Table 41–1**) and drug therapy are appropriate for each sleep complaint.
- Determine if medication doses are optimal for treatment of various sleep disorders (see **Tables 41–2** and **41–3**).
- For insomnia, select medications whose duration of action matches the timing of the difficulty sleeping (eg, difficulty initiating or maintaining sleep).

Implement the Care Plan:

- Educate patient about medication changes, sleep hygiene, and importance of proper medication use and adherence.
- Address patient concerns about the sleep medication and possible adverse effects.

Follow-up: Monitor and Evaluate:

- Evaluate improvement in the specific sleep complaint (eg, how has therapy affected sleep latency or sleep maintenance?).
- Monitor daytime sleepiness, sleep diaries, and diaries of sleep events (PLMS, hallucinations, snoring, apneas, etc) and monitor cataplexy and other daytime symptoms to determine if therapy is effective.
- Make appropriate changes to therapy to address inadequately controlled symptoms and reported adverse effects.

Abbreviations Introduced in This Chapter

AutoPAP	Auto-titrating continuous positive airway pressure
BiPAP	Bilevel positive airway pressure
BMI	Body mass index
BZDRA	Benzodiazepine receptor agonist
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CRD	Circadian rhythm disorder
DA	Dopamine agonist
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
ESS	Epworth sleepiness scale
FDA	Food and Drug Administration
GABA	γ-Aminobutyric acid
MSLT	Multiple sleep latency test
NPSG	Nocturnal polysomnography
NREM	Non–rapid eye movement
OSA	Obstructive sleep apnea
PLMS	Periodic limb movements of sleep
RBD	REM-sleep behavior disorder
RDI	Respiratory disturbance index
REM	Rapid eye movement
RLS	Restless legs syndrome
SNRI	Serotonin/norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

REFERENCES

1. Vaughn BV, D'Cruz OF. Cardinal manifestations of sleep disorders. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine, 6th ed. St. Louis: Elsevier Saunders; 2017:576–586.
2. NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. U.S. Department of Health and Human Services, National Institutes of Health. Available from: http://consensus.nih.gov/2005/insomnia.htm. Accessed July 19, 2018.
3. Carskadon MA, Dement WC. Normal human sleep: an overview. In: Kryger M, Roth T, Dement W, eds. Principles and Practice of Sleep Medicine, 6th ed. St. Louis: Elsevier Saunders; 2017:15–24.
4. Roth T. Insomnia: definition, prevalence, etiology, and consequences. J Clin Sleep Med. 2007;15(suppl 5):S7–S10.
5. Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R. An epidemiological study of insomnia among the Japanese general population. Sleep. 2000;23:41–47.
6. McCall WV. A psychiatric perspective on insomnia. J Clin Psychiatry. 2001;62(suppl 10):27–32.
7. Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. Sleep. 2002;25:197–202.
8. Tashiro T, Kambayashi T, Hishikawa Y. An epidemiological study of narcolepsy in Japanese. Proceedings of the 4th International Symposium on Narcolepsy. Tokyo, Japan. June 16–17, 1994:13.
9. Lavie P, Peled R. Narcolepsy is a rare disease in Israel. Sleep. 1987;10:608–609.
10. Mignot E, Hayduk R, Black J, Grumet FC, Guilleminault C. HLA DQB1*0602 is associated with cataplexy in 509 narcoleptic patients. Sleep. 1997;20:1012–1020.
11. Berger K, Kurth T. RLS epidemiology—frequencies, risk factors and methods in population studies. Mov Disord. 2007;22(suppl):S420–S423.
12. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med. 2000;160:2137–2141.
13. Lee KA, Zaffke ME, Baratte-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. J Womens Health Gend Based Med. 2001;10:335–341.
14. Bonati MT, Ferini-Strambi L, Aridon P, Oldani A, Zucconi M, Casari G. Autosomal dominant restless legs syndrome maps on chromosome 14q. Brain. 2003;126:1485–1492.
15. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230–1235.
16. Ohayon MM, Caulet M, Priest RG. Violent behavior during sleep. J Clin Psychiatry. 1997;58:369–376.
17. Mignot E, Lin X, Arrigoni J, et al. DQB10602 and DQA1*0102(DQ1) are better markers than DR2 for narcolepsy in Caucasian and black Americans. Sleep. 1994;17:S60–S67.
18. Mignot E, Kimura A, Lattermann A, et al. Extensive HLA class II studies in 58 non-DRB1*15(DR2) narcoleptic patients with cataplexy. Tissue Antigens. 1997;49:329–341.
19. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol. 2002;59(10):1553–1562.
20. Connor JR, Boyer PJ, Menzies SL, et al. Neuropathological examination suggests impaired brain iron acquisition in restless legs syndrome. Neurology. 2003;61:304–309.
21. Salminen AV, Rimpila V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). Neurology. 2014;82:1856–1861.
22. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute, National Center on Sleep Disorders Research (National Institutes of Health). Circulation. 2008;118:1080–1111.
23. Sahlin C, Sandberg O, Gustafson Y, et al. Obstructive sleep apnea is a risk factor for death in patients with stroke: a 10-year follow-up. Arch Intern Med. 2008;168:297–301.
24. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med. 2000;342:1378–1384.
25. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest. 1995;96:1897–1904.
26. Buscemi N, Vandermeer B, Friesen C, et al. The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. J Gen Intern Med. 2007;22:1335–1350.
27. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4:487–504.
28. Krystal AD, Walsh JK, Laska E, et al. Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. Sleep. 2003;26:793–799.
29. Becker WC, Fiellin DA, Desai RA. Non-medical use, abuse and dependence on sedatives and tranquilizers among U.S. adults: psychiatric and socio-demographic correlates. Drug Alcohol Depend. 2007;90:280–287.
30. Roth T, Roehrs T. Issues in the use of benzodiazepine therapy. J Clin Psychiatry. 1992;53(suppl):S14–S18.
31. Roth T, Roehrs TA, Stepanski EJ, Rosenthal LD. Hypnotics and behavior. Am J Med. 1990;88(3A):S43–S46.

32. Greenblatt D, Harmatz JS, Shapiro L, Engelhardt N, Gouthro TA, Shader RI. Sensitivity to triazolam in elderly. N Engl J Med. 1991;324:1691–1698.
33. Golden RN, Dawkins K, Nicholas L. Trazodone and nefazodone. In: Schatzberg A, Nemeroff CB, eds. The American Psychiatric Textbook of Psychopharmacology. Washington, DC: American Psychiatric Publishing; 2004:315–325.
34. Bucknall C, Brooks D, Curry PV, Bridges PK, Bouras N, Ankier SI. Mianserin and trazodone for cardiac patients with depression. Eur J Clin Pharmacol. 1988;33:565–569.
35. Kudo Y, Kurihara M. Clinical evaluation of diphenhydramine hydrochloride for the treatment of insomnia in psychiatric patients. J Clin Pharmacol. 1990;30:1041–1048.
36. Product Information: Belsomra, (suvorexant). Whitehouse Station, NJ: Merck & Co., Inc., 8/2014.
37. Johnson MW, Suess PE, Griffiths RR. A novel hypnotic lacking abuse liability and sedative adverse effects. Arch Gen Psychiatry. 2006;63:1149–1157.
38. Kryger M, Roth T, Wang-Weigand S, Zhang J. The effects of ramelteon on respiration during sleep in subjects with moderate to severe chronic obstructive pulmonary disease. Sleep Breath. 2009;13:79–84.
39. Kryger M, Wang-Weigand S, Roth T. Safety of ramelteon in individuals with mild to moderate obstructive sleep apnea. Sleep Breath. 2007;11:159–164.
40. Morganthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin an American Academy of Sleep Medicine Report. Sleep. 2007;30:1705–1711.
41. Earley CJ, Allen RP. Pergolide and carbidopa/levodopa treatment of the restless legs syndrome and periodic leg movements in sleep in a consecutive series of patients. Sleep. 1996;19:801–810.
42. Benes H, Garcia-Borreguero D, Ferini-Strambi L, Schollmayer E, Fichtner A, Kohnen R. Augmentation in the treatment of restless legs syndrome with transdermal rotigotine. Sleep Med. 2012;13:589–597.
43. Aurora RN, Kristo DA, Bista SR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep. 2012;35:1039–1062.
44. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology. 2002;59:1573–1579.
45. Product Information: Horizant, gabapentin enacarbil. Research Triangle Park, NC: GlaxoSmithKline Pharmaceuticals, 2011.
46. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. New Engl J Med. 2014;370:621–631.
47. Earley CJ. Restless legs syndrome. N Engl J Med. 2003;348:2103–2109.
48. Stradling JR, Smith D, Crosby J. Post-CPAP sleepiness—a specific syndrome? J Sleep Res. 2007;16:436–438.
49. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev. 2005;(4):CD001520.

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42 Attention-Deficit/ Hyperactivity Disorder

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LEARNING OBJECTIVES

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

LO

1. Explain accepted criteria necessary for the diagnosis of attention-deficit/hyperactivity disorder (ADHD).
2. Recommend a therapeutic plan, including drug selection, initial doses, dosage forms, and monitoring parameters, for a patient with ADHD.
3. Differentiate among the available pharmacologic agents used for ADHD with respect to pharmacology and pharmaceutical formulation.
4. Recommend second-line and/or adjunctive agents that can be effective alternatives in the treatment of ADHD when stimulant therapy is less than adequate.
5. Address potential cost–benefit issues associated with pharmacotherapy of ADHD.
6. Recommend strategies for minimizing adverse effects of ADHD medications.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity. It can have a severe impact on a patient's ability to function in both academic and social environments. Early diagnosis and appropriate treatment are essential to compensate for areas of deficit.

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT This disorder usually begins in young children and must occur before 12 years of age to meet current diagnostic criteria. In the United States, ADHD is the most common neurobehavioral disorder that affects children.[1] ADHD has been diagnosed in approximately 11% of school-aged children.[2] ADHD occurs more than twice as often in school-aged boys than girls.[3]

Although ADHD generally is considered a childhood disorder, symptoms can persist into adolescence and adulthood. The prevalence of adult ADHD is estimated to be 2.5%; majority of adults with ADHD have symptoms that manifested in childhood.[3,4] Furthermore, problems associated with ADHD (eg, social, marital, academic, career, anxiety, depression, smoking, and substance abuse problems) increase with the transition of patients into adulthood. Untreated adults with ADHD have high rates of psychopathology, substance abuse, and social and occupational dysfunction.

PATHOPHYSIOLOGY

KEY CONCEPT The exact pathologic cause of ADHD has not been identified. ADHD is generally thought of as a disorder of self-regulation or **response inhibition** and **cognitive deficits**.[5] Patients who meet the criteria for ADHD have difficulty maintaining self-control, resisting distractions, concentrating on ideas, and often alternate between inattentiveness to overexcitement.[3,6]

KEY CONCEPT Dysfunction of the **neurotransmitters** is thought to be key in the pathology of ADHD. Norepinephrine is responsible for maintaining alertness and attention; dopamine is responsible for regulating learning, motivation, goal setting, and memory. Both of these neurotransmitters predominate in the frontal subcortical system, an area of the brain responsible for maintaining attention and memory. Genetics appears to play a role because a child who has a parent with ADHD has a 50% chance of developing ADHD. An association has been made between the development of ADHD and fetal alcohol syndrome, lead poisoning, maternal smoking, and hypoxia.[3,6]

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT ADHD is rarely encountered without comorbid conditions such as oppositional defiant and conduct disorder and often is misdiagnosed.[1] It is important to identify and appropriately treat coexisting conditions in patients with ADHD.

According to most recent diagnostic guidelines, all patients 4 to 18 years of age presenting with inattention, hyperactivity, impulsivity, academic, and/or behavioral problems should be evaluated for ADHD. Additional behavior information from various settings should be gathered from the patient, family, and teachers. The age of onset, frequency, severity, and duration of symptoms should be documented.[3,6]

LO 1

The most useful diagnostic criteria for ADHD is the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*).[3] The *DSM-5* defines three presentations of ADHD: (a) predominately inattentive; (b) predominantly hyperactive-impulsive; and (c) combined, in which both inattentive and hyperactive or impulsive symptoms are evident.[3,6] It is recommended that parents and teachers complete a standardized rating scale based on the *DSM-5* criteria.[3] Rating scales are not by themselves diagnostic but are diagnostic aids when added to a careful history and interview.[7]

TREATMENT

Desired Outcomes

KEY CONCEPT The primary therapeutic objectives in ADHD are to improve behavior and increase attention or response inhibition; secondary goals of treatment are to:

- Improve interpersonal relationships and academic performance
- Decrease disruptive behavior
- Increase independence
- Minimize adverse effects of therapy

Nonpharmacologic (Behavioral) Therapy

LO 2 Behavioral therapy can be useful; however, it is generally not recommended as first-line monotherapy except in preschool-aged children (4–5 years of age).[3,6] KEY CONCEPT Studies have demonstrated pharmacotherapy alone is superior to behavioral intervention alone in improving attention. However, combined behavioral and stimulant therapy is better at improving opposition and aggression.[8] Behavioral modification involves training caregivers and teachers to change environmental factors and establish a reward/consequence system.[6] Success of behavioral modifications depends on the cooperation of the caregivers and teachers.

Pharmacologic Therapy

LO 3 The proposed mechanism of ADHD pharmacotherapy is to modulate neurotransmitter function in order to improve academic and social functioning. Pharmacotherapy can be divided into two categories—stimulants and nonstimulants.

▶ *Stimulants*

KEY CONCEPT Psychostimulants (eg, methylphenidate and amphetamines) are the most effective agents in treating ADHD. Following diagnosis of ADHD, a stimulant medication should be considered first-line therapy in patients 6 years of age or older. Stimulants theoretically exert their primary effect by blocking the reuptake of dopamine and norepinephrine. In preschool-aged children, methylphenidate can be added to the patient's treatment if behavioral modification monotherapy is not sufficient.[6] Generally, LO 2 a trial of at least 3 months on a stimulant is appropriate, and this includes dose titration to response as tolerated.[6] KEY CONCEPT If treatment with the first stimulant formulation fails, it is recommended to switch to a different stimulant formulation.[3,6] For example, if the patient was started on methylphenidate but could not tolerate the side effects, switching to dextroamphetamine with or without amphetamine is appropriate. Most patients LO 4 who fail one stimulant will respond to an alternative stimulant.[6] KEY CONCEPT If the patient fails two adequate trials of different stimulant medications, a third stimulant formulation or second-line nonstimulant such as bupropion, atomoxetine, guanfacine, or clonidine can be considered. The diagnosis of ADHD should be revalidated as well.

Stimulants theoretically exert their primary effect by blocking the reuptake of dopamine and norepinephrine. They have been shown to decrease fidgeting and finger tapping, increase on-task classroom behavior and positive interactions at home and in social environments, and ameliorate conduct and anxiety disorders.[9]

LO 2 Stimulants should be initiated at recommended starting doses and titrated up with a consistent dosing schedule to the appropriate response while minimizing side effects (Table 42–1). Generally, stimulants should not be used in patients who have glaucoma, severe hypertension or cardiovascular disease, hyperthyroidism, severe anxiety, or previous illicit or stimulant drug abuse.

LO 3 Stimulant drug formulations can be divided into short-, intermediate-, and long-acting preparations (see Table 42–1). Initial response to short-acting stimulant formulations (eg, methylphenidate and dextroamphetamine) is seen within 30 minutes and can last for 4 to 6 hours.[6] Thus short-acting stimulant formulations must frequently be dosed at least twice daily, increasing the chance of missed doses and noncompliance. Patients using any stimulant formulation, but especially short-acting formulations, can experience a rebound effect of ADHD symptoms as the stimulant wears off.[9]

Most intermediate-acting stimulants release the medication in a slow, continuous fashion without any early release (except Dexedrine Spansules). The onset of action for this category of stimulants (typically 60–90 minutes) may be inadequate for some patients. Some practitioners prescribe a short-acting stimulant concurrently with an intermediate-acting stimulant to curtail the delay in onset of action of the intermediate-acting stimulant. However, this practice can increase patient copay costs.

To minimize rebound symptoms associated with short-acting formulations and still achieve early stimulant release, long-acting formulations with rapid onsets have been developed. These formulations have an early release of medication and deliver a delayed release of stimulant in either a pulsed (Adderall XR, Focalin XR, Metadate CD, Quillivant XR, and Ritalin LA) or continuous manner (Concerta). Formulations available as capsules contain coated beads that can be opened and sprinkled on semisolid food. Concerta tablets have an immediate-release overcoat and an oral osmotic controlled-release that delivers methylphenidate in an extended manner. Patients should be counseled that the empty tablet shell of Concerta can be seen in the stool.

Clinical Presentation and Diagnosis of ADHD

General

Patients with ADHD can present with inattention, hyperactivity–impulsivity, or both. ADHD is typically encountered with comorbid conditions.

Symptoms

- Inattentive type: difficulty paying attention to details in all activities; difficulty completing tasks that require a lot of mental effort; easily distracted; forgetful
- Hyperactive–impulsive type: difficulty sitting still, fidgets; has trouble playing quietly and waiting turns; frequently interrupts
- Combined: exhibits both inattention and hyperactivity–impulsivity

Diagnostic Criteria

- Must exhibit at least 6 diagnostic symptoms before 12 years of age that persist for at least 6 months
- Symptoms must be present in two or more settings and adversely affect functioning in social situations, school, or work
- Must meet the diagnostic criteria in *DSM-5* for ADHD
- Symptoms cannot be better explained by another mental disorder (eg, autism)

Table 42–1

Selected Medications for ADHD[a]

Drug, Generic (Brand Name)	Initial Dose	Titration Schedule Increments	Typical Dosing Range (Maximum Dose)
Stimulants			
Short Acting			
Methylphenidate[b] (Methylin, Ritalin)	5 mg twice daily	5–10 mg/day in weekly intervals	5–20 mg two to three times daily (60 mg/day)
Dexmethylphenidate[b] (Focalin)	2.5 mg twice daily	2.5–5 mg/day in weekly intervals	5–10 mg twice daily (20 mg/day)
Dextroamphetamine[b] (Dexedrine)	2.5–5 mg every morning	2.5–5 mg/day in weekly intervals	5–20 mg twice daily (40 mg/day)
Intermediate Acting			
Methylphenidate[b] (Ritalin SR, Metadate ER, Methylin ER)	10 mg once daily	10 mg/day in weekly intervals	20–40 mg daily in the morning (60 mg/day)
Dextroamphetamine–amphetamine[b] (Adderall)	2.5–5 mg once to twice daily	2.5–5 mg/day in weekly intervals	10–30 mg every morning or 5–20 mg twice daily (40 mg/day)
Dextroamphetamine[b] (Dexedrine Spansule)	5 mg every morning	5 mg/day in weekly intervals	5–30 mg daily or 5–15 mg twice daily (40 mg/day)
Long-Acting			
Methylphenidate[b] (Concerta)	18 mg every morning	9–18 mg/day in weekly intervals	18–54 mg every morning (54 mg/day in children)
(Metadate CD)	20 mg every morning	10–20 mg/day in weekly intervals	20–40 mg daily in the morning (60 mg/day)
(Ritalin LA)	20 mg every morning	10 mg/day in weekly intervals	20–40 mg daily in the morning (60 mg/day)
(Quillivant XR)[c]	20 mg every morning	10–20 mg/day in weekly intervals	20–40 mg daily in the morning (60 mg/day)
(Aptensio XR)	10 mg every morning	10 mg/day in weekly intervals	10–60 mg daily in the morning (60 mg/day)
(Cotempla XR-ODT)	17.3 mg every morning	8.6–17.3 mg/day in weekly intervals	17.3–51.8 mg daily in the morning (51.8 mg/day)
Dextroamphetamine/amphetamine[b] (Adderall XR)	5–10 mg every morning (children); 20 mg once daily (adults)	5–10 mg/day in weekly intervals	10–30 mg every morning or 5–15 mg twice daily (30 mg/day, children) (60 mg/day, adult)
Dexmethylphenidate[b] (Focalin XR)	5 mg every morning (children); 10 mg every morning (adults)	5 mg/day in weekly intervals	10–20 mg daily in the morning (20 mg/day)
Lisdexamfetamine[b] (Vyvanse)	30 mg every morning (children and adults)	10–20 mg/day in weekly intervals	30–70 mg daily in the morning (70 mg/day)
Amphetamine[b] (Dyanavel XR)	2.5–5 mg every morning	2.5–10 mg/day every 4–7 days	2.5–20 mg daily in the morning (20 mg/day)
(Evekeo)	2.5 mg every morning (3–5 years) or 5 mg every morning or twice daily (6 years or older)	2.5 mg/day (3–5 years) or 5 mg/day (6 years or older) in weekly intervals	2.5–40 mg daily in a single morning or twice daily divided dose (40 mg/day)
Nonstimulants			
Atomoxetine[b,d] (Strattera)	≤ 70 kg: 0.5 mg/kg/day divided once to twice daily > 70 kg: 40 mg once daily	To target dose of 1.2 mg/kg/day after 3 days 40 mg/day after 3 days (may ↑ to total of 100 mg/day after 2–3 weeks)	40–60 mg/day (1.4 mg/kg or 100 mg/day, whichever is less) 40–80 mg/day divided once to twice daily (100 mg/day)
Clonidine (Catapres)	0.05 mg once daily	0.05 mg/day every 3–7 days	0.1 mg 1 to 4 times daily (0.4 mg/day)
(Kapvay)[b]	0.1 mg at bedtime	0.1 mg/day in weekly intervals	0.1–0.2 mg twice daily (0.4 mg/day)
Guanfacine (Tenex)	0.5 mg at bedtime	0.5 mg every 3–14 days	1.5–3 mg/day divided into 2–3 doses (4 mg/day)
(Intuniv)[b]	1 mg once daily	No more than 1 mg/week	1–4 mg daily (4 mg/day)
Bupropion (Wellbutrin, Wellbutrin SR, Wellbutrin XL)	3 mg/kg/day for 7 days (children); 150 mg once daily of SR or XL (adults)	3 mg/kg/day in weekly intervals (children); increase 150–300 mg/day in weekly intervals (adults)	6 mg/kg/day or 400 mg/day—whichever is smaller (children); 150–450 mg/day (400 mg/day SR; 450 mg/day XL—adults)

[a]Pediatric dosing except when adult dosing specified.

[b]Approved by the US FDA for the treatment of ADHD.

[c]Oral extended-release suspension.

[d]Dose adjustment required in patients with hepatic insufficiency.

CD, extended release (biphasic immediate release with extended release); ER, extended release; LA, long acting; ODT, orally disintegrating tablet; SR, sustained release; XL, extended release; XR, extended-release.

Two long-acting stimulants, Daytrana and Vyvanse, have slower onsets of action than the other long-acting stimulants with a rapid release. Daytrana transdermal patches are to be applied for only 9 hours per day and have a delayed onset of 2 hours, and their effects persist for 3 hours after being removed. Some patients report skin sensitization and irritation. Vyvanse is a prodrug that is hydrolyzed to its active form, dextroamphetamine, after oral ingestion. Inhalation or injection abuse potential is minimized because of impeded hydrolysis by these routes. Onset of action for Vyvanse has been reported to be 2 hours.[10]

LO 6

Adverse effects of stimulants can be generalized to the whole class (Table 42–2). Most side effects can be managed by changing the dosing routine (ie, giving with food, dividing daily dose, or giving the dose earlier in the day). Serious side effects (eg, hallucinations and abnormal movements) require discontinuation of medication.[9] To avoid potential drug–food interactions and absorption issues, stimulants should be given 30 to 60 minutes before eating.

Growth suppression or delay is a major concern for parents of children taking stimulants. Growth delay appears to be transient and to resolve by mid-adolescence, but more data are needed to resolve this issue. Another concern is risk of substance abuse with stimulant use. A diagnosis of ADHD alone increases the risk of substance abuse in adolescents and adults. However, stimulant use has not been shown to further increase this risk but actually may decrease this risk, provided ADHD is treated adequately.[11]

The choice of ADHD medication should be made based on the patient's condition, prescriber's familiarity with the medications, ease of administration, and cost. Stimulants should be used as first-line agents in most ADHD patients, although studies in groups of patients have shown no clear advantage of one stimulant over another.[4]

Table 42–2

Patient Monitoring and Management of Selected Adverse Effects of ADHD Medications

Drug	Adverse Effects	Management	Monitoring
Stimulants			
Methylphenidate Dexmethylphenidate Dextroamphetamine Amphetamine Lisdexamfetamine	GI upset, nausea, decreased appetite, potential growth delay	Administer after breakfast and lunch Encourage high-calorie meals/beverages and snacks after dinner Divide dose Change to shorter-acting stimulant Discontinue on weekends and during holidays	Height, weight, blood pressure, pulse ECG if warranted Eating and sleeping patterns Evaluate every 2–4 weeks until stable dose is achieved; then evaluate every 3 months
	Insomnia	Move dose(s) earlier in the day and discontinue later day dose if problem persists Change to a shorter-acting stimulant Consider adjunct hypnotic (eg, melatonin) or alternate medication (eg, guanfacine, bupropion)	
	Headache	Decrease dose Change to longer-acting stimulant or nonstimulant (eg, atomoxetine) Consider analgesic (eg, acetaminophen)	
	Irritability, dysphoria, agitation	Early onset (peak related): Decrease dose or change to longer-acting stimulant Late onset (withdrawal related): Change to longer-acting stimulant Evaluate for comorbidity and treat if present	
	Tics	Decrease dose Change to a different stimulant or a nonstimulant (eg, guanfacine, atomoxetine) Add an antipsychotic (eg, risperidone)	
Nonstimulants			
Atomoxetine	Increased blood pressure and pulse, nausea, vomiting, fatigue, and insomnia	Decrease dose or change to another medication (eg, guanfacine, bupropion)	Same as above but with baseline and routine liver function tests for hepatotoxicity
	Hepatotoxicity, suicidal thoughts	Discontinue or change to another medication	
Clonidine and guanfacine	Sedation	Decrease dose Administer closer to bedtime	Same as above
Bupropion	GI upset, restlessness, sleep disturbances, tremor	Decrease dose or change to another medication (eg, guanfacine)	Height, weight, blood pressure, pulse every month
	Tics, rash, seizures	discontinue medication	Eating and sleeping patterns

ECG, electrocardiography; GI, gastrointestinal.

Patient Encounter Part 1

Rorin, an 8-year-old boy with combined type ADHD comes to your clinic. Three months ago, Rorin's dose of generic Concerta increased from 18 mg to 36 mg daily. At school he still often is in trouble for not listening to teachers, losing interest easily, not remaining seated, talking excessively, blurting out answers, interrupting others, not participating in groups, being disruptive and easily distracted, and hitting other children. The beneficial effects of generic Concerta wear off by 4 PM and no adverse effects have occurred.

Wt: 31.8 kg or 70 lb (86th percentile)

Allergies: None known

Ht: 132 cm or 4'4" (70th percentile)

BP: 95/63 mm Hg

P: 83 beats/min

What other information should be collected and possible comorbid conditions investigated before continuing therapy for ADHD?

Which of Rorin's symptoms are suggestive of ADHD?

What help or suggestions could you offer Rorin's caregivers?

What change to Rorin's stimulant therapy should be made at this clinic appointment?

▶ *Nonstimulants*

LO 4

Atomoxetine Atomoxetine is approved for the treatment of ADHD in both children and adults. In clinical studies, it demonstrated superior efficacy over placebo and either equivalent efficacy compared with a suboptimal immediate-release methylphenidate dose or inferior to Concerta.[12] KEY CONCEPT Atomoxetine may be used as a second- or third-line medication for ADHD.

Atomoxetine selectively inhibits the reuptake of adrenergic neurotransmitters, principally norepinephrine.[12] Atomoxetine is metabolized through the cytochrome P450 (CYP) 2D6 pathway. Concurrent use of certain antidepressants (ie, fluoxetine, paroxetine) may inhibit this enzyme and necessitate slower dose titration of atomoxetine. Approximately 5% to 10% of the population are CYP2D6 poor metabolizers, and atomoxetine's half-life is increased significantly in this population.[13] The recommended dosing for atomoxetine depends on patient weight and is given once or twice daily[13] (see Table 42–1). In poor metabolizers, atomoxetine should be dosed once daily at 25% to 50% of the dose typically used in normal metabolizers.[13] Onset of therapeutic effect of atomoxetine may take up to 2 to 8 weeks, significantly longer than with stimulants.[14] Common side effects of atomoxetine are similar to those of stimulants.[12] It can slow growth rate and cause weight loss; thus, height and weight should be monitored routinely in children[12] (see Table 42–2). Atomoxetine's labeling includes warnings about severe hepatotoxicity and increased association with suicidal thinking.

Atomoxetine can be given once daily in many patients. It appears to lack any abuse potential and is not a controlled substance.[15] One big disadvantage of atomoxetine is cost compared with other ADHD medications, despite a generic being approved by the FDA in May 2017 (Table 42–3).

Because of the high cost, lack of long-term efficacy data, and few comparison studies with stimulants, atomoxetine should be advocated only if the patient has failed or is intolerant to stimulant therapy.

LO 4

Bupropion Bupropion is a monocyclic antidepressant that weakly inhibits the reuptake of norepinephrine and dopamine. Some studies suggest it may be effective for symptoms of ADHD in children, and may be as effective as methylphenidate in children and adults.[16,17] Other evidence suggests that bupropion lacks efficacy and has high-incidence withdrawal effects.[18] Bupropion is generally well tolerated with minimal side effects (eg, insomnia, headache, nausea, and tremor) which typically disappear with continuation of therapy and with slow titration of dose. Bupropion can worsen tics and movement disorders. It is a rational choice in an ADHD patient with comorbid depression.[17] However, seizures have been associated with bupropion at high doses. Seizures risk can be minimized by reducing the dose or switching to a longer-acting formulation. Bupropion can increase the risk of suicidal ideation and is contraindicated in patients with seizure and eating disorders.

LO 4

Clonidine and Guanfacine Clonidine and guanfacine are central α_2-adrenergic agonists that inhibit the release of norepinephrine presynaptically. Both of these agents are less effective than stimulants in treating ADHD but typically are used as adjuncts to stimulants to control disruptive or aggressive behavior and alleviate insomnia.[19] The effects of immediate-release guanfacine typically last 3 to 4 hours longer than immediate-release clonidine, and the drug requires less frequent dosing. Extended-release formulations of guanfacine (Intuniv) and clonidine (Kapvay) were developed to minimize dosing frequency and improve treatment of anger, hostility, and irritability in patients with ADHD. Similar to other nonstimulants, these two dosage forms can also be used in patients who are intolerant to stimulants. However, use of these dosage forms is limited because of a lack of comparative trials to stimulants. Common side effects with clonidine and guanfacine are low blood pressure and sedation. Sedation generally subsides after 2 to 3 weeks of therapy.[20,21] Rarely, severe side effects such as bradycardia, rebound hypertension, irregular heartbeats, and sudden death have been reported.

Pharmacoeconomic and Treatment Adherence Considerations

LO 5

Annual health care costs for people with ADHD was almost 60% higher than people without ADHD.[19] The financial burden of ADHD is attributed to the direct cost of pharmacotherapy, office visits, diagnostic measurements, therapy monitoring, and indirect costs (eg, lost work time and productivity). When selecting a treatment, the cost burden to the patient's family should be considered. Short-acting stimulants may be more cost effective in many patients compared with longer-acting stimulant formulations (see Table 42–3), but in certain circumstances, longer-acting stimulant formulations may provide a greater benefit owing to increased adherence to the medication and prolonged control of symptoms of ADHD. All intermediate-acting and various long-acting (Concerta, Ritalin LA, Metadate CD, Focalin XR, and Adderall XR) stimulant formulations are now available as generic products, making them potentially more affordable. In addition, some nonstimulant ADHD medications (eg, bupropion and immediate-release α_2-adrenergic agonists) appear to be less costly than many stimulant formulations; however, these agents have not been consistently proven to have superior efficacy over stimulants. Decisions on selection of specific ADHD medications should not be based solely on cost but also on efficacy and safety along with adherence to the prescribed regimen.

Table 42–3

Cost[a] of 30-Day Supply of Selected ADHD Medication Regimens

Medications	Regimens	Cost[a]
Short-Acting Rapid-Onset Stimulants		
Methylphenidate		
Generic	5-, 10-, or 20-mg tablet twice daily	$
Dexmethylphenidate		
Generic	2.5-, 5-, or 10-mg tablet twice daily	$
Dextroamphetamine		
Generic	5-mg tablet twice daily	$$
Intermediate-Acting Slower-Onset Stimulants		
Methylphenidate		
Methylin ER	10- or 20-mg ER tablet daily	$$
Dextroamphetamine[b]		
Generic	10- or 15-mg capsule daily	$$
Dextroamphetamine/amphetamine		
Generic	5-, 7.5-, 10-, 12.5-, 15-, 20-, or 30-mg tablet daily	$
Long-Acting Rapid-Onset Stimulants		
Methylphenidate		
Concerta (brand and generics)[b]	18-, 27-, 36-, or 54-mg tablet daily	$$$
Metadate CD (brand and generics)[c]	10-, 20-, 30-, or 40-mg capsule daily	$$
Ritalin LA (brand and generics)[c]	10-, 20-, 30-, or 40-mg capsule daily	$$
Quillivant XR[c]	10-, 20-, 25-, or 30-mg of suspension daily	$$$
Aptensio XR	10-, 15-, 20-, 30-, 40-, 50-, or 60-mg capsule daily	$$$
Cotempla XR-ODT	8.6-, 17.3-, or 25.9-mg oral disintegrating tablet daily	$$$
Dextroamphetamine/amphetamine		
Adderall XR (brand and generics)	5-, 10-, 15-, 20-, 25-, or 30-mg capsule daily	$$
Dexmethylphenidate		
Focalin XR (brand and generics)[c]	5-, 10-, 15-, 20-, 25-, 30-, 35-, or 40-mg capsule daily	$$$
Amphetamine		
Dyanavel XR	5-, 10-, 12.5-, 15-, or 20-mg of suspension daily	$$$
Long-Acting Slower-Onset Stimulants		
Lisdexamfetamine		
Vyvanse	10-, 20-, 30-, 40-, 50-, 60-, or 70-mg capsule/chew tab daily	$$$
Amphetamine		
Evekeo	5- or 10-mg tablet once or twice daily	$$$
Dextroamphetamine/amphetamine		
Mydayis	12.5-, 25-, 37.5-, or 50-mg ER cap	$$$
Nonstimulants		
Atomoxetine		
Generic	10-, 18-, 25-, 40-, 60-, 80-, or 100-mg capsule daily	$$
Clonidine		
Generic	0.1-, 0.2-, or 0.3-mg tablet twice daily	$
Generic ER	0.1-mg tablet twice daily	$$$
Guanfacine		
Generic	1- or 2-mg tablet twice daily	$
Generic ER	1-, 2-, 3-, or 4-mg tablet daily	$
Bupropion		
Generic	75-mg tablet twice daily	$
Generic	150- or 200-mg SR tablet twice daily	$
Generic	150-mg XL tablet daily	$

[a]Cost based on brand regimen specified without a dispensing fee or discount for a 30-day supply. (From GoodRx.com or various online State Maximum Allowable Costs [SMAC])

[b]Ascending release (early then gradual/continuous).

[c]Bimodal release (early then late; mimics twice daily dosing of shorter-acting stimulant counterpart).

$, less than $60; $$, $60–$140; $$$, greater than $140.

CD, controlled release (biphasic immediate release with extended release); ER, extended release; LA, long-acting; ODT, orally disintegrating tablet; SR, sustain release; XR, extended release.

Patient Encounter Part 2

Rorin returns to clinic the following month. Previously Medicaid paid for Rorin's generic Concerta but that benefit has lapsed and the family cannot afford to pay.

What medication(s) for ADHD will maximize efficacy, minimize potential side effects, and offer an acceptable cost for Rorin's family?

What are important counseling points to discuss with the parents before starting a different ADHD medication?

OUTCOME EVALUATION

Carefully document core ADHD symptoms at baseline to provide a reference point from which to evaluate effectiveness of treatment. Improvement in individualized patient outcomes is desired, such as (a) family and social relationships, (b) disruptive behavior, (c) completing required tasks, (d) self-motivation, (e) appearance, and (f) self-esteem. Elicit evaluations of the patient's behavior from family, school, and social environments in order to assess these outcomes. Using standardized rating scales (eg, Conners Rating Scales—Revised, Child Behavior Checklist-Attention Problem scale, and Conners Abbreviated Symptoms Questionnaire, Vanderbilt) leads to favorable diagnostic precision.[22] Assess eating and sleeping patterns, height, weight, pulse, and blood pressure at baseline and after initiation of pharmacotherapy every 2 to 4 weeks to determine efficacy of treatment and potential effects on growth and cardiac system. Use physical examinations or liver function tests as appropriate to monitor for adverse effects. In children being considered for ADHD pharmacotherapy, obtain baseline electrocardiograms (ECGs) when known or suspected cardiac disease exists or the clinician judges it necessary.[23] Recent evidence suggests that overall cardiac risk with ADHD pharmacotherapy is low but presence of risk factors is associated with increased risk of serious cardiac events.[24] Typically, therapeutic benefits will be seen within days of initiating stimulants and within 1 or 2 months of starting bupropion and atomoxetine. When a maintenance dose has been achieved, schedule follow-up visits every 3 months. At these visits, assess height and weight, and screen for possible adverse drug effects. If a patient has failed to respond to multiple agents,

Patient Encounter Part 3

Rorin returns to clinic in a month after having received generic Adderall tablets at his last clinic appointment. As an outpatient, he has been titrated from generic Adderall 5 mg twice daily to 10 mg twice daily without any adverse effects. His grades, performance, and behaviors in the classroom have greatly improved. Other children have started to tease Rorin when he goes to the principal's office at noon for his second dose. This is very humiliating to Rorin and he is refusing to take a dose at school anymore.

What medication change appears best in order to maintain the beneficial effects he has seen, help him avoid peer ridicule, maintain adherence, and minimize personal cost to his family?

What monitoring parameters should be followed in order to assess efficacy and safety of treatment?

Patient Care Process

Collect Information:

- Current and past medication use including prescription and nonprescription products
- Identify allergies
- Medication history, physical assessment (blood pressure, pulse, height, and weight), ECG (baseline and periodically in children with known or suspected cardiac disease) neurological assessment, home assessment
- Signs and symptoms of hyperactivity, impulsivity, and/or inattention from patient, parents, teachers, and/or other people spending significant amount of time with the patient
- Patient and family lifestyle habits (subacademic performance, poor sleep hygiene, inadequate nutrition), beliefs system, functional goals, socioeconomic factors (insurance vs ability to pay for prescriptions)

Assess the Information:

- Determine if medications or lifestyle habits could be contributing to signs and symptoms of ADHD
- Evaluate medications for indication, side effects, adherence and effectiveness, interactions, and drug-related problems
- Assess overall health status, signs and symptoms of ADHD
- Identify patient/family cost effectiveness/burden of therapy and ability to remain adherent to therapy

Develop a Care Plan:

- Address any drug-related problems, interactions, adherence issues
- Patients < 6 years old, consider behavioral modification before pharmacotherapy
- Patients > 6 years old, consider low-dose stimulant (see Table 42–1)
- If initial stimulant therapy is not effective after 2 to 4 weeks, consider switching to a different stimulant (see Table 42–1)
- Try at least two stimulant medications before considering nonstimulant pharmacotherapy
- Reevaluate the diagnosis if all pharmacotherapy treatment attempts fail

Implement the Care Plan:

- Initiate medication at appropriate dose (see Table 42–1) and titrate to effect as tolerated (see Table 42–2), while considering cost (see Table 42–3)
- Emphasize medication adherence
- Educate patient/family on effectiveness and safety (see Table 42–2)

Follow-up: Monitor and Evaluate:

- Evaluate effectiveness and safety of stimulant therapy monthly for the first 3 months
- Evaluate every 3 months once on maintenance dose
- Monitor height and weight in children and blood pressure in adults quarterly
- Evaluate for improvement in function, use rating scales for consistent evaluation

reevaluate for other possible causes of behavior dysfunction. Counsel patients and their families that treatment generally is long term. Typically, appropriately treated patients learn to better control their ADHD symptoms as adults.

Abbreviations Introduced in This Chapter

ADHD	Attention-deficit hyperactivity disorder
CYP	Cytochrome P450
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders,* 5th edition,
ECG	Electrocardiogram

REFERENCES

1. Ryan-Krause P. Attention deficit hyperactivity disorder: Part I. J Pediatr Health Care. 2010;24(3):194–198.
2. Visser SN, Danielson ML, Bitsko RH, et al. Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003–2011. J Am Acad Child Adolesc Psychiatry. 2014;53(1):34–46.e2.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth edition: DSM-5. Washington: American Psychiatric Association; 2013.
4. Feldman HM, Reiff MI. Clinical practice. Attention deficit-hyperactivity disorder in children and adolescents. N Engl J Med. 2014;370(9):838–846.
5. Albrecht B, Uebel-von Sandersleben H, Gevensleben H, Rothenberger A. Pathophysiology of ADHD and associated problems—starting points for NF interventions? Frontiers in Human Neuroscience. 2015;9:359.
6. Subcommittee on Attention-Deficit/Hyperactivity Disorder; Steering Committee on Quality Improvement and Management. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128(5):1007–1022.
7. Pliszka S. AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:894–921.
8. MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 1999;56(12):1073–1086.
9. Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. J Am Acad Child Adolesc Psychiatry. 2002;41(suppl 2):S26–S49.
10. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry. 2007;62:970–976.
11. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics. 2003;111:179–185.
12. Newcorn JH, Kratochvil CJ, Allen AJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008;165(6):721–730.
13. Belle DJ, Ernest S, Sauer J, Smith BP, Thomasson HR, Witcher JW. Effect of potent CYP2D6 inhibition by paroxetine on atomoxetine pharmacokinetics. J Clin Pharmacol. 2002;42:1219–1227.
14. Kohn MR, Tsang TW, Clarke SD. Efficacy and safety of atomoxetine in the treatment of children and adolescents with attention deficit hyperactivity disorder. Clin Med Insights Pediatr. 2012;6:95–162.
15. Heil SH, Holmes HW, Bickel WK, et al. Comparison of the subjective physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users. Drug Alcohol Depend. 2002;67(2):149–156.
16. Ng QX. A systematic review of the use of bupropion for attention-deficit/hyperactivity disorder in children and adolescents. J Child Adolesc Psychopharmacol. 2017;27(2):112–116.
17. Maneeton N, Maneeton B, Intaprasert S, Woottiluk P. A systematic review of randomized controlled trials of bupropion versus methylphenidate in the treatment of attention-deficit/hyperactivity disorder. Neuropsychiatr Dis Treat. 2014;10:1439–1449.
18. Li Y, Gao J, He S, Zhang Y, Wang Q. An evaluation on the efficacy and safety of treatments for attention deficit hyperactivity disorder in children and adolescents: a comparison of multiple treatments. Mol Neurobiol. 2017;54(9):6655–6669.
19. Gupte-Singh K Singh RR, Lawson KA. Economic burden of attention-deficit/hyperactivity disorder among pediatric patients in the United States. Value Health. 2017;20(4):602–609.
20. Scrahill L. Alpha-2 adrenergic agonists in children with inattention, hyperactivity and impulsiveness. CNS Drugs. 2009;23(suppl 1): 43–49.
21. Connor DF, Findling RL, Kollins SH, et al. Effects of guanfacine extended release on oppositional symptoms in children aged 6–12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized double-blind, placebo-controlled trial. CNS Drugs. 2010;24(9):755–768.
22. Collett BR, Ohan JL, Myers KM. Ten-year review of rating scales. V: Scales assessing attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2003;42(9):1015–1037.
23. Vetter VL, Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. Circulation. 2008;117:2407–2423.
24. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med. 2011;365:1896–1904.

43 Diabetes Mellitus

Julie Sease

LEARNING OBJECTIVES

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

LO

1. Discuss the incidence of diabetes mellitus (DM).
2. Distinguish clinical differences in type 1, Latent Autoimmune Diabetes of Adulthood, type 2, and gestational diabetes.
3. List screening and diagnostic criteria for DM.
4. Discuss therapeutic goals for blood glucose (BG) and blood pressure (BP) for a patient with diabetes.
5. Recommend nonpharmacologic therapies, including meal planning and physical activity, for patients with diabetes.
6. Compare oral agents used in treating diabetes by their mechanisms of action, time of action, side effects, contraindications, and effectiveness.
7. Select appropriate insulin therapy based on onset, peak, and duration of action.
8. Discuss the signs, symptoms, and treatment of hypoglycemia.
9. Define *diabetic ketoacidosis* and discuss treatment goals.
10. Develop a comprehensive therapeutic monitoring plan for a patient with diabetes based on patient-specific factors.

INTRODUCTION

Diabetes mellitus (DM) describes a group of chronic metabolic disorders. KEY CONCEPT DM is characterized by hyperglycemia that may result in long-term **microvascular** and neuropathic complications. These complications contribute to DM being the leading cause of (a) new cases of blindness among adults, (b) end-stage renal disease, and (c) nontraumatic lower limb amputations. Macrovascular complications (coronary artery disease, peripheral vascular disease, and stroke) are also associated with DM.

EPIDEMIOLOGY

LO 1

DM affects an estimated 30.3 million persons in the United States, or 9.4% of the population.[1] Although an estimated 23.1 million persons have been diagnosed, another 7.2 million have DM but are unaware they have the disease.

DM is characterized by a complete lack of insulin, a relative lack of insulin, or **insulin resistance** as well as disorders of other hormones. These defects result in an inability to use glucose for energy. The increasing prevalence of DM is partly caused by three influences: lifestyle, ethnicity, and age.

Lifestyle

A sedentary lifestyle coupled with greater consumption of high-fat, high-carbohydrate foods, and larger portion sizes have resulted in increasing rates of obesity. Current estimates indicate that 36.5% of the US population is obese when obesity is defined as a body mass index (BMI) of greater than 30 kg/m^2.[2] Only 1 in 5 adults currently meet physical activity guidelines set forth by the Centers for Disease Control and Prevention (CDC) and persons living in the American South are less likely to be physically active than those living in other areas of the country.[3]

Ethnicity

Certain ethnic groups are at a disproportionately high risk for developing type 2 DM (T2DM). The prevalence of DM is 15.1% among American Indians/Alaska Natives, 12.7% among non-Hispanic blacks, and 12.1% among persons of Hispanic ethnicity; whereas, among non-Hispanic whites, the prevalence is only 7.4%.[1] Socioeconomic status, when examined as a function of education level, also plays a role in the development of DM. The rate of DM is 12.6% for persons with less than a high school education versus 7.2% for those with education beyond high school.

Age

The third factor contributing to the increased prevalence of T2DM is age. In 2015, 9.9 million people in the United States who were 65 years of age or older had been diagnosed with DM compared with only 3 million between the ages of 18 and 44.[1] As the population ages, the incidence of T2DM is expected to increase.

KEY CONCEPT Type 1 DM (T1DM) is usually diagnosed before age 30 years but can develop at any age. As a result, patients over 30 years of age who newly develop T1DM may be misdiagnosed as having T2DM. Autoimmune destruction of the β-cells causes insulin deficiency. T2DM accounts for approximately 90% to 95% of all diagnosed cases of DM, is progressive in its development, and is often preceded by an increased risk for diabetes (previously

known as **prediabetes**). A combination of insulin deficiency, insulin resistance, and other hormonal irregularities, primarily involving **glucagon**, are key problems with T2DM. The majority of people with T2DM are overweight, and an increasing number of cases in children have been observed.

ETIOLOGY

LO 2

T1DM is an autoimmune disease in which insulin-producing β-cells in the pancreas are destroyed, leaving the individual insulin deficient.[4] Individuals with T1DM may develop islet cell antibodies, insulin autoantibodies, glutamic acid decarboxylase autoantibodies, protein tyrosine phosphatase autoantibodies, or zinc transporter protein autoantibodies, though most laboratories do not have reliably sensitive or specific assays to measure all five. As more β-cells are destroyed, glucose metabolism becomes compromised because of reduced insulin release after a glucose load. At the time of diagnosis of T1DM, it is commonly believed that most patients have an 80% to 95% loss of β-cell function.[5] The remaining β-cell function at diagnosis creates a "honeymoon period" during which smaller amounts of insulin are required to manage glucose levels. After this, remaining β-cell function is lost, and patients become completely insulin deficient and require more exogenous insulin.

KEY CONCEPT Latent autoimmune diabetes in adults (LADA), slow-onset type 1 or type 1.5 DM, is a form of autoimmune T1DM that occurs in individuals older than the usual age of T1DM onset.[6] Patients often are mistakenly thought to have T2DM because the person is older and may respond initially to treatment with oral BG–lowering agents, possibly taking years to eventually require exogenous insulin. These patients do not have insulin resistance, but antibodies are present in the blood that are known to destroy pancreatic β-cells. **C-peptide**, a surrogate marker for insulin secretion, may be used to establish or verify a diagnosis of T1DM.[4] When C-peptide levels are drawn, a simultaneous BG level should also be taken.

Categories of increased risk for DM include impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or hemoglobin A_{1c} (A_{1c}) between 5.7% and 6.4% (0.057 and 0.064; 39 and 46 mmol/mol hemoglobin [Hgb]).[7] IFG is defined as having a fasting blood glucose (FBG) level between 100 and 125 mg/dL (5.6 and 6.9 mmol/L). IGT is defined by a postprandial BG level between 140 and 199 mg/dL (7.8 and 11.0 mmol/L).

LO 2

T2DM is usually slow and progressive in its development. Risk factors include:

- First-degree family history of DM (ie, parents or siblings)
- Overweight or obese
- Habitual physical inactivity
- Race or ethnicity (Native American, Latino or Hispanic American, Asian American, African American, and Pacific Islanders)
- Previously identified IFG, IGT, or A_{1c} between 5.7% and 6.4% (0.057 and 0.064 or 39 and 46 mmol/mol Hgb)
- Hypertension (≥ 140/90 mm Hg or on therapy for hypertension)
- High-density lipoprotein (HDL) cholesterol less than 35 mg/dL (0.91 mmol/L) and/or a triglyceride level greater than 250 mg/dL (2.83 mmol/L)
- History of gestational diabetes
- History of cardiovascular disease
- History of polycystic ovarian syndrome
- Other conditions associated with insulin resistance (eg, **acanthosis nigricans**)

Gestational diabetes mellitus (GDM) is defined as glucose intolerance in women during pregnancy. Clinical detection of and therapy for GDM are important because blood sugar levels within range produces significant reductions in adverse maternal, fetal, and neonatal outcomes.

Diabetes insipidus is unrelated to DM despite the similar nomenclature.[8] Four types of diabetes insipidus exist including central, nephrogenic, dipsogenic, and gestational. Central diabetes insipidus results from damage to a patient's hypothalamus or pituitary causing irregular production, storage and/or release of vasopressin leading to excessive elimination of fluid by the kidneys. Nephrogenic diabetes insipidus occurs when the kidneys no longer respond appropriately to the action of vasopressin. Dipsogenic diabetes insipidus results from a hypothalamic dysfunction which causes increased thirst and liquid intake in the affected patient. Gestational diabetes insipidus occurs during pregnancy and results either from placental destruction of the mother's vasopressin or from prostaglandin's action on the kidneys causing them to lose sensitivity to the action of vasopressin.

DM from other causes includes genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas such as cystic fibrosis, and drug- or chemical-induced diabetes. Drugs that may cause increased BG include glucocorticoids, pentamidine, nicotinic acid, β-adrenergic agonists, thiazides, phenytoin, and γ-interferon.[9]

PATHOPHYSIOLOGY

Normal Carbohydrate Metabolism

The body's main fuel source is glucose. Cells metabolize glucose completely through glycolysis and the Krebs cycle, producing adenosine triphosphate (ATP) as energy.[10] Glucose is stored in the liver and muscles as glycogen. **Glycogenolysis** converts stored glycogen back to glucose.[11] Glucose also may be stored in adipose tissue, which may subsequently undergo lipolysis yielding free fatty acids.[10] In the fasting state, free fatty acids supply much of the energy needs for the body except for the central nervous system, which requires glucose to function normally.[11] Proteins also can be converted to glucose through **gluconeogenesis**.[10] Homeostasis is achieved through a balance of the metabolism of glucose, free fatty acids, and amino acids to maintain a BG level sufficient to provide an uninterrupted supply of glucose to the brain.[11]

Insulin and glucagon are produced in the pancreas by cells in the islets of Langerhans. β-Cells make up 70% to 90% of the islets and produce insulin and **amylin**, whereas α-cells produce glucagon.[10] The main function of insulin is to decrease BG levels. Glucagon, along with other counterregulatory hormones such as growth factor, cortisol, and epinephrine, increases BG levels.[11] Although BG levels vary, the opposing actions of insulin and glucagon, along with the counterregulatory hormones, normally maintain fasting values between 79 and 99 mg/dL (4.4–5.5 mmol/L).

▶ *Normal Insulin Action*

Fasting insulin levels in the circulation average from 43 to 186 pmol/L (6–26 μIU/mL).[10] After food is consumed, BG levels rise, and the insulin-secretion response occurs in two phases.

An initial burst, known as *first phase insulin response,* lasts approximately 5 to 10 minutes and serves to suppress hepatic glucose production and cause insulin-mediated glucose disposal in adipose tissue. This bolus of insulin minimizes hyperglycemia during meals and during the postprandial period. The *second phase of insulin response* is characterized by a gradual increase in insulin secretion, which lasts 60 to 120 minutes and stimulates glucose uptake by peripheral insulin-dependent tissues, namely muscle. Slower release of insulin allows the body to respond to the new glucose entering from digestion while maintaining BG levels. Basal insulin secretion is the low rate of continuous insulin secreted by the pancreas to maintain normal FBG levels.

Amylin is a naturally occurring hormone that is cosecreted from β-cells with insulin. People with DM have either a relative or complete lack of amylin. Amylin has three major mechanisms of action: suppression of postmeal glucagon secretion; regulation of the rate of gastric emptying from the stomach to the small intestine, which increases satiety; and regulation of plasma glucose concentrations in the bloodstream.

▶ *Impaired Insulin Secretion*

A pancreas with normal β-cell function is able to adjust insulin production to maintain normal BG levels.[11] In T2DM, more insulin is secreted to maintain normal BG levels until eventually the pancreas can no longer produce sufficient insulin.[10] The resulting hyperglycemia is enhanced by extremely high insulin resistance, pancreatic burnout in which β-cells lose functional capacity, or both. Impaired β-cell function results in a reduced ability to produce a first-phase insulin response sufficient to signal the liver to stop producing glucose after a meal.[12] Progressive β-cell decline is hypothesized to result from ongoing glucotoxicity and lipotoxicity. A recent study showed that early resolution of glucotoxicity through use of basal insulin in those at risk for developing DM reduced the incidence of diabetes diagnosis.[13]

▶ *Insulin Resistance*

Insulin resistance is the primary factor that differentiates T2DM from other forms of diabetes. Insulin resistance may be present for several years prior to the diagnosis of DM and can continue to progress throughout the course of the disease.[10] Resistance to insulin occurs in adipose tissue, skeletal muscle, and the liver.[9] Insulin resistance in the liver poses a double threat because the liver becomes nonresponsive to insulin for glucose uptake, and hepatic production of glucose after a meal does not cease, leading to elevated fasting and postmeal BG levels.

Table 43–1

Five Components of Metabolic Syndrome[14]

Risk Factor	Defining Level
1. Abdominal obesity	Based on ethnic group[a]
Plus any two of the following:	
2. Triglycerides	≥ 150 mg/dL (1.70 mmol/L) or treated
3. HDL cholesterol	
• Men	< 40 mg/dL (1.03 mmol/L) or treated
• Women	< 50 mg/dL (1.29 mmol/L) or treated
4. Blood pressure	≥ 130 or ≥ 85 mm Hg or treated
5. Fasting glucose	≥ 100 mg/dL (5.6 mmol/L) or diagnosed type 2 diabetes

[a]102 cm (40 in) for males and 88 cm (35 in) for females likely to be used clinically.

HDL, high-density lipoprotein.

▶ *Metabolic Syndrome*

Insulin resistance has been associated with a number of other cardiovascular risks, including abdominal obesity, hypertension, dyslipidemia, hypercoagulation, and hyperinsulinemia.[14] The clustering of these risk factors has been termed **metabolic syndrome**. Criteria defining the metabolic syndrome as established by the International Diabetes Federation are summarized in Table 43–1.[14] Patients having these additional risk factors are at much higher cardiovascular risk than would be expected from individual components of the syndrome.

Clinical Presentation and Diagnosis

Characteristic	T1DM	T2DM	LADA
Usual age of onset	Childhood or adolescence	Adult	Over 30
Speed of onset	Abrupt	Gradual	Gradual
Family history	Negative	Positive	Positive
Body type	Thin	Obese or history of obesity	Thin
Metabolic syndrome	No	Often	No
Autoantibodies	Present	Rare	Present
Symptoms	Polyuria, polydipsia, polyphagia, rapid weight loss	Asymptomatic	Polyuria, polydipsia, polyphagia, rapid weight loss
Ketones at diagnosis	Present	Uncommon	Dependent upon β-cell function at time of diagnosis
Acute complications	Diabetic ketoacidosis (DKA)	Rare	DKA possible
Microvascular complications at diagnosis	Rare	Common	Dependent on length of disease at time of diagnosis
Macrovascular complications at or before diagnosis	Rare	Common	Dependent on length of disease at time of diagnosis

▶ *Incretin Effect*

When nutrients enter the stomach and intestines, incretin hormones are released, which stimulate insulin secretion.[15] This so-called **incretin effect** is mediated by two hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), with GLP-1 being studied the most. GLP-1 is secreted by the L cells of the ileum and colon primarily, and GIP is secreted by the K cells. GLP-1 secretion is caused by endocrine and neural signals started when nutrients enter the gastrointestinal (GI) tract. Within minutes of food ingestion, GLP-1 levels rise rapidly. A glucose-dependent release of insulin occurs, and the dipeptidyl peptidase-4 (DPP-4) enzyme cleaves GLP-1 rapidly to an inactive metabolite. Much of the research on glucose-lowering products involves prolonging the action of GLP-1. Other glucose-lowering effects of GLP-1 include suppression of glucagon, slowing gastric emptying, and increasing satiety.

▶ *Selective Sodium-Dependent Glucose Cotransporter-2 (SGLT2)*

Glucose is filtered by the kidney at a rate of approximately 162 grams per day.[16] The SGLT2 transporter reabsorbs the majority (90%) of the filtered glucose in the convoluted proximal tubule. The SGLT1 transporter reabsorbs the remaining glucose in the descending proximal tubule. The end result is that no glucose is excreted in the urine when BG levels are normal. In patients with DM, rather than allowing glucose to be dumped into the urine to assist with the correction of hyperglycemia in the blood, the kidney holds onto glucose. Renal tubular cells from T2DM patients show increased levels of SGLT2, thereby offering a mechanism by which the kidney of a patient with DM achieves its increased ability for glucose reabsorption.

CLINICAL PRESENTATION AND DIAGNOSIS

Screening

LO 3

Currently, the American Diabetes Association (ADA) recommends routine screening for T2DM every 3 years in all adults starting at 45 years of age.[7] Testing for T2DM should be considered, regardless of age, in adults who have a BMI greater than or equal to 25 kg/m^2 (or BMI ≥ 23 kg/m^2 for Asian Americans) and one or more additional risk factors. The ADA does not currently recommend widespread screening for T1DM, although measurement of islet autoantibodies may be appropriate for high-risk individuals, including those who have relatives with T1DM. See Table 43–2[7] for complete screening guidelines.

Gestational Diabetes

LO 3

All pregnant women who have risk factors for T2DM should be screened for undiagnosed T2DM at their first prenatal visit using standard diagnostic criteria. Any woman found to have diabetes at that early point in pregnancy is considered to have T2DM, not GDM. All other pregnant women not currently known to have DM should be screened for GDM. Two possible strategies exist for GDM screening. They are a "one-step" 2-hour 75-gram **oral glucose tolerance test** (OGTT) and a "two-step" process which includes a 1-hour 50-gram nonfasting screen followed by a 3-hour 100-gram OGTT for those with a 1-hour screening glucose of greater than or equal to 140 mg/dL (7.8 mmol/L). The diagnostic criteria for the "one-step" 2-hour 75-gram OGTT are listed in Table 43–3.[7] Any woman diagnosed with GDM should be retested at 4 to 12 weeks postpartum using the OGTT with nonpregnant diagnostic criteria.

Table 43–2

American Diabetes Association (ADA) Screening Recommendations for Diabetes[7]

Asymptomatic Type 1

The ADA does not recommend screening for T1DM because of the low incidence in the general population and due to the acute presentation of symptoms

Asymptomatic Type 2

1. The ADA recommends screening for T2DM every 3 years in all adults beginning at 45 years of age
2. Testing should be considered for persons younger than 45 years of age or more frequently in individuals who are overweight (BMI ≥ 25 kg/m^2 for the general population and ≥ 23 kg/m^2 for Asian Americans) and have additional risk factors:
   - Habitually inactive
   - First-degree relative with diabetes
   - Member of a high-risk ethnic population (eg, African American, Latino, Native American, Asian American, Pacific Islander)
   - Previous diagnosis of GDM
   - Hypertensive (≥ 140/90 mm Hg or on therapy)
   - HDL cholesterol level < 35 mg/dL (0.91 mmol/L) and/or triglyceride level > 250 mg/dL (2.83 mmol/L)
   - Polycystic ovary syndrome
   - Previous IGT or IFG or A_{1c} ≥ 5.7% (0.057 or 39 mmol/mol Hgb)
   - Other clinical conditions associated with insulin resistance (eg, acanthosis nigricans)
   - History of cardiovascular disease

Type 2 in Children and Adolescents

Criteria:
- Overweight (BMI > 85th percentile for age and sex, weight for height > 85th percentile, or weight > 120% of ideal for height)

Plus any two of the following risk factors:
- Family history of T2DM in first- or second-degree relatives
- Race or ethnicity (Native American, African American, Latino or Hispanic American, Asian American, Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary disease)
- Maternal history of diabetes or GDM during child's gestation

Age of initiation:
Age 10 years or at onset of puberty, if puberty occurs at a younger age

Frequency of testing:
Every 3 years
Test method: FPG or OGTT possibly more suitable than A_{1c}

GDM

1. Screen for undiagnosed T2DM at first prenatal visit in those with risk factors using standard criteria
2. All women not already known to have diabetes should be screened with an OGTT between weeks 24 and 28 of gestation

A_{1c}, hemoglobin A_{1c}; BMI, body mass index; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; Hgb, hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Diagnostic Criteria

LO 3

Diagnosis of DM includes glycemic outcomes exceeding threshold values with one of three testing options (Table 43–4).[7] For a diagnosis, confirmation of an initial abnormal value must be made using a new blood sample unless unequivocal symptoms of hyperglycemia exist, such as polydipsia, polyuria,

Table 43–3

Diagnosis of Gestational Diabetes Mellitus With a 75-g Glucose Load[7]

	Plasma Glucose	
Time	**mg/dL**	**mmol/L**
Fasting	92 or more	5.1 or more
75-g glucose load		
1 hour	180 or more	10.0 or more
2 hours	153 or more	8.5 or more

A positive diagnosis of diabetes is made when any of the listed glucose values are exceeded. The test should be done in the morning after an 8-hour fast.

Note: These values are based on American Diabetes Association guidelines.

and polyphagia. Either A_{1c}, fasting plasma glucose (FPG), or OGTT are appropriate tests for detecting and confirming DM. Use of the same type of test for initial screening and confirmation is recommended, but diagnostic results from two different testing options can also be used.

The categorization thresholds of glucose status for FPG determination and the OGTT are listed in Table 43–5.[7] IFG and IGT may coexist or may be identified independently. FPG level represents hepatic glucose production during the fasting state, whereas postprandial glucose (PPG) levels in the OGTT may reflect glucose uptake in peripheral tissues, insulin sensitivity, or a decreased first-phase insulin response. The OGTT identifies people with either IFG or IGT and therefore potentially more people at increased risk for DM and cardiovascular disease. The OGTT is a more cumbersome test to perform than either the A_{1c} or FPG; however, the efficacy of interventions for primary prevention of T2DM has been demonstrated among patients with IGT, not among those with IFG or specific A_{1c} levels.

Table 43–4

American Diabetes Association Criteria for Diagnosis of Diabetes[7]

Symptoms of diabetes plus a casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L). *Casual* is defined as any time of day without regard to time since the last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

FPG ≥ 126 mg/dL (7.0 mmol/L). *Fasting* is defined as no caloric intake for at least 8 hours.

or

Two-hour postload glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.

or

A_{1c} ≥ 6.5% (0.065; 48 mmol/mol Hgb). The test should be performed in a laboratory using a method that is NGSP certified to the DCCT assay.

A_{1c}, hemoglobin A_{1c}; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; Hgb, hemoglobin; NGSP, National Glycohemoglobin Standardization Program; OGTT, oral glucose tolerance test; WHO, World Health Organization.

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use.

Table 43–5

American Diabetes Association Categorization of Glucose Status[7]

	mg/dL	mmol/L
FPG		
Normal	< 100	< 5.6
IFG (prediabetes)	100–125	5.6–6.9
Diabetes	≥ 126	≥ 7.0
2-hour postload plasma glucose (OGTT)		
Normal	< 140	< 7.8
IGT (prediabetes)	140–199	7.8–11.0
Diabetes	≥ 200	≥ 11.1

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

TREATMENT

Goals of Therapy

LO 4

KEY CONCEPT DM treatment goals include reducing, controlling, and managing long-term microvascular, macrovascular, and neuropathic complications; preserving β-cell function;

Patient Encounter Part 1

A 38-year-old white male presents to his provider for a follow-up appointment. On questioning, he states that he was told during a recent workplace wellness program screening that his blood sugar was "high." Today, he has no particular complaint though he does admit to having regular headaches which he treats successfully with acetaminophen over-the-counter.

PMH: Noncontributory

FH: Mother has dyslipidemia and hypertension and is living at age 65; father has hypertension and dyslipidemia and is living at age 68; no siblings and children without chronic health conditions.

SH: Prior history of smoking one half pack per day for 10 years, but quit 6 years ago; denies alcohol or illicit drug use; denies physical activity.

Allergies: Penicillin

Meds: Acetaminophen 500 mg-1000 mg PRN headache

VS: BP 152/86 mm Hg, P 82 beats/min, RR 20 breaths/min, T 37°C (98.6°F), Ht 5'3" (160 cm), Wt 165 lb (75 kg)

ROS: (+) Fatigue, (–) N/V/D, HA, SOB, chest pain

What risk factors does this patient have for diabetes?

Which type of diabetes do his characteristics suggest?

What additional information is needed to diagnose this patient with diabetes?

preventing acute complications from high BG levels; minimizing hypoglycemic episodes; and maintaining the patient's overall quality of life. To achieve the majority of these goals, near-normal BG levels are fundamental; thus, glycemic control remains a primary objective in diabetes management. Two landmark trials, the Diabetes Control and Complications Trial (DCCT)[17] and the United Kingdom Prospective Diabetes Study (UKPDS),[18] showed that lowering BG levels decreased the risk of developing chronic complications. A near-normal BG level can be achieved with appropriate patient education, lifestyle modification, and medications.

▶ *Setting and Assessing Glycemic Targets*

KEY CONCEPT Patients and clinicians can evaluate how well a patient's DM is managed by monitoring daily BG values and the A_{1c} quarterly to biannually. Self-monitoring of blood glucose (SMBG) enables patients to obtain their current BG level at any time easily and relatively inexpensively. The A_{1c} test provides a weighted-mean BG level from approximately the previous 3 months.

Self-Monitoring of Blood Glucose SMBG is the standard method for routinely checking BG levels. Most often, a small drop of blood obtained from a fingertip using a lancet device is used for testing. Some home BG meters require very little blood and can be used for alternative site testing, where small samples can be obtained from the palm, forearm or thigh. Each reading provides a point-in-time evaluation of glucose levels that can vary widely depending on numerous factors, including food, exercise, stress, illness, and time of day.

By examining multiple individual points of data, glucose patterns can be established. Therapy can be evaluated from these patterns, and adjustments can be made to improve overall BG levels. The ADA premeal plasma glucose goals are 80 to 130 mg/dL (4.4–7.2 mmol/L) and peak postprandial plasma glucose goals are less than 180 mg/dL (10.0 mmol/L).[7] The American Association of Clinical Endocrinologists (AACE) supports tighter SMBG levels, with premeal goals of less than 110 mg/dL (6.1 mmol/L) and peak postmeal goals of less than 140 mg/dL (7.8 mmol/L).[19] For patients using multiple daily insulin injections or insulin pump therapy, SMBG may need to be performed six to eight times per day.[7] The optimal frequency of testing in patients using less frequent insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) is less clear.

LO 4

Continuous glucose sensors are now available that work with or independently of insulin pumps. These monitors provide BG readings, primarily through interstitial fluid (ISF). A small sterile disposable glucose-sensing device called a sensor is inserted into the subcutaneous tissues. This sensor measures the change in glucose in ISF and sends the information to a monitor, which stores the results. Some devices allow analysis of data collected over time to aid in clinical decision making. While older continuous glucose sensors require calibration with SMBG measurements, newer sensors allow patients to forego this process.

Hemoglobin A_{1c} Glucose interacts spontaneously with Hgb in red blood cells to form glycated derivatives. The most prevalent derivative is A_{1c}. Greater amounts of glycation occur when BG levels increase. Because a red blood cell has a life span of approximately 3 months, levels of A_{1c} provide a marker reflecting the average glucose levels over this timeframe.[7] The ADA goal for persons with DM is less than 7% (0.07; 53 mmol/mol Hgb), whereas the AACE supports a goal of less than or equal to 6.5% (0.065; 48 mmol/mol Hgb) if achievable without resultant hypoglycemia.[7,19] A less stringent A_{1c} goal of less than 8% (0.08; 64 mmol/mol Hgb) may be utilized in some patients such as those with limited life expectancy, long-standing diabetes that is otherwise difficult to control, and those with multiple comorbid conditions including advanced microvascular and/or macrovascular complications. Testing A_{1c} levels should occur at least twice a year for patients who are meeting treatment goals and four times per year for patients not meeting goals or those who have had recent changes in therapy. Table 43–6 presents goals for A_{1c} and monitoring parameters for concomitant conditions (such as blood pressure [BP] measurements and complications associated with DM).[7]

LO 4

LO 4

Table 43–6

American Diabetes Association Recommended Goals of Therapy in Adults[7]

Area	Goals
Glycemia	
A_{1c}	< 7% (0.07; 53 mmol/mol Hgb) Evaluate every 3 months until in goal; then every 6 months
Preprandial plasma glucose	80–130 mg/dL (4.4–7.2 mmol/L)
Peak postprandial plasma glucose[a]	< 180 mg/dL (10.0 mmol/L)
Blood Pressure[b]	< 140/90 mm Hg Evaluate at every visit
Lipids	Evaluate at diagnosis and/or age 40, then every 1–2 years thereafter
Monitoring for Complications	
Eyes	Dilated eye examination yearly
Feet	Feet should be examined at every visit
Urinary microalbumin	Yearly

[a]Peak postprandial glucose measurements should be made 1–2 hours after the beginning of the meal.

[b]American College of Cardiology/American Heart Association hypertension guidelines recommend goal of < 130/80 mm Hg for patients with diabetes.

A_{1c}, hemoglobin A_{1c}; Hgb, hemoglobin.

Ketone Monitoring Urine and blood ketone testing is important in people with T1DM, in pregnancy with preexisting diabetes, and in GDM. People with T2DM may have positive ketones and develop DKA if they are ill.

The presence of ketones may indicate a lack of insulin or ketoacidosis, a condition that requires immediate medical attention. When there is a lack of insulin, peripheral tissues cannot take up and store glucose. This causes the body to think it is starving, and because of excessive lipolysis, ketones, primarily β-hydroxybutyric acid and acetoacetic acid, are produced as byproducts of free fatty acid metabolism in the liver. Glucose and ketones are osmotically active, and when an excessive amount of ketones is formed, the body gets rid of them through urine, leading to dehydration. Patients with T1DM should test for ketones during acute illness or stress or when BG levels are consistently elevated above 300 mg/dL (16.7 mmol/L). This commonly occurs when insulin is omitted or when DM is not well managed due to nonadherence, illness, or other reasons. Women with preexisting diabetes before pregnancy or with GDM should check ketones using their first morning urine sample or when any symptoms of ketoacidosis such as nausea,

vomiting, or abdominal pain are present. Blood ketone testing methods that quantify β-hydroxybutyric acid, the predominant ketone body, are available and are the preferred ways to diagnose and monitor ketoacidosis. Home tests for β-hydroxybutyric acid are available. The specific treatment of DKA may include rehydration, correction of electrolyte imbalances, and insulin administration.

General Approach to Therapy

▶ *Type 1 Diabetes Mellitus*

Treatment of T1DM requires providing exogenous insulin to replace the endogenous loss of insulin from the nonfunctional pancreas. Ideally, insulin therapy mimics normal insulin physiology. The basal-bolus approach attempts to reproduce basal insulin response using intermediate- or long-acting insulin, whereas short- or rapid-acting insulin replicates bolus release of insulin physiologically seen around a meal in individuals without diabetes. A number of different regimens have been used through the years to more closely follow natural insulin patterns. As a rule, basal insulin makes up approximately 50% of the total daily dose. The remaining half is provided with bolus doses around three daily meals.

Exact doses are individualized to the patient and the amount of food consumed. T1DM patients frequently are started on about 0.6 unit/kg/day, and then doses are titrated until glycemic goals are reached. Most people with T1DM use between 0.6 and 1 unit/kg/day.

Currently, the most advanced form of insulin delivery is the insulin pump, also referred to as continuous subcutaneous insulin infusion (CSII). See Figure 43–1. Insulin pumps have been linked to improvement in quality of life. Using rapid-acting insulin most often, these pumps are programmed to provide a slow release of small amounts of insulin as the basal portion of therapy, and larger boluses of insulin are administered by the patient to account for the consumption of food or correction of hyperglycemia. Insulin pump settings may be adjusted to address exercise, illness, and other factors. Pramlintide, a synthetic analog of the naturally occurring hormone amylin, is another injectable BG–lowering medication that can be used in people with T1DM or in people with T2DM using insulin for treatment. In addition to medication management with insulin, patients with T1DM must also be educated to live a healthy lifestyle including eating a healthy diet and exercising.

▶ *Type 2 Diabetes Mellitus*

Treatment of patients with T2DM has changed dramatically over the past decade with the addition of a number of new drugs and recommendations to maintain tighter glycemic levels.[20,21] Technology available to individuals with T1DM can also be used for those with T2DM. However, lifestyle modifications including education, nutrition, and exercise are paramount to managing the disease successfully.

▶ *Gestational Diabetes*

An individualized meal plan consisting of three meals and three snacks per day is commonly recommended in GDM. Preventing ketosis, promoting adequate growth of the fetus, maintaining satisfactory BG levels, and preventing nausea and other undesired GI side effects are desired goals in these patients. Glucose goals for SMBG for pregnant women as per the ADA include fasting of 95 mg/dL (5.3 mmol/L), 1-hour postprandial of 140 mg/dL (7.8 mmol/L), and 2-hour postprandial of 120 mg/dL (6.7 mmol/L).[7] An abundance of glucose causes excessive insulin production by the fetus, which, if left above glucose target, can lead to the development of an abnormally large fetus. Infant hypoglycemia at delivery, hyperbilirubinemia, and complications associated with delivery of a large baby also may occur when BG levels are not controlled adequately. Due to concerns that metformin crosses the placenta to the fetus and that glyburide has been identified in cord blood when taken by pregnant women, the ADA currently advocates for insulin as the primary pharmacotherapeutic choice for GDM. Insulin should be used when BG levels are not maintained adequately by diet and physical activity. Insulin detemir, insulin aspart, lispro, and regular insulin carry Category B safety ratings.

Nonpharmacologic Therapy

▶ *Medical Nutrition Therapy (MNT)*

MNT is considered an integral component of DM management and self-management education. People with DM should receive individualized MNT, preferably by a registered dietitian. MNT

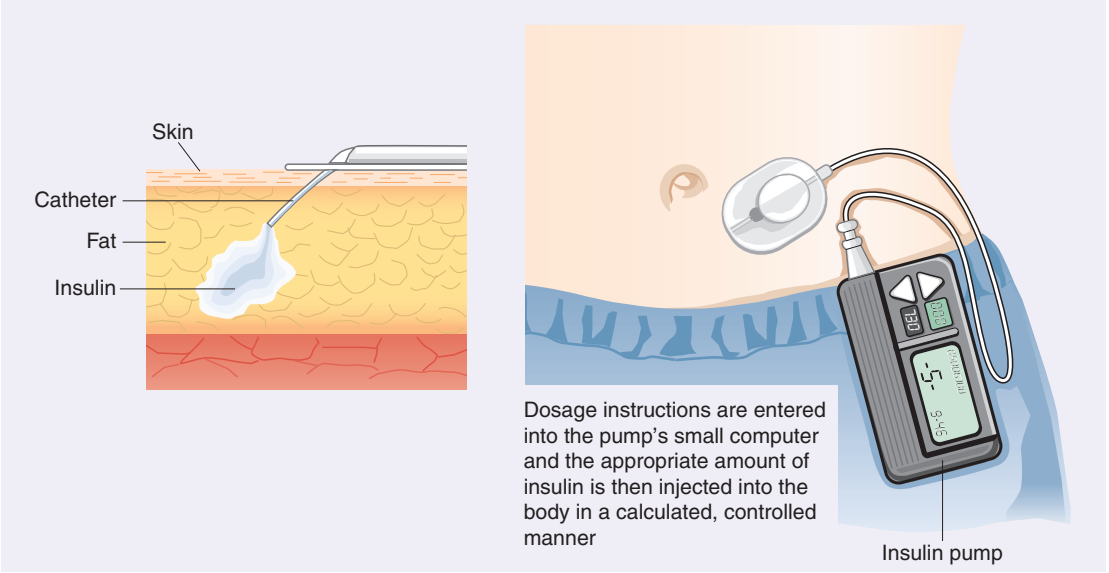

FIGURE 43–1. Insulin pump and placement.

should be provided as an ongoing dialogue customized to take into account cultural, lifestyle, and financial considerations.

LO 5 The primary focus of MNT for patients with T1DM is matching optimal insulin dosing to carbohydrate consumption while maintaining a healthy balance. In T2DM, the primary focus is portion control and controlling BG, BP, and lipids through individualizing limits of carbohydrates, saturated fats, sodium, and calories. Carbohydrates are the primary contributor to postmeal glucose levels. The percentages of fat, protein, and carbohydrate included in each meal should be individualized based on the specific goals of each patient.[7]

► *Dietary Supplements*

There is insufficient evidence of efficacy for improved BG control for any individual herb or supplement.[7] Herbs and supplements commonly touted to improve glucose control include chromium, magnesium, vitamin D, and cinnamon. Patients may inquire about and use dietary supplements. It is important that clinicians respect the patient's health beliefs, address their questions and concerns, and educate them on the differences between dietary supplements and prescribed therapies. Additional information can be found at the National Institutes of Health Office of Dietary Supplements (https://ods.od.nih.gov).

► *Weight Management*

LO 5 Moderate weight loss in patients with T2DM has been shown to reduce cardiovascular risk, as well as delay or prevent the onset of DM in those with prediabetes.[7,22] The recommended primary approach to weight loss is therapeutic lifestyle change (TLC), which integrates a 7% reduction in body weight and an increase in physical activity.[7] A slow but progressive weight loss of 0.45 to 0.91 kg (1–2 lb) per week is preferred.[23] Individual target caloric goals should be set. In the Diabetes Prevention Program, this was done by estimating daily caloric intake needed to maintain a person's current weight and then subtracting 500 to 1000 calories per day (about 2100–4200 kJ per day) depending on initial weight. Metabolic surgeries, such as Roux-en-Y gastric bypass, are recommended for patients with T2DM and a BMI that is or exceeds 40 kg/m^2 regardless of glycemic control.[7] Metabolic surgery is also recommended in those patients with a BMI above 35 kg/m^2 but less than 40 kg/m^2 whose glucose is not adequately controlled. Five drug therapy options have been approved for weight loss in patients with a BMI greater than or equal to 27 kg/m^2 with one or more obesity-related conditions and in patients with a BMI greater than or equal to 30 kg/m^2. Options include orlistat (a lipase inhibitor), lorcaserin (a selective serotonin 5-HT$_{2c}$ receptor agonist), phentermine/topiramate extended release (a sympathomimetic amine anorectic/antiepileptic combination), naltrexone/bupropion (an opioid antagonist/aminoketone antidepressant combination), and liraglutide (a GLP-1 receptor agonist).

► *Physical Activity*

Regular physical activity has been shown to improve BG control by improving insulin sensitivity, and reduce cardiovascular risk factors such as hypertension and elevated serum lipid levels.[22] Physical activity is also a primary factor associated with long-term maintenance of weight loss and overall weight control. Regular physical activity also may prevent the onset of T2DM in high-risk persons.

LO 5 Before initiating a physical activity program, patients should undergo a detailed physical examination, including screening for microvascular or macrovascular complications that may be worsened by a particular activity. Initiation of physical activities in an individual with a history of a sedentary lifestyle should begin with a modest increase in activity. Walking, swimming, and cycling are examples of low-impact exercises that could be encouraged; gardening and usual housecleaning tasks are good exercises as well. Recommended physical activity goals for patients with T2DM include 150 minutes per week of moderate to vigorous aerobic exercise spread out during at least 3 days of the week with no more than two consecutive days between bouts of aerobic activity and moderate to vigorous resistance training at least 2 to 3 days per week.[7]

► *Psychological Assessment and Care*

Mental health and social state have been shown to have an impact on a patient's ability to carry out DM management care tasks.[7] Clinicians should incorporate psychological assessment and treatment into routine care. The ADA guidelines recommend ongoing psychological screening, including determining the patient's attitudes regarding DM; expectations of medical management and outcomes; mood and affect; general and diabetes-related quality of life; and financial, social, and emotional resources. Patients demonstrating poor self-management should be screened for diabetes-related distress, depression, anxiety, an eating disorder, and/or cognitive impairment.

► *Immunizations*

LO 5 Influenza and pneumonia are common preventable infectious diseases that increase mortality and morbidity in persons with chronic diseases, including DM. Yearly influenza vaccinations, commonly called flu shots, are recommended for all patients with DM 6 months of age or older.[7] Pneumococcal vaccination with the polysaccharide vaccine 23 is also recommended for patients with DM who are 2 years of age or older as a one-time vaccination. At age greater than or equal to 65 years of age, patients should receive the pneumococcal conjugate vaccine. It should be administered no earlier than 1 year after vaccination with the polysaccharide vaccine. Once administered, the conjugate vaccine should then be followed by the polysaccharide vaccine again 12 months later. The 3-dose hepatitis B vaccine series is recommended for those aged 19–59 years and should be considered in those 60 years of age and older.

Pharmacologic Therapy

LO 6 Figures 43–2 and 43–3 summarize treatment algorithms for T2DM per the ADA and AACE, respectively.[7,20,21] While similar, these treatment algorithms differ in that the ADA guidelines do not advocate for the use of several treatment options that the AACE guidelines include; namely, colesevelam, α-glucosidase inhibitors, and bromocriptine. Also, the AACE guidelines take a more aggressive approach, including consideration for starting a patient on two drugs if their presenting A$_{1c}$ is greater than or equal to 7.5% (0.075; 58 mmol/mol Hgb). While the ADA guidelines include metformin alone as the first-line therapy option for T2DM, the AACE guidelines include six other noninsulin initial therapy options as possibilities. As noted earlier, the AACE guidelines also advocate for lower A$_{1c}$ and SMBG goals. Because T2DM generally tends to be a progressive disease, BG levels will eventually increase, making insulin therapy the eventual required therapy in many patients, and therefore insulin should not be used rhetorically as a prophylactic deterrent as this may result in patient trust issues and/or feelings of failure. This is usually done when several oral agents have been used with inadequate glucose-lowering results. Addition of GLP-1 receptor agonists

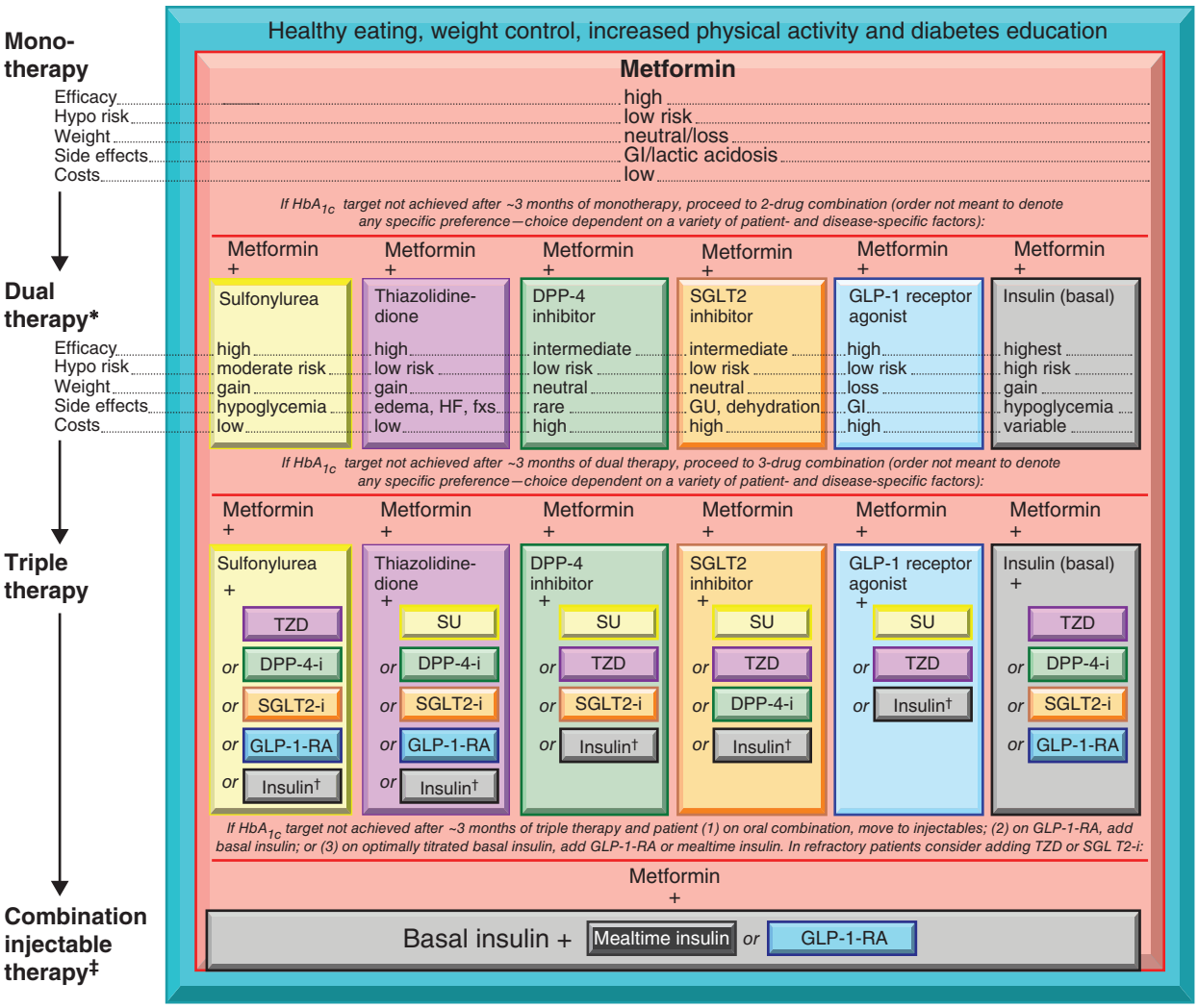

FIGURE 43–2. Patient-centered approach to antihyperglycemic therapy in type 2 diabetes as per the American Diabetes Association/European Association for the Study of Diabetes. Begin with lifestyle changes and add metformin monotherapy at or soon after diagnosis. If hemoglobin A_{1c} (HbA_{1c}) target is not achieved after 3 months, consider one of six treatment options combined with metformin: a SU, TZD, DPP-4-i, SGLT2-i, GLP-1 RA, or basal insulin. Choice is based on patient and drug characteristics. Consider meglitinides in patients with irregular meal schedules or who develop postprandial hypoglycemia on sulfonylureas. *Consider beginning at this stage in patients with HbA_{1c} greater than 9% (0.09; 75 mmol/mol Hgb). †Usually a basal insulin (eg, glargine, detemir, degludec). ‡Consider beginning at this stage if patient presents with glucose greater than 300 mg/dL (16.7 mmol/L). (DPP-4-i, dipeptydal peptidase-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1-RA, glucagon-like peptide-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, sodium-dependent glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.) (From Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140–149, with permission.)

is recognized by the ADA as an alternative to mealtime insulin in those already receiving maximally titrated basal regimens; in addition to GLP-1 receptor agonists, the AACE guidelines also suggest DPP-4 or SGLT2 inhibitors as options in this scenario. Figure 43–4 is one illustration of a way to start insulin therapy in a patient with T2DM.[21]

KEY CONCEPT Oral and injectable agents are available to treat patients with T2DM who are unable to achieve glycemic control through meal planning and physical activity. Table 43–7[19,21,24] lists the oral agents, Table 43–8 lists each noninsulin drug class with site of action and mechanism of action, and Table 43–9 lists the expected A_{1c} reduction for each noninsulin antiglycemic drug class.[9] The various classes of BG-lowering agents target different organs and have different mechanisms of action. Each of these agents may be used individually or in combination with other medications that target different organs for synergistic effects. In addition to single agent products, there are many combination products marketed as well.

LO 6

► *Sulfonylureas*

Sulfonylureas enhance insulin secretion by blocking ATP-sensitive potassium channels in the cell membranes of pancreatic β-cells. This action results in membrane depolarization, allowing an influx of calcium to cause the translocation of secretory granules of insulin to the cell surface, and enhances insulin secretion in a non–glucose dependent manner. Insulin is then

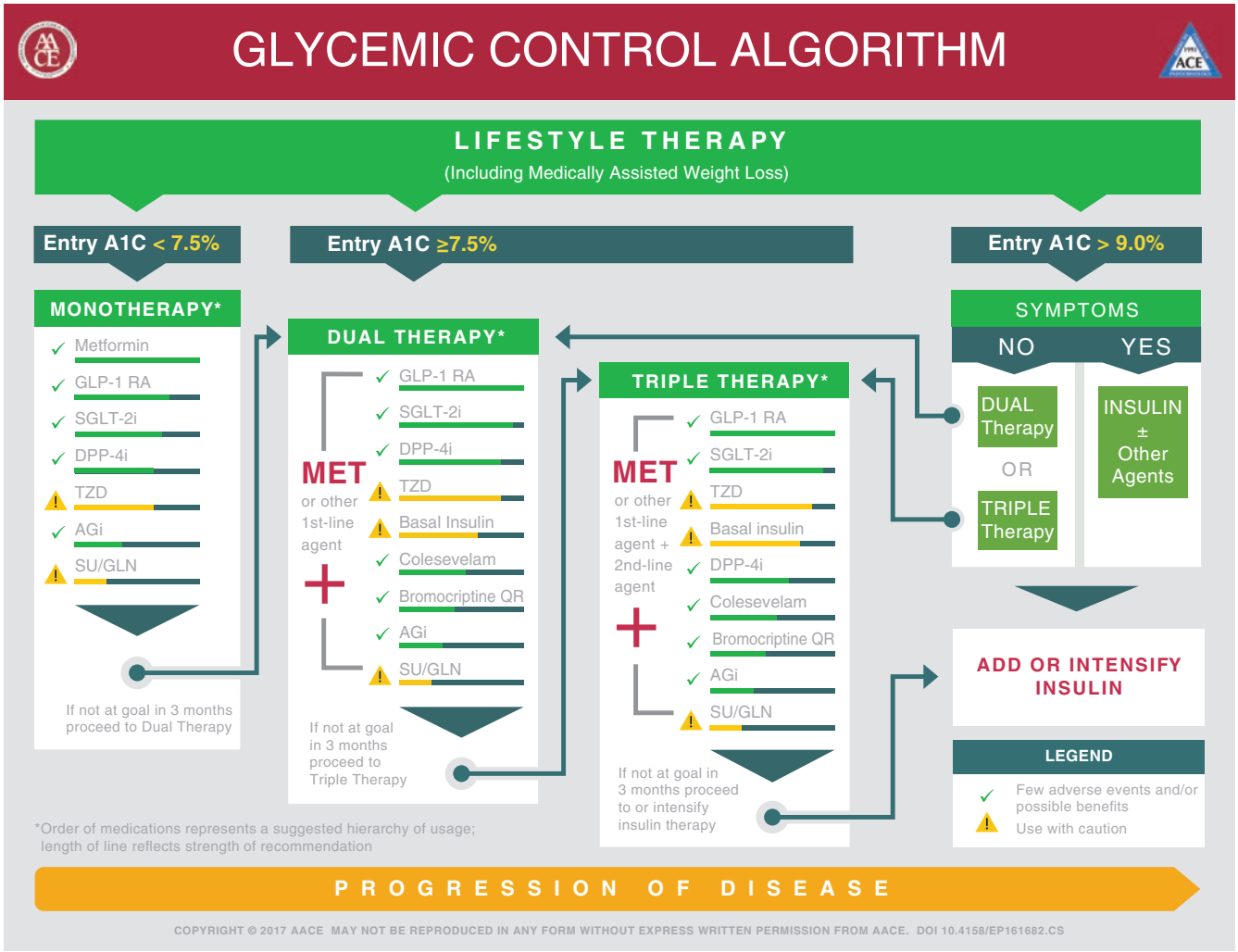

FIGURE 43–3. Algorithm for the metabolic management of type 2 diabetes as per the American Association of Clinical Endocrinologists (AACE). (A_{1c}, hemoglobin A_{1c}; AGi, alpha glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLN, meglitinides; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MET, metformin; QR, quick release; SGLT-2i, sodium-dependent glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.) (Reprinted with permission from American Association of Clinical Endocrinologists © 2018 AACE. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive type 2 diabetes management algorithm 2018. Endocr Pract.2018;24:91–120.)

transported through the portal vein to the liver, suppressing hepatic glucose production. These drugs are classified as being either first- or second-generation agents. Both classes of sulfonylureas are equally effective when given at equipotent doses. Today, the vast majority of patients receiving a sulfonylurea are prescribed a second-generation agent.

All sulfonylureas undergo hepatic biotransformation, with most agents being metabolized by the cytochrome P450 2C9 pathway. First-generation sulfonylureas are more likely to cause drug interactions than second-generation agents. All sulfonylureas, except tolbutamide, require a dosage adjustment or are not recommended in renal impairment.[24] In elderly patients or those with compromised renal or hepatic function, lower starting dosages are necessary.

Sulfonylureas' BG-lowering effects can be observed in both fasting and postprandial levels. Monotherapy with these agents generally produces a 1.5% to 2% (0.015–0.02 or 17–22 mmol/mol Hgb) decline in A_{1c} concentrations and a 60 to 70 mg/dL (3.3–3.9 mmol/L) reduction in FBG levels.[9] Secondary failure with these drugs occurs as a result of continued pancreatic β-cell destruction. One limitation of sulfonylurea therapy is the inability of these products to stimulate insulin release from β-cells at extremely high glucose levels, a phenomenon called glucose toxicity. Common adverse effects include hypoglycemia and weight gain. There may be some cross-sensitivity in patients with sulfa allergy.

▶ *Nonsulfonylurea Secretagogues (Glinides)*

Although producing the same effect as sulfonylureas, nonsulfonylurea secretagogues, also referred to as meglitinides, have a much shorter onset and duration of action. Meglitinides produce a pharmacologic effect by interacting with ATP-sensitive potassium channels on the β-cells; however, this binding is to a receptor adjacent to those to which sulfonylureas bind.

The primary benefit of nonsulfonylurea secretagogues is in reducing postmeal glucose levels. These agents have demonstrated a reduction in A_{1c} levels between 0.3% and 1% (0.003 and 0.01; 3–11 mmol/mol Hgb).[9] Because they have a rapid onset and short duration of action, they should be taken 15 to 30 minutes before a meal.

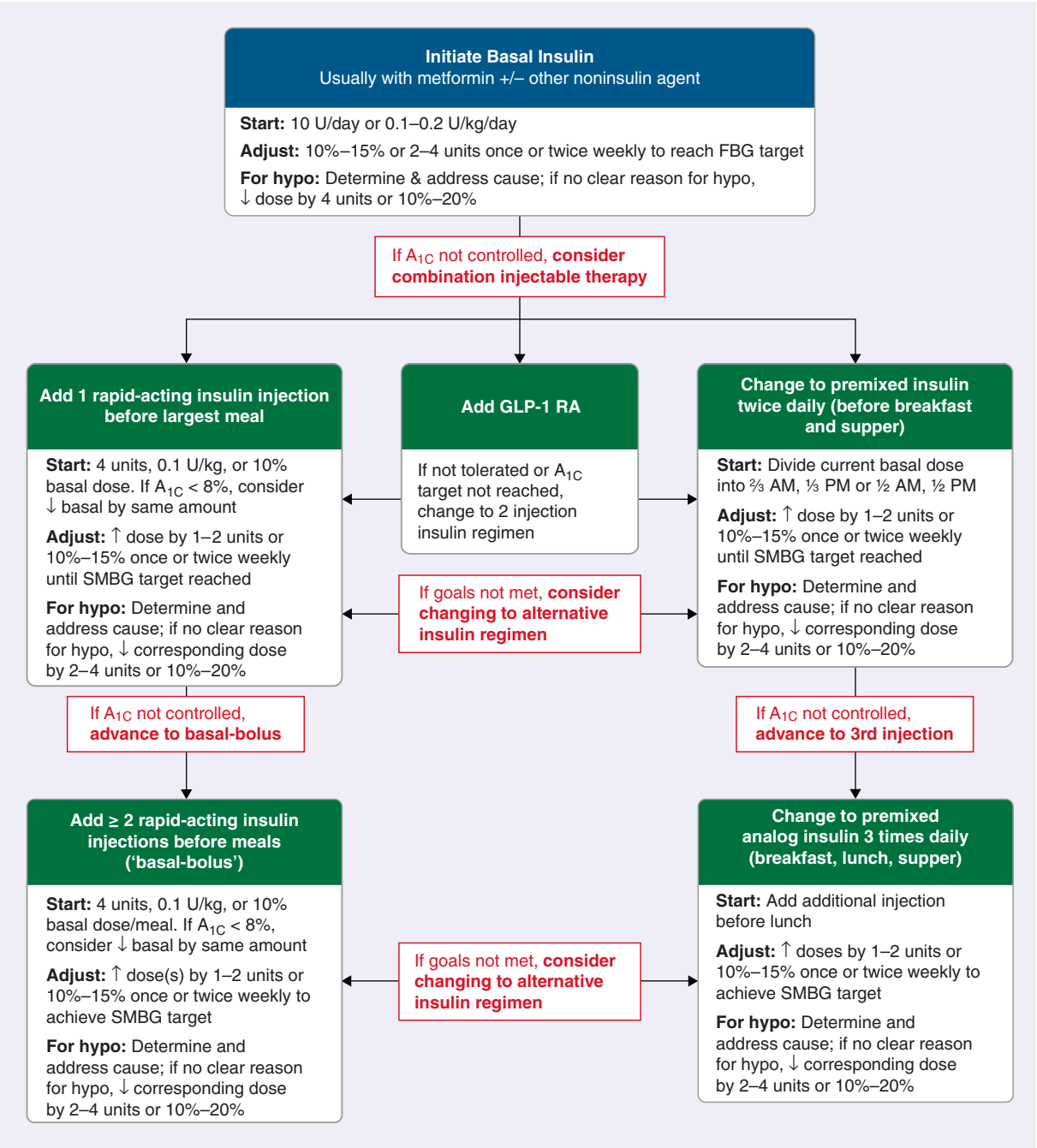

FIGURE 43–4. Initiation and adjustment of insulin regimens. (A_{1c}, hemoglobin A_{1c}; FBG, fasting blood glucose; GLP-1-RA, GLP-1 receptor agonist; hypo, hypoglycemia; kg, kilogram; SMBG, self-monitoring of blood glucose; U, unit(s).) (From American Diabetes Association. Standards of medical care in diabetes—2017. Diabetes Care. 2017;40(Suppl 1):S4–S135, with permission.)

► *Biguanides*

LO 6

Metformin is the only biguanide approved by the Food and Drug Administration (FDA) and currently available in the United States. This agent is thought to lower BG by decreasing hepatic glucose production and increasing insulin sensitivity in both hepatic and peripheral muscle tissues; however, the exact mechanism of action remains unknown. Metformin reduces A_{1c} levels by 1.5% to 2% (0.015–0.02; 17–22 mmol/mol Hgb) and FPG levels by 60 to 80 mg/dL (3.3–4.4 mmol/L) when used as monotherapy.[9] Unlike sulfonylureas, metformin retains the ability to reduce FBG levels when they are over 300 mg/dL (16.7 mmol/L). Metformin does not affect insulin release from β-cells of the pancreas, so hypoglycemia is not a common side effect.[24]

Metformin significantly reduced all-cause mortality and risk of stroke in overweight patients with T2DM compared with intensive therapy with sulfonylurea or insulin in the UKPDS.[25] It also reduced diabetes-related death and myocardial infarction compared with a conventional therapy arm. Metformin is considered foundational therapy along with lifestyle modification for T2DM and is often used in combination with other antihyperglycemics for synergistic effects.[7]

Per US labeling, metformin is contraindicated in patients with estimated glomerular filtration rates (eGFR) less than

Table 43–7

Oral Agents for the Treatment of Type 2 Diabetes Mellitus (T2DM)[19,21,24]

Drug Class	Drugs: Trade	Drugs: Generic/ Commercially Available	Target Area	Blood Glucose Affected	Dosing Strategy (All Agents Are Taken Orally)	Adjustment for Renal Impairment: CrCl 30–50 mL/min (0.50–0.83 mL/s)	Adjustment for Renal Impairment: CrCl < 30 mL/min (0.50 mL/s)	Adjustment for Hepatic Impairment	Common Adverse Drug Reactions
α-Glucosidase Inhibitors	Precose	Acarbose/Y	Brush border of small intestine	Postprandial	25 mg three times daily with first bite of each main meal Advance at 4–8 week intervals to a maximum of 100 mg three times daily	SCr > 2 mg/dL (177 µmol/L): Not recommended	SCr > 2 mg/dL (177 µmol/L): Not recommended	No specific dose adjustment recommended	GI (flatulence, diarrhea)
	Glyset	Miglitol/Y			25 mg three times daily with first bite of each main meal Advance at 4–8 week intervals to a maximum of 100 mg three times daily	SCr > 2 mg/dL (177 µmol/L): Not recommended	SCr > 2 mg/dL (177 µmol/L): Not recommended	No adjustment necessary	GI (flatulence, diarrhea)
Meglitinides (should not be used in combination with other insulin secretagogues)	Prandin	Repaglinide/Y	Pancreas	Postprandial	0.5 mg 15–30 minutes before each meal Double preprandial dose every 7 days to a maximum of 4 mg/dose or 16 mg/day (To be taken only if eating)	20–40 mL/min (0.33–0.67 mL/s): Initial dose: 0.5 mg with careful titration	< 20 mL/min (0.33 mL/s): Not studied	Use conservative initial and maintenance doses and use longer intervals between dose adjustments	Hypoglycemia (although less risk than with sulfonylureas)
	Starlix	Nateglinide/Y			120 mg three times daily before meals (To be taken only if eating)	No specific dose adjustment recommended	Use with caution in severe dysfunction	No dose adjustment needed in mild impairment; use with caution in moderate to severe dysfunction	Hypoglycemia (although less risk than with sulfonylureas)
Second-generation sulfonylureas	Micronase	Glyburide/Y	Pancreas	Fasting and postprandial	1.5–3 mg/day with breakfast	Not recommended	Not recommended	Use conservative dosing and avoid in severe disease	Hypoglycemia, weight gain

					Increase by 1.5 mg weekly to a maximum of 12 mg/day				
	DiaBeta	Glyburide/Y			2.5–5 mg/day with breakfast Increase by 2.5 mg weekly to a maximum of 20 mg/day	Not recommended	Not recommended	Use conservative dosing and avoid in severe disease	Hypoglycemia, weight gain
	Glucotrol	Glipizide/Y			5 mg/day 30 minutes before a meal Increase by 5 mg weekly to a maximum of 40 mg/day; divide dose if > 15 mg/day	No specific dose adjustment recommended	No specific dose adjustment recommended	Initial dose: 2.5 mg/day	Hypoglycemia, weight gain
	Glucotrol XL	Glipizide ER/Y			5 mg once daily before a meal Increase by 5 mg weekly to a maximum of 20 mg/day	No specific dose adjustment recommended	No specific dose adjustment recommended	No specific dose adjustment recommended	Hypoglycemia, weight gain
	Amaryl	Glimeperide/Y			1–2 mg with breakfast Increase by 2 mg every 1–2 weeks to a maximum of 8 mg/day	No specific dose adjustment recommended	< 22 mL/min (0.37 mL/s): Initial starting dose should be 1 mg	No specific dose adjustment recommended	Hypoglycemia, weight gain
Biguanides	Glucophage	Metformin/Y	Liver	Fasting and postprandial	500 mg/day to twice daily with meals. Advance weekly to a maximum of 2000–2550 mg/day	Do not start or, if already taking, continue cautiously if eGFR 30–45 mL/min/1.73 m^2. Consider 50% dose reduction and monitoring of renal function every 3 months.	Contraindicated	Avoid or use cautiously in patients at risk for lactic acidosis (renal impairment or alcohol abuse)	GI (diarrhea, abdominal pain)
	Glucophage ER, Glumetza, Fortamet	Metformin, ER/Y							
	Riomet	Metformin, solution/N			500–1000 mg/day; dose may be increased by 500 mg weekly to a maximum of 2000 mg/day				

(*Continued*)

Table 43–7

Oral Agents for the Treatment of Type 2 Diabetes Mellitus (T2DM)[19,21,24] (*Continued*)

Drug Class	Drugs: Trade	Drugs: Generic/ Commercially Available	Target Area	Blood Glucose Affected	Dosing Strategy (All Agents Are Taken Orally)	Adjustment for Renal Impairment: CrCl 30–50 mL/min (0.50–0.83 mL/s)	Adjustment for Renal Impairment: CrCl < 30 mL/min (0.50 mL/s)	Adjustment for Hepatic Impairment	Common Adverse Drug Reactions
Thiazolidinediones	Actos	Pioglitazone/Y	Peripheral tissue	Fasting and postprandial	15–30 mg/day Increase after 12 weeks to a maximum of 45 mg/day	No adjustment necessary	No adjustment necessary	Clearance lower in Child-Pugh grade B/C; do not start if transaminases > 2.5 × ULN and discontinue if ALT rises to and remains at more than three times ULN	Weight gain
	Avandia	Rosiglitazone/N	Peripheral tissue	Fasting and postprandial	4 mg/day Increase after 8–12 weeks to maximum of 8 mg/day	No adjustment necessary	No adjustment necessary	Do not initiate if active liver disease or ALT > 2.5 times ULN	Weight gain
Dipeptidyl peptidase-4 inhibitors	Januvia	Sitagliptin/N	GI tract (increases GLP-1)	Fasting and postprandial	100 mg/day	50 mg once daily	25 mg once daily	Child-Pugh score 7–9: No dosage adjustment necessary Child Pugh score > 9: Not studied	Upper respiratory, diarrhea
	Onglyza	Saxagliptin/N			2.5 or 5 mg/daily	2.5 mg once daily	2.5 mg once daily	No dose adjustment necessary	UTI, headache
	Tradjenta	Linagliptin/N			5 mg/day	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary	Headache, arthralgia, nasopharyngitis
	Nesina	Alogliptin/N			25 mg/day	> 30 mL/min (0.50 mL/s) but < 60 mL/min (1 mL/s): 12.5 mg/day	> 15 mL/min (0.25 mL/s) but < 30 mL/min (0.50 mL/s): 6.25 mg/day < 15 mL/min (0.25 mL/s): 6.25 mg/day	No dose adjustment necessary Child Pugh score > 9: Not studied	Headache, increased ALT greater than three times ULN, nasopharyngitis, upper respiratory

Selective sodium-dependent glucose cotransporter-2 inhibitor	Invokana	Canagliflozin/N	Kidney	Fasting and postprandial	100 mg/day in the morning; may increase to 300 mg/day	> 45 mL/min (0.75 mL/s) but < 60 mL/min (1.0 mL/s): 100 mg/day 30 mL/min (0.50 mL/s) to 45 mL/min (0.75 mL/s): not recommended	< 30 mL/min (0.50 mL/s): contraindicated	Mild to moderate: no adjustment necessary Severe: not recommended	Hyperkalemia, genitourinary infection, hypovolemia, renal insufficiency, hypotension
	Farxiga	Dapagliflozin/N			5 mg/day in the morning; may increase to 10 mg/day	< 60 mL/min (1.0 mL/s): not recommended	< 30 mL/min (0.50 mL/s): contraindicated	Mild to moderate: No adjustment necessary Severe: not studied	Genitourinary infection, hypovolemia/ hypotension, dysuria, polyuria, dyslipidemia, mild hypoglycemia, nasopharyngitis
	Jardiance	Empagliflozin/N			10 mg/day in the morning; may increase to 25 mg/day	Not yet available	Not yet available	Not yet available	Genitourinary infection, hypovolemia/ hypotension, dysuria, polyuria, mild hypoglycemia
Dopamine receptor agonist	Cycloset	Bromocriptine mesylate/N	Hypothalamus	Postprandial	0.8 mg once daily within 2 hours of waking; may increase in weekly intervals to 4.8 mg once daily	No dose adjustment necessary	No dose adjustment necessary	No specific dose adjustment recommended, although adjustment may be necessary because of extensive hepatic metabolism	Nausea, headache
Bile acid sequestrant	Welchol	Colesevelam/N	Intestinal lumen	Fasting	1.875 g twice daily or 3.75 g once daily	No dose adjustment necessary	No dose adjustment necessary	No dose adjustment necessary	Constipation

ALT, alanine aminotransferase; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ER, extended release; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; SCr, serum creatinine; ULN, upper limit of normal; UTI, urinary tract infection.

Table 43–8

Site and Mechanism of Action for Noninsulin Agents

Site of Action	Drug Class	Mechanism of Action
Pancreas	Sulfonylureas	Enhances insulin secretion
	Nonsulfonylurea secretagogues	Enhances insulin secretion
	GLP-1 agonists	Enhances insulin secretion and suppresses glucagon secretion
	Pramlintide	Suppresses glucagon secretion
Liver	Biguanide	Decreases hepatic glucose production and increases insulin sensitivity
	Thiazolidinedione	Increases insulin sensitivity
Muscle	Biguanide	Increases insulin sensitivity
	Thiazolidinedione	Increases insulin sensitivity
Adipose tissue	Thiazolidinedione	Increases insulin sensitivity
Intestines	GLP-1 agonists	Increases satiety and regulates gastric emptying
	Pramlintide	Increases satiety and regulates gastric emptying
	Dipeptidyl peptidase-4 inhibitors	Increases endogenous GLP-1
	α-Glucosidase inhibitors	Delays absorption of carbohydrates
Kidney	SGLT-2 inhibitors	Inhibits glucose reabsorption in the kidney's proximal tubule

GLP-1, glucagon-like peptide-1; SGLT-2, sodium-dependent glucose cotransporter-2.

30 mL/min/1.73m^2.[24] It is not recommended for new start in patients whose eGFR is 30 to 45 mL/min/1.73m^2. In those whose eGFR falls to less than 45 mL/min/1.73m^2, a consideration of benefits and risks should be undertaken or a dose reduction to 50% of the maximum dose (or 50% of the patient's current dose) with renal monitoring every 3 months could be chosen. No adjustment is required for patients with an eGFR greater than 45 mL/min/1.73m^2, though more frequent monitoring (every 3–6 months versus annually) is recommended for patients with eGFR greater than 45 but less than 60 mL/min/1.73m^2. Additionally, therapy with metformin should be withheld in patients undergoing radiographic procedures in which a nephrotoxic dye is used if their eGFR is between 30 and 60 mL/min/1.73m^2. Therapy should be withheld the day of the radiographic procedure, and renal function should be assessed 48 hours after the procedure. If renal function is normal, therapy may be resumed. Metformin should also be held 24 hours before surgery and restarted after oral intake is resumed and renal function is evaluated as normal.

Primary side effects associated with metformin therapy are GI in nature, including decreased appetite, nausea, and diarrhea. These side effects can be minimized through use of extended-release products and slow titration of the dose and often subside within 2 weeks.[26] Interference with vitamin B_{12} absorption has also been reported and therefore periodic B_{12} testing is recommended especially in those patients with macrocytic anemia or peripheral neuropathy.[9] Metformin is thought to inhibit mitochondrial oxidation of lactic acid, thereby increasing the chance of lactic acidosis, a condition which rarely occurs. Patients at greatest risk for developing lactic acidosis include those with renal impairment and those who are of advanced age.[24] Metformin should be withheld promptly in cases of hypoxemia, sepsis, or dehydration. Patients should avoid consumption of excessive amounts of alcohol while taking metformin, and use of the drug should be avoided in patients with liver disease.

► *Thiazolidinediones (TZDs)*

LO 6

TZDs are known to increase insulin sensitivity by stimulating peroxisome proliferator-activated receptor gamma (PPAR-γ) which increases insulin sensitivity and decreases plasma fatty acids. As monotherapy, TZDs reduce FPG levels by around 60 to 70 mg/dL (3.3–3.9 mmol/L), and the effect on A_{1c} is an up to 1.5% (0.015; 17 mmol/mol Hgb) reduction.[9] The onset of action

Table 43–9

Expected A_{1c} Reduction for Noninsulin Antiglycemic Drug Classes[9]

Drug Class	Efficacy	A_{1c} Reduction (%)	A_{1c} Reduction (mmol/mol Hgb)
Biguanides	High	1.5%–2% (0.015–0.02)	17–22 mmol/mol Hgb
Sulfonylureas	High	1.5%–2% (0.015–0.02)	17–22 mmol/mol Hgb
GLP-1 agonists	High	0.78%–1.6% (0.0078–0.016)	8.8–18 mmol/mol Hgb
Thiazolidinedione	High	up to 1.5% (0.015)	17 mmol/mol Hgb
Dipeptidyl peptidase-4 inhibitors	Intermediate	0.7%–1% (0.007–0.01)	8–11 mmol/mol Hgb
SGLT-2 inhibitors	Intermediate	0.5%–1% (0.005–0.01)	5–11 mmol/mol Hgb
Nonsulfonylurea secretagogues	Intermediate	0.3%–1% (0.003–0.01)	3–11 mmol/mol Hgb
α-Glucosidase inhibitors	Intermediate	0.3%–1% (0.003–0.01)	3–11 mmol/mol Hgb
Central-acting dopamine agonists	Low	0.3%–0.6% (0.003–0.006)	3–7 mmol/mol Hgb
Pramlintide	Low	0.4%–0.5% (0.004–0.005)	5–6 mmol/mol Hgb
Bile acid sequestrants	Low	0.4% (0.004)	5 mmol/mol Hgb

A_{1c}, hemoglobin A_{1c}; GLP-1, glucagon-like peptide-1; Hgb, hemoglobin; SGLT-2, sodium-dependent glucose cotransporter-2.

for TZDs is delayed for several weeks and may require 12 weeks or more before maximum effects are observed.

TZDs may produce fluid retention and edema. Thus, these drugs are contraindicated in situations in which an increased fluid volume is detrimental such as New York Heart Association Class III and IV heart failure. Fluid retention appears to be dose related and increases when combined with insulin therapy. While rare, TZDs can worsen macular edema in the eye. Weight gain of 4 kg (8.8 lb) is common with TZDs and results from both fluid retention and fat accumulation.[9]

Increased rates of upper and lower limb fractures are known to occur with TZD therapy. Premenopausal anovulatory women may begin to ovulate on TZD therapy, and therefore counseling regarding this should be provided to all women capable of becoming pregnant. A slight increased risk for bladder cancer has been noted with pioglitazone therapy, especially among men and smokers.

The safety of TZD therapy in patients with cardiovascular disease is unclear and seems to differ between specific drugs. A meta-analysis reported a significantly greater risk of myocardial infarction with rosiglitazone compared with other oral agents.[27] A subsequent study found rosiglitazone use was associated with a nonsignificant increase in myocardial infarction risk and a nonsignificant reduction in stroke, but a trend toward increased cardiovascular risk in patients with a history of ischemic heart disease.[28] Pioglitazone, added to standard therapy in patients with a history of cardiovascular event or peripheral vascular disease, was shown to decrease the secondary composite endpoint of all-cause mortality, nonfatal myocardial infarction, or stroke.[29]

► α-Glucosidase Inhibitors

LO 6

Acarbose and miglitol are α-glucosidase inhibitors that compete with the enzymes of the small intestines that break down complex carbohydrates. These drugs delay absorption of carbohydrates and reduce postprandial BG concentrations as much as 40 to 50 mg/dL (2.2–2.8 mmol/L); however, A_{1c} reductions range only from 0.3% to 1% (0.003–0.01; 3–11 mmol/mol Hgb).[9] High incidences of GI side effects, including flatulence (42%–74%), abdominal discomfort (12%–19%), and diarrhea (29%–31%), have limited their use.[24] Low initial doses followed by gradual titration may minimize GI side effects. The α-glucosidase inhibitors are contraindicated in patients with chronic intestinal diseases including inflammatory bowel disease. In addition, neither drug in this class is recommended for patients with a serum creatinine (SCr) greater than 2 mg/dL (177 μmol/L).

► Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

LO 6

DPP-4 inhibitors (or gliptins; sitagliptin, saxagliptin, linagliptin, and alogliptin) are approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM. They lower BG concentrations by inhibiting DPP-4, the enzyme that degrades endogenous GLP-1, thereby increasing the amount of endogenous GLP-1. The BG-lowering effect of the gliptins is primarily on postprandial levels. Typical A_{1c} reductions are 0.7% to 1% (0.007–0.01; 8–11 mmol/mol Hgb).[9] Common adverse effects include headache and nasopharyngitis. Hypoglycemia is not a common adverse effect with these agents because insulin secretion results from GLP-1 activation caused by meal-related glucose detection and not from direct pancreatic β-cell stimulation. Acute pancreatitis, including hemorrhagic and necrotizing pancreatitis, has been reported in patients taking glipitins.[24]

► Sodium-Dependent Glucose Cotransporter-2 (SGLT2) Inhibitors

LO 6

SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin) are approved as adjunct to diet and exercise to improve glycemic control in adults with T2DM and may be used as monotherapy or add-on. Inhibition of SGLT2 in the proximal tubules reduces reabsorption of filtered glucose and lowers the renal threshold for glucose which together cause increased urinary excretion of glucose and decreased plasma glucose concentrations.[24] Typical A_{1c} reductions are 0.5% to 1% (0.005–0.01; 5–11 mmol/mol Hgb).[9]

Empagliflozin, added to standard of care, was shown to reduce the composite of cardiovascular death, all-cause mortality, and death from cardiovascular causes.[30] Canagliflozin was evaluated in two trials which enrolled patients with T2DM at high cardiovascular risk.[31] Canagliflozin reduced the risk of primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. An increased risk for amputation was detected in this study, primarily involving the toe or metatarsal. A cardiovascular outcome study is currently ongoing with dapagliflozin.

Possible adverse reactions with SGLT2 inhibitors include urinary tract infections (UTIs) and genital mycotic infections which are increased due to increased glucose excretion that occurs as a function of the drugs' mechanism of action.[24] Osmotic diuresis occurs as well which may result in symptomatic hypotension. Renal function should be monitored at baseline to guide initial dosing and periodically during treatment to assess suitability of continuation. Volume status including BP, hematocrit, serum potassium, serum magnesium, serum phosphate, and low-density lipoprotein (LDL) cholesterol are also recommended monitoring parameters for this class of drug. Cases of euglycemic ketoacidosis have been reported with SGLT2 inhibitors. Before initiation, patients should have their risk for ketoacidosis assessed (some risk factors include insulin deficiency, dose decreases of insulin, caloric restriction, surgery, and infection). Should ketoacidosis occur, the SGLT2 inhibitor should be held or discontinued. Increased risk for bone fracture has also been associated with SLGT2 inhibitor use as well as newly diagnosed bladder cancer with dapagliflozin.

► Central-Acting Dopamine Agonist

LO 6

A quick release formulation of the central-acting dopamine agonist, bromocriptine, is approved for the treatment of T2DM. The mechanism of action for how bromocriptine regulates glycemic control is unknown, but data indicate that bromocriptine administered in the morning improves insulin sensitivity, and this is likely a result of its effect on dopamine oscillations.[9] When used to treat patients with T2DM, bromocriptine should be taken 2 hours after waking in the morning with food.[24] A modest A_{1c} reduction of 0.3% to 0.6% (0.003–0.006; 3–7 mmol/mol Hgb) can be expected from this drug.[9] Main side effects include rhinitis, dizziness, asthenia, headache, sinusitis, constipation, and nausea. Contraindications include syncopal migraine and women who are nursing.[24]

► Bile Acid Sequestrants

LO 6

Colesevelam is the only bile acid sequestrant currently approved as adjunctive therapy to improve glycemic control in conjunction with diet, exercise, and insulin or oral agents for the treatment of T2DM. It acts on the intestinal lumen to bind bile acid, but the drug's exact mechanism that results in plasma glucose lowering is unknown. An A_{1c} reduction of approximately 0.4%

(0.004; 5 mmol/mol Hgb) and an FPG reduction of about 5 to 10 mg/dL (0.3–0.6 mmol/L) can be expected when colesevelam is added.[9] Common adverse effects include constipation and dyspepsia. Drug–drug interactions are possible because of absorption and can be particularly important in patients who are taking levothyroxine, glyburide, oral contraceptives, phenytoin, warfarin, and digoxin. These medications should not be taken together, and they should be separated by at least 4 hours before dosing colesevelam. Malabsorption of fat-soluble vitamins (A, D, E, and K) is also a concern.

▶ *Insulin*

Insulin is the one agent that can be used in all types of DM and has no specific maximum dose, meaning it can be titrated to suit each individual patient's needs. KEY CONCEPT Insulin is the primary treatment to lower BG levels for patients with T1DM, and injected amylin can be added to decrease fluctuations in BG levels. An insulin treatment algorithm for T2DM is found in Figure 43–2.[21]

LO 7

Insulin can be divided into two main classes, basal and bolus, based on their length of action to mimic endogenous insulin physiology. Most formulations are available as U-100, indicating a concentration of 100 unit/mL, though more concentrated insulin formulations have become available in recent years including 200 units/mL (insulin degludec and insulin lispro) and 300 units/mL (insulin glargine), which join the older 500 units/mL regular insulin which has been traditionally available. Insulin is typically refrigerated, though most vials are good for 28 days at room temperature.[24] Insulin products are listed in Table 43–10.[24,32-34]

The most common route of insulin administration is subcutaneous injection using a syringe or pen device. Patients should be educated to rotate injection sites to minimize lipohypertrophy, a buildup of fat that decreases or prevents proper insulin absorption. Additionally, patients should understand that the absorption rate may vary among injection sites (abdomen, thigh, arm, and buttocks) because of differences in blood flow, with absorption occurring fastest in the abdomen and slowest in the buttocks.

Both insulin syringes and pens are now available with shorter needles (4–6 mm, compared to traditional lengths of 8–12.7 mm) that do not require the patient to pinch up their skin before injecting. With the no pinch technique, the needle is injected straight in at a 90-degree angle until flush with the skin. However, these products require a 10-second count to allow enough time for the insulin to be injected. This technique makes injections easier, especially the traditionally more difficult sites such as arms and buttocks.

Bolus Insulins

Regular Regular insulin is unmodified crystalline insulin commonly referred to as natural or human insulin. It is a clear solution that has a relatively short onset and duration of action and is designed to cover insulin response to meals. On subcutaneous injection, regular insulin forms small aggregates called hexamers that undergo conversion to dimers followed by monomers before systemic absorption can occur. Patients should be counseled to inject regular insulin subcutaneously 30 minutes before consuming a meal. Regular insulin, insulin lispro (100 units/mL), insulin aspart, and insulin glulisine can be administered intravenously (IV).

Rapid-Acting Three rapid-acting injectable insulins have been approved in the United States: aspart, glulisine, and lispro (available as 100 units/mL and 200 units/mL). Substitution of one or two amino acids in regular insulin results in the unique pharmacokinetic properties characteristic of these agents. Onset of action of injectable rapid-acting insulins (typically dosed 15 minutes before or immediately prior to meals) varies from 15 to 30 minutes, with peak effects occurring 1 to 2 hours after administration. An inhaled rapid-acting insulin is also available, with peak effect expected to occur around 12 to 15 minutes following a dose and a duration of action of approximately two and one-half to three hours.

Basal Insulins

Intermediate-Duration Neutral Protamine Hagedorn (NPH) insulin is prepared by a process in which protamine is conjugated with regular insulin, rendering a product with a delayed onset but extended duration of action, and is designed to cover insulin requirements in between meals and/or overnight. With the advent of the long-acting insulins, NPH insulin use has declined because of (a) an inability to predict accurately when peak effects occur and (b) a duration of action of less than 24 hours. Additionally, protamine is a foreign protein that may increase the possibility of an allergic reaction.

NPH insulin can be mixed with regular insulin and used immediately or stored for future use. NPH insulin can be mixed with either aspart or lispro insulins, but it must be injected immediately after mixing. Whenever mixing insulin products with NPH insulin, the shorter acting insulin should be drawn into the syringe first.

When utilized in the 500 units/mL (U-500) concentration, regular insulin takes on a different pharmacokinetic/pharmacodynamic profile than when utilized in the 100 units/mL concentration.[9] While its onset of action remains about 30 minutes post injection, its duration of action extends to be more similar to that of NPH. Insulin regular U-500 is now available in a pen device to improve patient safety.[33] The pen device dials in 5-unit increments and takes care of dosing conversion for the patient, meaning that the dose displayed in the pen window is the actual number of units being delivered. Capable of delivering a single dose of up to 300 units at one time, a single pen holds 1500 units total.

Long-Duration Glargine, detemir, and degludec are designed as once-daily-dosing basal insulins which provide a relatively constant insulin concentration over 24 hours.[34] Insulin glargine differs from regular insulin by three amino acids, resulting in a low solubility at physiologic pH. The clear solution is supplied at a pH of 4, which precipitates on subcutaneous administration. Detemir binds to albumin in the plasma, which gives it sustained action. Neither glargine nor detemir completely mimic physiological insulin since, when delivered at high doses, a peak occurs and, when delivered at low doses, the dose may not cover 24 hours.

Recently, insulin glargine at a concentration of 300 units/mL (U-300) became available. This higher concentration product forms a depot with a smaller surface area which creates a more prolonged release than the 100 units/mL (U-100) formulation and a flatter pharmacokinetic/pharmacodynamic response curve. U-300 has been found to result in fewer episodes of hypoglycemia including nocturnal hypoglycemia and decreased weight gain as compared with U-100 glargine. The duration of action for U-300 glargine is approximately 36 hours, about 12 hours longer than that of the U-100 product. Insulin glargine U-300 is available in a pen device which delivers up to 80 units in a single injection.[24] The pen window displays actual units delivered, meaning that no dosing conversion is required. Insulin should not be transferred

Table 43–10

Insulin Agents for the Treatment of Type 1 and Type 2 Diabetes Mellitus[24,32-34]

Generic Name (Insulin)	Brand/Rx Status	Manufacturer	Strength	Onset	Peak (hours)	Duration (hours)	Administration Options
Rapid-Acting Insulin							
Lispro	Humalog/Rx	Eli Lilly	U-100, U-200	15–30 minutes	0.5–2.5	3–4	CSII, IV, SC; 10-mL vial, 3-mL cartridge, and disposable pen
Aspart	Novolog/Rx	Novo-Nordisk	U-100	15–30 minutes	1–3	3–5	CSII, IV, SC; 10-mL vial, 3-mL cartridge, and disposable pen
Glulisine	Apidra/Rx	Aventis	U-100	15–30 minutes	1–2	3–4	CSII, IV, SC; 10-mL vial, 3-mL cartridge, and disposable pen
Recombinant human insulin regular	Afrezza/Rx	MannKind	Not applicable	12–15 minutes	1	2.5–3	Inh; Technosphere insulin particles for oral inhalation
Short-Acting Insulin							
Regular	Humulin R/OTC	Eli Lilly	U-100, U-500	30-60 minutes	2-3	3-6	CSII, IV, SC; U-100 10-mL vial; U-500 20-mL vial
	Novolin R/OTC	Novo-Nordisk	U-100				CSII, IV, SC; 10-mL vial, 3-mL cartridge, 3-mL *Innolet*
Intermediate-Acting Insulin							
Neutral protamine Hagedorn	Humulin N/OTC	Eli Lilly	U-100	2–4 hours	4–6	8–12	SC; 10-mL vial, 3-mL cartridge
	Novolin N/OTC	Novo-Nordisk	U-100				SC; 10-mL vial, 3-mL cartridge, 3-mL *InnoLet*
Long-Acting Insulin							
Glargine	Lantus/Rx	Sanofi-Aventis	U-100	4-5 hours	Flat	22–24	SC; 10-mL vial, 3-mL cartridge for *Opticlik* (available in SoloSTAR disposable pen)
	Toujeo/Rx		U-300				SC;1.5-mL SoloSTAR disposable pen
Detemir	Levemir/Rx	Novo-Nordisk	U-100	3–4 hours	Flat	Up to 24	SC; 10-mL vial, 3-mL cartridge, 3-mL *Innolet*, 3-mL disposable *FlexPen*
Degludec	Tresiba/Rx	Novo-Nordisk	U-100, U-200	1 hour	Flat	42	SC; 3-ml disposable *FlexTouch* pen
Combination Insulin Products							
Neutral protamine Hagedorn and regular	Humulin 70/30/OTC	Eli Lilly	U-100	30–60 minutes	1.5–16	10–16	SC: 10-mL vial, 3-mL disposable pen SC; 10-mL vial, 3-mL cartridge, 3-mL *Innolet*
	Novolin 70/30/OTC	Novo-Nordisk	U-100	30–60 minutes	2–12	10–16	
	Humulin 50/50/OTC	Eli Lilly	U-100	30–60 minutes	2–5.5	10–16	SC; 10-mL vial
Neutral protamine lispro and lispro	Humalog Mix 75/25/Rx	Eli Lilly	U-100	15–30 minutes	1–6.5	15–18	SC; 10-mL vial, 3-mL disposable pen
Neutral protamine aspart and aspart	Novolog Mix 70/30/Rx	Novo-Nordisk	U-100	15–30 minutes	1–4	Up to 24	SC; 10-mL vial, 3-mL cartridge, 3-mL disposable *FlexPen*
Combination Insulin GLP-1 agonist Products							
Degludec and liraglutide	Xultophy/Rx	Novo-Nordisk	U-100 degludec/ 3.6 mg/mL liraglutide	N/A	N/A	N/A	SC; 3-ml pen-injector
Glargine and lixisenatide	Soliqua/Rx	Sanofi	U-100 glargine/ 33 mcg/mL liraglutide	N/A	N/A	N/A	SC; 3-mL pen-injector

CSII, continuous subcutaneous insulin infusion; GLP-1, glucagon like peptide; Inh, inhalation; IV, intravenous; N/A, not applicable; OTC, over-the-counter; Rx, prescription required; SC, subcutaneous.

from the pen to a syringe as incorrect dosing and subsequent adverse effects can occur.

Further search for a more physiologically perfect basal insulin lead to the development of degludec.[34] A modified B chain analogue which forms hexamers and di-hexamers when injected, insulin degludec provides a flatter pharmacokinetic/pharmacodynamic profile than detemir or glargine. Zinc molecules, present in the hexamers, slowly diffuse allowing insulin monomers to be absorbed. This ultra-slow insulin release allows degludec to have a half-life of 25 hours and duration of action that exceeds 42 hours. Though still recommended for daily dosing at the same time each day, degludec's long duration of action means that patients taking it can miss or delay a dose as long as they make sure to keep an 8-hour interval between any two doses.

Combination Products A number of combination insulin products are available commercially.[24,32] These combination products allow some patients to manage their insulin therapy with only two injections per day, and avoids the difficulty and possible errors that can occur when manually mixing insulins. NPH is available in a combination of 70/30 (70% NPH and 30% regular insulin). Three short-acting insulin analog mixtures are also available. Humalog mix 75/25 contains 75% neutral protamine lispro suspension and 25% insulin lispro. Novolog mix 70/30 contains 70% insulin aspart protamine suspension and 30% insulin aspart. Humalog 50/50 contains 50% neutral protamine lispro and 50% lispro. The lispro and aspart insulin protamine suspensions were developed specifically for these mixture products and are not commercially available separately.

Insulin Pump Therapy Insulin pump therapy consists of a programmable infusion device that allows for basal infusion of insulin 24 hours daily (see Figure 43–1), as well as bolus administration before meals and snacks. Regular or rapid-acting insulin is delivered from a reservoir either by infusion set tubing or through a small canula. Most pump infusion sets are inserted in the abdomen, arm, or other infusion site by a small needle. Most patients prefer insertion in abdominal tissue because this site provides optimal insulin absorption. However, they must rotate sites to avoid development of scar tissue. Infusion sets should be changed every 2 to 3 days to reduce the possibility of infection.

Patients use a carbohydrate-to-insulin ratio to determine how many units of insulin are required. More specifically, an individual's ratio is calculated to determine how many units of the specific insulin being used in the pump "covers" for a certain amount of carbohydrates to be ingested at a particular meal. The 450 rule (for regular insulin) or the 500 rule (for rapid-acting insulin) is commonly used. To calculate the ratio using the 500 rule, the patient would divide 500 by his or her total daily dose of insulin. Once this ratio is determined, patients can eat more or fewer carbohydrates at a given meal and adjust the bolus dose accordingly.

In addition to mealtime boluses, correction doses based on premeal glucose readings are also used. The amount of additional insulin for the correction is based on either the 1500 rule for regular insulin or the 1800 rule for rapid-acting insulin. If using rapid-acting insulin, divide 1800 by the patient's total daily insulin dose. The resulting value will represent the reduction in glucose (mg/dL) produced by one unit of insulin. The correction dose would be given in addition to the bolus dose needed based on the patient's carbohydrate-to-insulin ratio and the amount of carbohydrates present in the meal he or she is about to consume.

Insulin pump therapy may be used to lower BG levels in any type of DM; however, patients must be on multiple daily insulin injections and therefore patients with T1DM are always candidates and those with T2DM are sometimes candidates to use these devices. Use of an insulin pump may improve BG levels, reduce wide fluctuations in BG levels, and allow individuals to have more flexibility in timing and content of meals and exercise schedules, resulting in improved quality of life.

► *Noninsulin Injectable Agents*

LO 6

Glucagon-Like Peptide 1 (GLP-1) Agonists Exenatide, liraglutide, albiglutide, dulaglutide, and lixisenatide are indicated for the treatment of T2DM to improve glycemic control. These agents are part of the group of drugs known as incretins (Table 43–11).[24,32,35]

GLP-1 agonists lower BG levels by: (a) producing glucose-dependent insulin secretion; (b) reducing postmeal glucagon secretion, which decreases postmeal glucose output; (c) increasing satiety which decreases food intake; and (d) regulating gastric emptying, which allows nutrients to be absorbed into the circulation more smoothly. Typical A_{1c} reductions vary between GLP-1 agonists and are also affected by baseline glucose control. Exenatide immediate release can be expected to lower A_{1c} around 0.9% (0.009; 10 mmol/mol Hgb) while exenatide extended-release lowers A_{1c} around 1.6% (0.016; 18 mmol/mol Hgb).[36] Reductions in A_{1c} from 0.99% to 1.36% (0.0099–0.0136; 11 mmol/mol Hgb to 15 mmol/mol Hgb) have been reported with liraglutide, reductions of around 1.42% have been reported with dulaglutide (0.00142; 16 mmol/mol Hgb), reductions of around 0.79% have been reported with lixisenatide (0.0079; 8.9 mmol/mol Hgb), and reductions around 0.78% (0.0078; 8.8 mmol/mol Hgb) have been reported with albiglutide.[35] GLP-1 agonists typically produce moderate weight loss of around 3 to 4 kg (6.6–8.8 lbs) depending on the drug chosen. Exenatide immediate release has less impact on fasting blood sugar levels as compared with the longer-acting GLP-1 agonists owing to its shorter duration of action.[9] Exenatide and lixisenatide are eliminated renally. Exenatide is not recommended in patients with a creatinine clearance (CrCl) of less than 30 mL/min (0.50 mL/s) and lixisenatide is not recommended in patients with CrCl less than 15 mL/min (0.25 mL/s).[24] No specific dose adjustments are recommended for liraglutide, albiglutide, or dulaglutide in renal impairment. The main side effects of GLP-1 agonist therapy include nausea, vomiting, and diarrhea. These GI adverse effects tend to lessen over time.[9] GLP-1 agonists have been associated with cases of acute pancreatitis. Any patient presenting with symptoms of acute pancreatitis, including abdominal pain, nausea, and vomiting, should have GLP-1 agonist therapy discontinued until pancreatitis can be ruled out. Albiglutide, liraglutide, exenatide extended-release, and dulaglutide packagings contain a black-box warning about thyroid C-cell tumors.[24] They are contraindicated in patients with a personal or family history of medullary thyroid cancer and in those with a history of multiple endocrine tumors. Antibody formation can occur with the GLP-1 agonists leading to treatment failure or increased allergic reaction side effects.

Liraglutide reduced the risk of cardiovascular death as compared with placebo in a clinical trial.[37] Given this potential cardiovascular outcome benefit coupled with their ability to produce weight loss and help control weight gain from insulin therapy, the GLP-1 agonists have had considerable increased utilization in recent years both as monotherapy and as add-on. As such, a market for combination insulin and GLP-1 agonist products has developed. There are now two basal insulin/GLP-1

Table 43–11

Noninsulin Injectable Agents for the Treatment of Diabetes[24,32,35]

Generic Name (Brand)	Type of Diabetes	Dosage Strengths[a]	Starting Dosage	Doses/Day	Titration Interval	Maximum Dose	Time to Effect (minutes)	Comments and Cautions
Pramlintide[b] (Symlin)	T1DM	15, 30, 45, 60 mcg	15 mcg	3	3–7 days	60 mcg	20	Take just before major meals; reduce insulin by 50% Maintenance dose 30–60 mcg Side effects: Hypoglycemia, nausea, vomiting Available in SymlinPen 60 and 120
	T2DM	60, 120 mcg	60 mcg	3	3–7 days	120 mcg	20	
Exenatide[b] (Byetta, Bydureon)	T2DM	Immediate-release: 5 mcg, 10 mcg; Extended-release: 2 mg	Immediate-release: 5 mcg; extended-release: 2 mg	Immediate-release: 2; extended-release: N/A; once-weekly	Immediate-release: 1 month; extended-release: N/A	Immediate-release: 10 mcg; extended-release: 2 mg	Immediate-release: 15–30	Inject immediate-release formulation 15–20 minutes before two meals of the day with 6 hours separating the meals; prefilled disposable pen; may delay absorption of oral drugs; separate doses by 1 hour Extended-release formulation can be administered regardless of meals Side effects: Nausea, vomiting, diarrhea, increased hypoglycemia with sulfonylureas
Liraglutide[b] (Victoza)	T2DM	6 mg/3 mL pen	0.6 mg	1	1 week	1.8 mg	N/A	Can be dosed at any time of day regardless of meals; may delay absorption of oral drugs; separate doses by 1 hour Side effects: Nausea, vomiting, increased hypoglycemia with sulfonylureas
Albiglutide[b] (Tanzeum)	T2DM	30 mg single-dose pen; 50-mg single-dose pen	30 mg	N/A; once weekly	6 weeks	50 mg	N/A	If missed dose occurs within 3 days of the regularly scheduled dose, dose should be administered at that time. If missed dose occurs more than 3 days past scheduled dose, wait until next regularly scheduled dose to administer next dose Side effects: upper respiratory infection, diarrhea, nausea, injection site reaction

(Continued)

Table 43–11

Noninsulin Injectable Agents for the Treatment of Diabetes[24,32,35] *(Continued)*

Generic Name (Brand)	Type of Diabetes	Dosage Strengths[a]	Starting Dosage	Doses/Day	Titration Interval	Maximum Dose	Time to Effect (minutes)	Comments and Cautions
Dulaglutide[b] (Trulicity)	T2DM	0.75 mg single-dose pen and prefilled syringe; 1.5-mg single-dose pen and prefilled syringe	0.75 mg	N/A; once weekly	Not specified	1.5 mg	N/A	If missed dose occurs within 3 days of the regularly scheduled dose, dose should be administered at that time. If missed dose occurs more than 3 days past scheduled dose, wait until next regularly scheduled dose to administer next dose Side effects: nausea, diarrhea, vomiting, abdominal pain, decreased appetite, dyspepsia, fatigue
Lixisenatide[b] (Adlyxin)	T2DM	10 mcg and 20 mcg pen-injector starter kit; 20 mcg pen-injector	10 mcg	1	14 days	20 mcg	N/A	If missed dose, administer within one hour of next meal

[a]Pramlintide supplied as 0.6 mg/mL in 5-mL vials. Exenatide immediate-release supplied as 250 mcg/mL, 1.2 mL for the 5-mcg prefilled pen, and 2.4 mL for the 10-mcg per dose prefilled pen. Exenatide extended-release supplied as 2 mg sterile powder plus 0.65 mL diluent in single use trays. Liraglutide supplied in 6 mg/3 mL prefilled pen, which can be dialed to the desired dose of 0.6, 1.2, or 1.8 mg. Albiglutide supplied in a 30-mg and a 50-mg single-dose pen. Dulaglutide supplied in a 0.75-mg and 1.5-mg single-dose pen and prefilled syringe. Lixisenatide supplied in a 10-mcg and a 20-mcg pen-injector starter kit and a 20-mcg pen-injector for maintenance use.

[b]Generic not available in the United States.

N/A, not applicable; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

agonist combination products available. One contains insulin glargine in combination with lixisenatide and the other contains insulin degludec in combination with liraglutide.

Amylin Pramlintide acetate is a synthetic analog of human amylin, which is a naturally occurring neuroendocrine peptide that is cosecreted with insulin by the β-cells of the pancreas in response to food. Amylin secretion is very low or completely deficient in patients with T1DM and lower than normal in patients with T2DM who require insulin. Pramlintide slows gastric emptying without altering absorption of nutrients, suppresses glucagon secretion, and leads to a reduction in food intake by increasing satiety. By slowing gastric emptying, the normal initial postmeal spike in BG is reduced.

Pramlintide is given by subcutaneous injection before meals to lower postprandial BG elevations in patients with types 1 or 2 DM. Pramlintide generally results in an additional A_{1c} reduction of 0.4% to 0.5% (0.004–0.005; 5–6 mmol/mol Hgb) and an average weight loss of 1.5 kg (3.3 lb).[9] Hypoglycemia, nausea, and vomiting are the most common side effects encountered with pramlintide therapy, although pramlintide itself does not produce hypoglycemia. To decrease risk of hypoglycemia, doses of short-acting, rapid-acting, or premixed insulins should be reduced by 30% to 50% before pramlintide is initiated. Primarily, the kidneys metabolize pramlintide, but dosage adjustments in liver or kidney impairment are not required.

Pramlintide has the potential to delay the absorption of orally administered medications. When rapid absorption is needed for the efficacy of an agent, pramlintide should be administered 1 hour after or 3 hours before the drug. Pramlintide should not be used in patients receiving medications that alter GI motility. A disposable pen formulation is now on the market and available as SymlinPen 60 for patients with T1DM and SymlinPen 120 for T2DM.

Treatment of Concomitant Conditions

The ADA standards of medical care address many of the common comorbid conditions, as well as complications that result from the progression of DM.

▶ *Cardiovascular Health*

Cardiovascular disease is the major cause of morbidity and mortality for patients with DM. Interventions targeting smoking cessation, BP control, lipid management, antiplatelet therapy, and lifestyle changes (including diet and exercise) can reduce the risk of cardiovascular events and should be considered as important as glycemic control in the management of a patient with DM. All patients with a history of cardiovascular disease should be prescribed aspirin 75 to 162 mg/day as a secondary prevention strategy.[7] Clopidogrel is an option for patients with atherosclerosis who are allergic to aspirin. The ADA currently recommends that antiplatelet therapy should be considered for patients with DM and no history of heart disease if that patient is 50 years of age or older and has at least one additional cardiovascular risk factor including family history of premature atherosclerotic cardiovascular disease (ASCVD), hypertension, dyslipidemia, smoking, or albuminuria.

The results of a number of trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD),[38] Action in Diabetes and Vascular Disease (ADVANCE),[39] and Veterans Affairs Diabetes Trial (VADT)[40] taken together with long-term follow-up information from the UKPDS[41] and DCCT[42,43] trials, have been used to formulate conclusions regarding the effect of glucose lowering on cardiovascular health. Those conclusions are: (1) short-term (3–5 years) intensive glycemic control does not improve the risk of macrovascular complications in patients with long-standing T2DM; and (2) a decrease in macrovascular risk from improved glycemic control may take more than a decade to be realized. Because of the results of these trials, the A_{1c} goal used for most patients with T2DM is less than 7% (0.07; 53 mmol/mol Hgb), whereas a goal of less than or equal to 6.5% (0.065; 48 mmol/mol Hgb) may be used for otherwise healthy individuals without cardiovascular disease who are thought to be early in the course of their DM and controlled with lifestyle or metformin only and who have a long life expectancy.[7,19] A more relaxed target of less than 8% (0.08; 64 mmol/mol Hgb) may be employed for those who are older, have numerous medical conditions limiting life expectancy, are at increased risk for hypoglycemia, or have had T2DM for a long period of time.

▶ *Dyslipidemia*

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults recommends statin therapy be considered if a patient falls into one of four statin benefit groups.[44] The ADA guidelines incorporate these statin benefit groups in their recommendations in the following manner:[7]

1. Patients with diabetes and atherosclerosis are recommended to receive high-intensity statin.
2. Patients with diabetes who are less than 40 years old but who have other ASCVD risk factors are recommended to receive moderate- or high-intensity statin.
3. Patients with diabetes aged 40–75 years who have no other ASCVD risk factors are recommended to receive moderate-intensity statin.
4. Patients with diabetes aged 40–75 years who have other ASCVD risk factors are recommended to receive high-intensity statin.
5. Patients with diabetes over 75 years without other ASCVD risk factors are recommended to receive moderate-intensity statin.
6. Patients with diabetes over 75 years with other ASCVD risk factors are recommended to receive moderate- to high-intensity statin.

Refer to Chapter 12, Dyslipidemias, for additional information.

▶ *Hypertension*

KEY CONCEPT Uncontrolled BP plays a major role in the development of macrovascular events and microvascular complications, including retinopathy, nephropathy, and erectile dysfunction, in patients with DM. The 2017 ACC/AHA High Blood Pressure Clinical Practice Guideline recommends patients with diabetes be started on antihypertensive drug therapy at a BP of 130/80 mm Hg.[45] A goal of less than 130/80 mm Hg is recommended. Various first-line antihypertensive agents can be utilized in patients with diabetes included diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers. However, when albuminuria is present, ACE inhibitors or ARBs are recommended because of their beneficial effects on renal

LO 4

function. Most patients will require more than one agent to reach BP goal. Renal function and serum potassium levels should be monitored closely in all patients taking an ACE inhibitor, ARB, and/or diuretic. ACE inhibitors and ARBs are contraindicated in patients who are pregnant and in those with bilateral renal artery stenosis.

▶ *Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS)*

Patients with HIV are known to be at increased risk for DM.[46] The cause of this increased risk is likely multifactorial with the disease itself playing a role (HIV-related increases in pro-inflammatory cytokines and free fatty acids) as well as typical concomitant disease states (obesity) and adverse effects of antiretroviral therapy used to combat HIV. Protease inhibitors like indinavir increase insulin resistance and decrease insulin secretion. Nucleoside reverse transcriptase inhibitors like stavudine cause lipohypertrophy which is associated with insulin resistance.[7] The ADA currently recommends that patients with HIV undergo screening for DM with an FBG every 6 to 12 months when not receiving antiretroviral therapy and then 3 months after starting or changing antiretroviral therapy.[7] Patients found to have normal FBG on screening should be retested annually. Those found to have prediabetes should be monitored every 3 to 6 months. Use of A_{1c} is not recommended as it is known to underestimate glycemia in patients with HIV. Management of DM in HIV patients includes weight loss through physical activity and nutrition, oral therapy (paying careful attention to drug interactions) or insulin, and even consideration of change in antiretroviral therapy away from the causative agent, though virological control must also be carefully weighed as part of that potential plan.

Patient Encounter Part 2: Follow-Up Visit

The patient returns 8 days later with results from his fasting blood work. The provider also requests an FBG, A_{1c}, and vitals at today's visit. The results are listed below.

VS: BP 148/76 mm Hg, P 70 beats/min, RR 19 breaths/min, T 38°C (100°F)

A_{1c} (today): 8.2% (0.082; 66 mmol/mol Hgb)

FPG (today): 189 mg/dL (10.5 mmol/L)

Labs (2 days ago): Na 136 mEq/L (mmol/L); K 3.6 mEq/L (mmol/L); Cl 98 mEq/L (mmol/L); CO_2 24 mEq/L (mmol/L); BUN 15 mg/dL (5.4 mmol/L); SCr 0.9 mg/dL (80 µmol/L); BG 172 mg/dL (9.5 mmol/L)

The patient is diagnosed with T2DM.

Identify the goals of treatment for this patient.

What nonpharmacologic alternatives are available for this patient for his diabetes?

What are the three general categories of pharmacologic alternatives used to lower blood glucose?

What is the most appropriate initial therapy for this patient in regards to his diabetes?

What additional interventions are recommended for this patient today?

▶ *Antipsychotic Drug Therapy*

An association has been recognized between second-generation antipsychotics and the development of diabetes. Risk seems to be highest with clozapine and olanzapine. The ADA recommends that patients prescribed atypical antipsychotics be screened annually for DM.[7] If a second generation antipsychotic is prescribed, weight, glycemic control, and cholesterol should be carefully monitored.

Treatment of Acute Complications

▶ *Hypoglycemia*

LO 8 Hypoglycemia, or low blood sugar, can be defined by the glucose alert value of less than or equal to 70 mg/dL (3.9 mmol/L).[7,47] Individuals with DM can experience symptoms of hypoglycemia at varying BG levels. Those with uncontrolled glucose can experience pseudohypoglycemia which is when symptoms of hypoglycemia occur even at normal glucose levels. Those with recent low BG levels may have no symptoms even at glucose values below the hypoglycemia threshold, and therefore patients with recurrent hypoglycemia may benefit from a period of more relaxed glycemic targets.[7] LO 8 Typical symptoms of hypoglycemia include shakiness, sweating, fatigue, hunger, headaches, and confusion.

Common causes of hypoglycemia include delayed or inadequate amounts of food intake, especially carbohydrates, excessive doses of medications (eg, sulfonylureas, insulin), exercising when insulin doses are reaching peak effect, or inadequately adjusted drug therapy in patients with impaired renal or hepatic function. LO 8 Patients experiencing symptoms of hypoglycemia should check their BG level, consume 15 g of carbohydrate, wait 15 minutes for symptom resolution, and retest.[47] Examples of 15 g of carbohydrate may include a small box of raisins, 4 oz (~120 mL) of orange juice, 8 oz (~240 mL) of skim milk, or three to four glucose tablets. In patients receiving an α-glucosidase inhibitor in combination with a sulfonylurea or insulin, hypoglycemia should be treated with glucose tablets or skim milk owing to the mechanism of action of the α-glucosidase inhibitors. For patients with hypoglycemia experiencing a loss of consciousness, a glucagon emergency kit should be administered by the intramuscular (IM) or subcutaneous route. It is important to contact emergency medical personnel in this particular situation. The patient should be rolled onto his or her side to prevent aspiration because many patients receiving the glucagon injection may vomit.

▶ *Diabetic Ketoacidosis (DKA)*

LO 9 DKA is a reversible but potentially life-threatening medical emergency that results from a relative or absolute deficiency in insulin. Without insulin, the body cannot use glucose as an energy source and must obtain energy via lipolysis. This process produces ketones and leads to acidosis. Although DKA occurs frequently in young patients with T1DM on initial presentation, it can occur in adults as well. Often, precipitating factors such as infection, omission, or inadequate administration of insulin can cause DKA. Signs and symptoms develop rapidly within 1 day or so and commonly include fruity or acetone breath; nausea; vomiting; dehydration; polydipsia; polyuria; and deep, rapid breathing.

LO 9 Hallmark diagnostic criteria for DKA include hyperglycemia (> 250 mg/dL [13.9 mmol/L]), ketosis (anion gap > 12 mEq/L [mmol/L]), and acidosis (arterial pH ≤ 7.3).[48] Typical fluid deficit is 5 to 7 L or more, and major deficits of serum sodium and potassium are common.

DKA severity depends on the magnitude of the decrease in arterial pH, serum bicarbonate levels, and mental state rather than the magnitude of hyperglycemia. Treatment goals of DKA consist of reversing the underlying metabolic abnormalities, rehydrating the patient, and normalizing serum glucose. Fluid replacement with normal saline at 1 to 1.5 L/hour for the first hour is recommended to rehydrate the patient and ensure the kidneys are perfused.

LO 9

Potassium and other electrolytes are supplemented as indicated by laboratory assessment. The use of sodium bicarbonate in DKA is controversial and generally only recommended when the pH is less than 7. Regular insulin at 0.1 unit/kg/hour by continuous IV infusion is the preferred treatment in DKA to regain metabolic control rapidly. When plasma glucose values drop below 250 mg/dL (13.9 mmol/L), dextrose 5% should be added to IV fluids. During the recovery period, it is recommended to continue administering insulin and allow patients to eat as soon as possible. Dietary carbohydrates combined with insulin assist in the clearance of ketones. See Table 43–12 for DKA management.[48]

LO 9

▶ *Hyperosmolar Hyperglycemic State (HHS)*

HHS is a life-threatening condition similar to DKA that also arises from inadequate insulin, but HHS occurs primarily in older patients with T2DM. DKA and HHS also differ in that HHS lacks the ketonemia and acidosis associated with DKA. Patients with hyperglycemia and dehydration lasting several days to weeks are at greatest risk of developing HHS. Infection, silent myocardial infarction, cerebrovascular accident, mesenteric ischemia, acute pancreatitis, and use of medications that affect carbohydrate metabolism including steroids and thiazide diuretics are known precipitating causes of HHS. Two main diagnostic criteria for HHS are a plasma glucose value of greater than 600 mg/dL (33.3 mmol/L) and a serum osmolality of greater than 320 mOsm/kg (mmol/kg).[48] The extreme hyperglycemia and large fluid deficits resulting from osmotic diuresis are major challenges to overcome with this condition. Similar to DKA, the treatment of HHS consists of aggressive rehydration, correction of electrolyte imbalances, and continuous insulin infusion to normalize serum glucose. BG levels should be reduced gradually to minimize risk of cerebral edema.

Table 43–12

Management of Diabetic Ketoacidosis[50]

1. Confirm diagnosis (increased plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive care setting may be necessary for frequent monitoring or if pH < 7 or unconscious.
3. Assess serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate), acid–base status—pH, HCO_3^-, PCO_2, β-hydroxybutyrate, and renal function (creatinine, urine output).
4. Replace fluids: 0.9% saline 1 L/hour over first 1–3 hours; subsequently, 0.45% saline at 4–14 mL/kg/hour; change to 5% dextrose with 0.45% saline when plasma glucose reaches 250 mg/dL (13.9 mmol/L).
5. Administer regular insulin: IV (0.15 U/kg bolus followed by 0.1 unit/kg/hour infusion); check glucose hourly and double insulin infusion until glucose level falls at steady hourly rate of 50–70 mg/dL (2.8–3.9 mmol/L). Alternatively, could use SC or IM routes, although dosing regimen different. If initial serum potassium is < 3.3 mEq/L (mmol/L), do not administer insulin until the potassium is corrected to > 3.3 mEq/L (mmol/L).
6. Assess patient: What precipitated the episode (eg, nonadherence, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, chest x-ray, ECG).
7. Measure chemistry (especially K^+, bicarbonate, phosphate, and anion gap) every 2–4 hours until stable.
8. Replace K^+: If K^+ is < 3.3 mEq/L (mmol/L), hold insulin and give 40 mEq (mmol) of K^+ per liter of IV fluid. If K^+ is > 5 mEq/L (mmol/L), do not give K^+ but check level every 2 hours. When K^+ > 3.3 mEq/L (mmol/L) but < 5 mEq/L (mmol/L), ECG normal, urine flow and normal creatinine documented, administer 20–30 mEq/L (mmol/L) of IV fluid to maintain K^+ at 4–5 mEq/L (mmol/L).
9. Continue above until patient is stable, glucose goal is 150–250 mg/dL (8.3–13.9 mmol/L), and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 unit/kg/hour.
10. Administer intermediate- or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

Cl, chloride; ECG, electrocardiogram; HCO_3, serum bicarbonate; IM, intramuscular; IV, intravenous; K, potassium; Mg, magnesium; Na, sodium; PCO_2, partial pressure of carbon dioxide in the arterial blood; SC, subcutaneous.

Treatment of Long-Term Complications

▶ *Retinopathy*

Diabetic retinopathy occurs when the microvasculature that supplies blood to the retina becomes damaged. This damage permits leakage of blood components through the vessel walls. The ADA recommends that patients with T2DM receive a dilated eye examination at the time of diagnosis by an ophthalmologist or optometrist.[7] Examinations should begin within 5 years of diagnosis of T1DM. Once one or more normal examinations occur, the dilated eye examination is recommended to be repeated at least every 2 years. In patients with documented retinopathy, an annual dilated eye examination is recommended. Glucose and BP control are the best strategies for decreasing risk and slowing the progression of retinopathy.

▶ *Neuropathy*

KEY CONCEPT Peripheral neuropathy is a possible complication of DM. The most common types of peripheral neuropathy include chronic sensorimotor distal peripheral neuropathy, which can cause pain, tingling, and numbness in the feet and hands, and autonomic neuropathy, which can lead to hypotension, gastroparesis, sexual dysfunction, and autonomic failure in response to hypoglycemia.[7] Two drugs, pregabalin and duloxetine, have been approved for relief of distal peripheral neuropathy pain. A number of other drugs are also sometimes used including venlafaxine, gabapentin, carbamazepine, tramadol, topical capsaicin, and tricyclic antidepressants.

▶ *Microalbuminuria and Nephropathy*

DM is a leading contributor to end-stage renal disease. Early evidence of nephropathy is the presence of albumin in the urine. Therefore, as the disease progresses, larger amounts of protein spill into the urine. The ADA recommends urine protein tests annually in T2DM patients.[7] For patients with T1DM, annual urine protein testing should begin 5 years after the diagnosis of diabetes. The most common form of screening for protein in the urine is a random collection for measurement of the urine albumin-to-creatinine ratio. The desirable value

Patient Encounter Part 3: Follow-Up

The patient returns in 3 months for a follow-up visit. He brings his BG readings from the past week for review in addition to more fasting blood work. BG readings are in units of mg/dL (mmol/L). His most recent medication list is below. There are no changes to his health record from previous visits.

Allergies: Penicillin

Meds: Acetaminophen 500–1000 mg PRN headache; metformin 1000 mg by mouth twice daily

VS: BP 154/96 mm Hg, P 78 beats/min, RR 18 breaths/min, T 37°C (98.6°F)

Labs: Total cholesterol 240 mg/dL (6.21 mmol/L); HDL cholesterol 41 mg/dL (1.06 mmol/L); LDL cholesterol 163 mg/dL (4.22 mmol/L); TG 183 mg/dL (2.07 mmol/L); AST 28 U/L (0.47 µkat/L); ALT 31 U/L (0.52 µkat/L)

Day	FPG	PPG
Monday	118 (6.5)	168 (9.3)
Tuesday	122 (6.8)	187 (10.4)
Wednesday	134 (7.4)	140 (7.8)
Thursday	110 (6.1)	244 (13.5)
Friday	98 (5.4)	257 (14.3)
Saturday	128 (7.1)	297 (16.5)
Sunday	116 (6.4)	240 (13.3)

Are this patient's blood glucose levels within target? What pattern seems to be established?

Which classes of antidiabetic drugs act in a manner that would specifically correct the undesirable glucose pattern?

Based on the information available from this encounter and previous encounters, develop a care plan for this patient. The plan should include (a) identification and assessment of all drug-related needs and/or problems, (b) a detailed therapeutic plan to address each need and problem, and (c) monitoring parameters to assess safety and efficacy.

is less than 30 mcg of albumin per milligram of creatinine (3.4 mg/mmol creatinine). The terms **microalbuminuria** and macroalbuminuria are being replaced by the term "persistent albuminuria," with the level of albuminuria further defined as either being between 30 and less than 299 mcg of albumin per milligram of creatinine (3.4–33.8 mg/mmol creatinine; previously referred to as microalbuminuria) or greater than or equal to 300 mcg of albumin per milligram of creatinine (≥ 34 mg/mmol creatinine; previously known as macroalbuminuria).

Glycemic control and BP control are primary measures for the prevention of progression of nephropathy. ACE inhibitors and ARBs prevent progression of renal disease in patients with T2DM. Treatment of advanced nephropathy includes dialysis and kidney transplantation.

▶ *Foot Ulcers*

KEY CONCEPT Lower extremity amputations are one of the most feared and disabling sequelae of long-term uncontrolled DM. A foot ulcer is an open sore that develops and penetrates to the subcutaneous tissues. Complications of the feet develop primarily as a result of peripheral arterial disease (PAD), neuropathies, and foot deformations.

PAD causes ischemia to the lower limbs. This decreased blood flow deprives the tissues of oxygen and nutrients and impairs the ability of the immune system to function adequately. Symptoms of PAD include intermittent claudication, cold feet, pain at rest, and loss of hair on the feet and toes. Smoking cessation is the single most important treatment for PAD. In addition, exercising by walking to the point of pain and then resting until pain subsides and resuming can be a vital therapy to maintain or improve the symptoms of PAD. Pharmacologic intervention with antiplatelet therapy (aspirin 160–325 mg/day or clopidogrel 75 mg/day) is indicated in patients with PAD.[49] For those that remain symptomatic, cilostazol 100 mg twice daily may be useful to improve blood flow and reduce the symptoms of PAD.

Neuropathies play a large part in the development of foot ulcers. Loss of sensation in the feet allows trauma to go unnoticed. Autonomic neuropathy can cause changes in blood flow, perspiration, skin hydration, and possibly, bone composition of the foot. Motor neuropathy can lead to muscle atrophy, resulting in weakness and changes in the shape of the foot. To prevent foot complications, the ADA recommends daily visual examination of the feet and a foot check performed at every provider visit as well as a comprehensive foot evaluation each year.[7] Sensory testing with a 10-gauge monofilament can detect areas of neuropathy. Treatment consists of glycemic control, preventing infection, debriding dead tissues, applying dressings, treating edema, and limiting ambulation. Additionally, individuals with diabetes should wear properly fitted, cushioned footwear and padded socks. Table 43–13 provides a list of various microvascular and macrovascular complications as well as their signs and symptoms.

LO 10

▶ *Erectile Dysfunction*

Compared to men who do not have diabetes, men with DM are at two to three times greater risk of erectile dysfunction. Additionally, men with DM may experience this complication several years earlier than men who do not have DM. Improved BG control can minimize risk of erectile dysfunction. Refer to Chapter 51, Erectile Dysfunction, for further information.

Special Situations

▶ *Hospitalized Care*

Current recommendations call for critically ill patients to be started on IV insulin therapy at a threshold of 180 mg/dL (10.0 mmol/L).[7] A goal range of 140 to 180 mg/dL (7.8–10.0 mmol/L) is recommended for the majority of patients. More stringent goals may be considered for selected critically ill patients, but only if hypoglycemia can be avoided. Scheduled subcutaneous insulin regimens with basal, nutritional, and correction components are recommended for patients who are not critically ill. Patients who required insulin during hospitalization but had previously not used insulin will need education/training to successfully transition home.

▶ *Sick Days*

Patients should monitor their BG levels more frequently during sick days because it is common for illness to increase BG values.[50] Patients with T1DM should check their glucose and urine for ketones every 4 hours when sick. Patients with T2DM may also need to check for ketones when their BG levels are greater than 240 mg/dL (13.3 mmol/L). Patients should continue to take their medications while sick. T1DM patients may require additional insulin coverage, and some

Table 43–13

Macrovascular and Microvascular Complications Signs and Symptoms

	Complication	Signs and Symptoms
Macrovascular	Coronary heart disease	Stable or unstable angina pectoris, MI, or dysrhythmias; however, many patients have unrecognizable symptoms.
	PAD	Exertional leg pain that can progress to pain at rest and ischemic ulcers. Most cases are asymptomatic.
	Cerebrovascular disease/Stroke	Sudden onset of a focal neurologic deficit such as facial droop, hemiparesis, or isolated weakness of an arm or leg. Dizziness, slurred speech, gait difficulties, and visual loss may also occur.
Microvascular	Retinopathy	Minimal until advanced disease ensues with loss or blurring of vision.
	Nephropathy	Hypertension, which often coincides with the development of microalbuminuria (persistent proteinuria).
	Neuropathy	Numbness, tingling, burning, muscle pain/cramps/weakness that often gets worse at night.
	Foot Care (Neuropathy and/or PAD)	Calluses and corns, tinea pedis, hammertoes, bunions, cracking of skin of the feed and heels.

MI, myocardial infarction; PAD, peripheral arterial disease.

with T2DM who are currently on oral medication regimens may require insulin during an acute illness. Patients should be advised to maintain their normal caloric and carbohydrate intake while ill as well as to drink plenty of noncaloric beverages to avoid dehydration. When having difficulty eating a normal diet, patients may be advised to use nondiet beverages, sports drinks, broths, crackers, soups, and nondiet gelatins to provide normal caloric and carbohydrate intake and avoid hypoglycemia. With proper management, patients can decrease their chance of illness-induced hospitalization, particularly DKA and HHS.

OUTCOME EVALUATION

LO 10

- KEY CONCEPT The success of therapy for DM is measured by the ability of the patient to manage his or her disease appropriately between health care provider visits.
- Appropriate therapy necessitates adequate patient education about the disease, development of a meal plan to which patients can comply, and integration of a regular exercise program.
- Patient care plans should include a number of daily evaluations to be performed by the patient, such as examining the feet for any sores, cuts, or abrasions; checking the skin for dryness to prevent cracking and chafing; and monitoring BG values as directed. Weekly appraisals of weight and BP are also advised.
- Until A_{1c} levels are at goal, quarterly visits with the patient's primary health care provider are recommended. Table 43–6 summarizes the specific ADA goals for

Patient Encounter Part 4: Insulin Therapy

The patient returns to the office for his annual checkup. It has been 5 years since he was first diagnosed with diabetes. His updated information is below. His past medical and family histories are unchanged. He states that he has been adherent to medications and lifestyle changes. He complains that he has burning and tingling constantly in both of his feet.

SH: Prior history of smoking one half pack per day for 10 years, but quit 11 years ago; denies alcohol or illicit drug use

Allergies: Penicillin

Meds: Lisinopril 20 mg by mouth once daily; atorvastatin 20 mg by mouth once daily; acetaminophen 500–1000 mg PRN headache; metformin 1000 mg by mouth twice daily; liraglutide 1.2 mg subcutaneously once daily; multivitamin by mouth once daily

Meal History: Has been consuming approximately 30 to 45 g of carbohydrates per meal three times a day; saturated fat is limited to 12 g/day, and sodium is 2000 mg/day

Physical Activity: Was walking 4 or 5 days per week for 30 minutes at moderate intensity but has not done so recently due to tingling in feet

VS: BP 135/82 mm Hg, P 85 beats/min, RR 20 breaths/min, T 38°C (100°F), Ht 5'3" (160 cm), Wt 155 lb (70.5 kg)

Labs: Na 139 mEq/L (mmol/L); K 5 mEq/L (mmol/L); Cl 103 mEq/L (mmol/L); CO_2 23 mEq/L (mmol/L); BUN 16 mg/dL (5.7 mmol/L); SCr 0.9 mg/dL (80 µmol/L); FPG 180 mg/dL (10.0 mmol/L); A_{1c} 9.7% (0.097; 83 mmol/mol Hgb); AST 28 U/L (0.47 µkat/L); ALT 31 U/L (0.52 µkat/L)

Fasting lipid profile:

- Total cholesterol: 202 mg/dL (5.22 mmol/L)
- LDL cholesterol: 108 mg/dL (2.79 mmol/L)
- HDL cholesterol: 43 mg/dL (1.11 mmol/L)
- Triglycerides: 205 mg/dL (2.32 mmol/L)

What additional pharmacologic options are available for this patient to lower his blood glucose to goal?

Which insulin and starting dose would be most appropriate for this patient?

How could the number of daily injections be reduced for this patient given his current medication regimen after insulin is initiated?

What additional medications, screenings, labs, and/or referrals are recommended for the patient at this point?

What is an important lifestyle modification this patient still needs to make?

Patient Care Process

Collect Information:

- Perform medication history of prescription, over-the-counter, and herbal product use.
- Collect laboratory data including chemistry panel, A_{1c}, lipid panel, and albumin-to-creatinine ratio.
- Measure BP.
- Examine patient for development or progression of DM complications.
- Record SMBG, including FPG and postprandial levels.
- Interview patient to gather information related to quality-of-life measures such as physical, psychological, and social functioning and well-being.

Assess the Information:

- SMBG for glycemic control, including FPG and postprandial levels (see Table 43–6).
  - Are the BG values too high or low?
  - Are there specific times of day or specific days not within glucose goals?
  - Is hypoglycemia occurring?
- Review laboratory data for attainment of goals (see Table 43–6). What goals are not being met?
- Are there any medication problems, including presence of adverse drug reactions, drug allergies, and drug interactions?
  - Is the patient taking medications that may affect glucose control?
- If patient is already receiving treatment for DM, has he/she been adherent to recommended lifestyle modifications and drug therapies? Is the patient having difficulty affording their therapies?
- Assess patient for quality-of-life measures such as physical, psychological, and social functioning and well-being.

Develop a Care Plan:

- Recommend appropriate therapy and develop a plan to assess effectiveness (see Tables 43–7, 43–10, and 43–11, and Figures 43–2, 43–3, and 43–4).

Implement the Care Plan:

- Stress adherence to prescribed lifestyle and medication regimen.
  - Ensure patient has prescription coverage and/or is able to afford prescribed regimen and self-care.
- Provide education on diabetes, lifestyle modifications, appropriate monitoring, and drug therapy:
  - Causes of DM complications and how to prevent them.
  - How diet and exercise can affect diabetes.
  - How to perform SMBG and what to do with the results.
  - When to take medications and what to expect, including adverse effects.
  - What warning sign(s) should be reported to the provider.
- What tests or referrals to other health care team members are needed?

Follow-up: Monitor and Evaluate:

- Set follow-up for SMBG and tolerability/presence of adverse effects based on therapy chosen.
- Follow-up A_{1c} every 3 months until patient reaches goal, then every 6 months. See Table 43–6 for other monitoring parameters and frequency.
- Monitor for macrovascular and microvascular signs and symptoms (Table 43–13).

therapy. The practitioner should review SMBG data and a current A_{1c} level for progress and address any therapeutic or educational issues.

- At a minimum, yearly laboratory evaluation of serum lipids, urinary albumin to creatinine ratio, and SCr should be performed.
- Appropriate monitoring and treatment for DM complications should occur (Table 43–13).

Abbreviations Introduced in This Chapter

A_{1c}	Hemoglobin A_{1c}
AACE	American Association of Clinical Endocrinologists
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
ATP	Adenosine triphosphate
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
Cl	Chloride
CrCl	Creatinine clearance
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
GI	Gastrointestinal

GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
HDL	High-density lipoprotein
HHS	Hyperosmolar hyperglycemic state
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IM	Intramuscular
ISF	Interstitial fluid
IV	Intravenous
K	Potassium
LADA	Latent autoimmune diabetes in adults
LDL	Low-density lipoprotein
Mg	Magnesium
MNT	Medical nutrition therapy
Na	Sodium
NGSP	National Glycohemoglobin Standardization Program
NPH	Neutral protamine Hagedorn
OGTT	Oral glucose tolerance test
PAD	Peripheral arterial disease
PCO_2	partial pressure of carbon dioxide
PPAR-γ	Proxisome proliferator-activated receptor gamma
PPG	Postprandial glucose
SC	Subcutaneous
SCr	Serum creatinine
SGLT2	Sodium-dependent glucose cotransporter-2
SMBG	Self-monitoring of blood glucose
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TLC	Therapeutic lifestyle change
TZD	Thiazolidinedione
UKPDS	United Kingdom Prospective Diabetes Study
ULN	Upper limit of normal
UTI	Urinary tract infection
VADT	Veterans Affairs Diabetes Trial
WHO	World Health Organization

REFERENCES

1. National Diabetes Statistics Report, 2017. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Available from: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed August 31, 2017.
2. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS data brief, no 219. Hyattsville, MD: National Center for Health Statistics; 2015 Available from: https://www.cdc.gov/nchs/data/databriefs/db219.pdf. Accessed August 31, 2017.
3. Facts about physical activity. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Available from: https://www.cdc.gov/physicalactivity/data/facts.htm. Accessed August 31, 2017.
4. Chiang JL, Kirkman MS, Laffel LMB, et al. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. Diabetes Care. 2014;37:2034–2054.
5. Klinke DJ. Extent of beta cell destruction is important but insufficient to predict the onset of type 1 diabetes mellitus. PLoS One. 2008;3(1):e1374.
6. Tuomi T, Santoro N, Caprio S, Cai M, Weng J, Groop L. The many faces of diabetes: a disease with increasing heterogeneity. Lancet. 2014;383:1084–1094.
7. American Diabetes Association. Standards of medical care in diabetes—2017. Diabetes Care. 2017;40(suppl 1):S4–S135.
8. Diabetes insipidus. National Institutes of Diabetes and Digestive and Kidney Diseases, U.S. Department of Health and Human Services. Available from: https://www.niddk.nih.gov/health-information/kidney-disease/diabetes-insipidus. Accessed August 31, 2017.
9. Triplitt CL, Repas T, Alvarez CA. Diabetes mellitus. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:1139–1181.
10. Molina PE. Endocrine pancreas. In: Endocrine Physiology, 4th ed. New York: McGraw-Hill; 2013:163–186.
11. Powers AC, D'Alessio D. Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. In: Brunton L, Chabner B, Knollman B, eds. Goodman and Gillman's The Pharmacological Basis of Therapeutics, 12th ed. New York: McGraw Hill; 2011:1237–1274.
12. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care. 2009;32:S151-S156.
13. The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367:319–328.
14. Alberti K, Zimmet P, Shaw J. Metabolic syndrome—a new world–wide definition. A consensus statement from the international diabetes federation. Diabet Med. 2006,23:469–480.
15. Cernea S, Raz I. Therapy in the early stage: incretins. Diabetes Care. 2011;34(suppl 2):S264–S271.
16. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773–795.
17. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977–986.
18. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837–853.
19. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinology-clinical practice guidelines for developing diabetes mellitus comprehensive care plan-2015. Endocr Pract. 2015;21(suppl 1):1–87.
20. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm-2017 executive summary. Endocr Pract. 2017;23:207–227.
21. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015;38:140–149.
22. American College of Sports Medicine and American Diabetes Association. Exercise and type 2 diabetes. Med Sci Sports Exerc. 2010;42:2282–2303.
23. Lindstrom J, Ilanne-Parikka P, Peltonen M, et al.; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006;368:1673–1679.
24. Lexicomp Online, Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.; 2017; September 5, 2017.
25. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854–865.
26. Nathan DM, Buse JB, Davidson MG, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm

for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:193–203.
27. Nissen SE, Wolski K. The effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Eng J Med. 2007;356:1–15.
28. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373:2125–2135.
29. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of vascular events in patients with type 2 diabetes in the PROactive study prospective pioglitazone clinical trial in macrovascular events: a randomized controlled trial. Lancet. 2005;366:1279–1289.
30. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128.
31. Neal B, Perkovic V, Wahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–657.
32. Facts & Comparisons eAnswers, Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.; 2017; September 6, 2017.
33. Humulin R U-500 KwikPen [package insert]. Indianapolis, IN: Eli Lilly and Company; 2016.
34. Eliaschewitz G, Barreto T. Concepts and clinical use of ultra-long basal insulin. Diabetol Metab Syndr. 2016;8:2.
35. Trujillo JM, Nuffer W, Ellis SL. GLP-1 receptor agonists: a review of head-to-head clinical studies. Ther Adv Endocrinol Metab. 2015;6:19–28.
36. Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly results in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. J Clin Endocrinol Metab. 2011;96:1301–1310.
37. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–322.
38. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–2559.
39. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–2572.
40. Duckworth W, Abraira C, Mortiz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:1–11.
41. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–1589.
42. EDIC Writing Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on developments and progression of diabetic neuropathy: the Epidemiology of Diabetes Interventions and Complications Study. JAMA. 2003;290;2159–2167.
43. DCCT/EDIC Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643–2653.
44. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation. 2014;129:S1–S45.
45. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017 Nov 13. [Epub ahead of print.]
46. Monroe AK, Glesby MJ, Brown TT. Diagnosing and managing diabetes in HIV-infected patients: current concepts. Clin Infect Dis. 2015;60:453–462.
47. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36:1384–1395.
48. Kitabachi AE, Upierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 2009;32:1335–1343.
49. Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(suppl 2):e669S–e690S.
50. When you're sick. American Diabetes Association. Available from: http://www.diabetes.org/living-with-diabetes/treatment-and-care/whos-on-your-health-care-team/when-youre-sick.html. Accessed September 7, 2017.

44 Thyroid Disorders

Michael D. Katz

LEARNING OBJECTIVES

LO

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

1. Discuss the prevalence of common thyroid disorders, including mild and overt hypothyroidism and hyperthyroidism.
2. Explain the major components of the hypothalamic–pituitary–thyroid axis and interaction among these components.
3. Discuss the relationship between serum thyroid-stimulating hormone (TSH) levels and primary thyroid disease, and the advantages for use of TSH levels over other tests such as serum T_4 (thyroxine) and T_3 (triiodothyronine) levels.
4. Identify typical signs and symptoms of hypothyroidism and the consequences of suboptimal treatment.
5. Describe clinical use of levothyroxine (LT_4) in the treatment of hypothyroidism.
6. Discuss the issues regarding LT_4 product bioequivalence and reasons for maintaining patients on the same product.
7. Describe the management of hypothyroidism and hyperthyroidism in pregnant women.
8. Identify typical signs and symptoms of Graves disease and consequences of inadequate treatment.
9. Discuss the pharmacotherapy of Graves disease, including advantages and disadvantages of antithyroid drugs versus radioactive iodine, adverse effects, and patient monitoring.
10. Describe the potential effects of selected drugs, including amiodarone, lithium, interferon-α, and tyrosine kinase inhibitors (TKIs) on thyroid function.

INTRODUCTION

Thyroid disorders are common. More than 2 billion people, or 38% of the world's population, have iodine deficiency, resulting in 74 million people with **goiter**. Although overt iodine deficiency is not a significant problem in developed countries, a number of common thyroid conditions exist. The most common are hypothyroidism and hyperthyroidism, which often require long-term pharmacotherapy. Undetected or improperly treated thyroid disease can result in long-term adverse sequelae, including increased mortality. It is important that clinicians are aware of the prevalence of thyroid disorders, methods of identifying thyroid disorders, and appropriate therapy. This chapter focuses on the most common pharmacologically treated thyroid disorders.

EPIDEMIOLOGY

LO 1

Among 4392 people 12 years of age and older in a sample representing the geographic and ethnic distribution of the US population, hypothyroidism was found in 3.7% (3.4% mild) and hyperthyroidism in 0.5%.[1] The prevalence of hypothyroidism correlated with age and was higher in older age groups, whites, and Hispanics, but was lower in blacks. Compared with the total population, people aged 50 to 79 years had an almost twofold higher prevalence, and those aged 80 years and older had a fivefold higher prevalence. Pregnant women also had a higher prevalence of hypothyroidism than nonpregnant women across all races and ethnicities. The Colorado Thyroid Health Survey assessed thyroid function in 25,862 subjects attending a health fair.[2] Overall prevalence of an abnormal thyroid-stimulating hormone (TSH; thyrotropin) level was 11.7% of the study population, with 9.4% hypothyroid (9% subclinical) and 2.2% hyperthyroid (2.1% subclinical). Of the 916 subjects taking thyroid medication, 60% were euthyroid (had normal thyroid function or hormone activity), with an equal distribution between subclinical hypothyroidism and hyperthyroidism. The National Health and Nutrition Examination Survey (NHANES) study also found that many patients receiving thyroid medications had an abnormal TSH level. These findings imply that many patients who are receiving thyroid medications are not being managed successfully.

PATHOPHYSIOLOGY

The thyroid gland is the largest endocrine gland in the body, residing in the neck anterior to the trachea between the cricoid cartilage and suprasternal notch. The thyroid gland produces two biologically active hormones, thyroxine (T_4) and triiodothyronine (T_3). Thyroid hormones are essential for proper fetal growth and development, particularly of the central nervous system (CNS). After delivery, the primary role of thyroid hormone is in regulation of energy metabolism. These hormones can affect the function of virtually every organ in the body. The parafollicular C cells of the thyroid gland produce **calcitonin**.

T_4 and T_3 are produced by the **organification** of iodine in the thyroid gland. Iodine is actively transported into the thyroid follicular cells. This inorganic iodine is oxidized by **thyroid peroxidase** and covalently bound to tyrosine residues of **thyroglobulin**. These iodinated tyrosine residues, monoiodotyrosine and diiodotyrosine, couple to form T_4 and T_3. Eighty percent of thyroid hormone is synthesized as T_4 and is stored in the thyroid bound to thyroglobulin. Thyroid hormones are released from the gland when needed, primarily under the influence of TSH (thyrotropin from the anterior pituitary). T_4 and T_3 are transported in the blood by three proteins, 70% bound to thyroid-binding globulin (TBG), 15% to transthyretin (thyroid-binding prealbumin), and 15% to albumin. T_4 is 99.97% protein bound, and T_3 is 99.7% protein bound, with only the unbound or free fractions physiologically active. The high degree of protein binding results in a long half-life of these hormones: approximately 7 to 10 days for T_4 and 24 hours for T_3.

Most of the physiologic activity of thyroid hormones is from the actions of T_3. T_4 can be thought of primarily as a prohormone. Eighty percent of needed T_3 is derived from conversion of T_4 to T_3 in peripheral tissue under the influence of tissue deiodinases. These deiodinases allow end organs to produce the amount of T_3 needed to control local metabolic functions. These enzymes also catabolize T_3 and T_4 to biologically inactive metabolites.

LO 2

KEY CONCEPT The production and release of thyroid hormones are regulated by the hypothalamic–pituitary–thyroid axis (Figure 44–1). Hypothalamic thyrotropin-releasing hormone (TRH) stimulates the release of TSH when there are physiologically inadequate levels of thyroid hormones. TSH promotes production and release of thyroid hormones. As circulating thyroid hormone levels rise to needed levels, negative feedback results in decreased release of TSH and TRH. Release of TRH is also inhibited by somatostatin and its analogs, and release of TSH can also be inhibited by dopamine, dopamine agonists, and high levels of glucocorticoids.

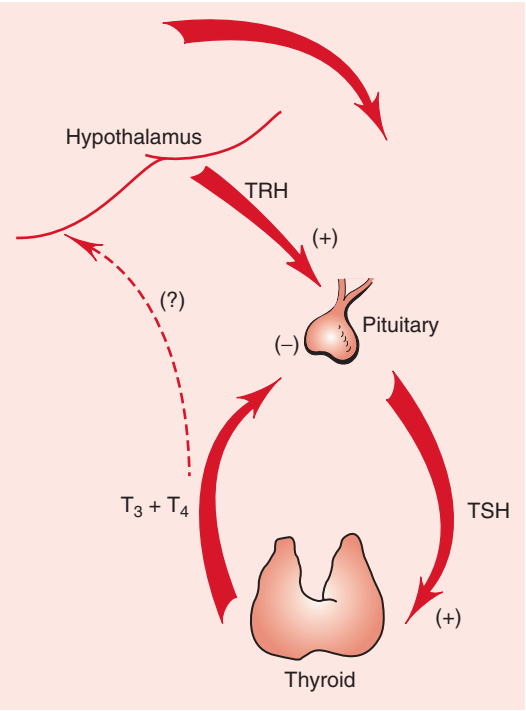

FIGURE 44–1. Hypothalamic–pituitary–thyroid axis. Thyrotropin-releasing hormone (TRH) is synthesized in the neurons within the paraventricular nucleus of the hypothalamus. TRH is released into the hypothalamic–pituitary portal circulation and carried to the pituitary, where it activates the pituitary to synthesize and release thyrotropin (TSH). TSH activates the thyroid to stimulate the synthesis and secretion of thyroxine (T_4) and triiodothyronine (T_3). T_4 and T_3 inhibit TSH secretion, closing the feedback loop. Negative feedback from T_4 and T_3 to hypothalamic TRH is less certain, hence the question mark.

SPECTRUM OF THYROID DISEASE

There are two general modes of presentation for thyroid disorders: changes in the size or shape of the gland and changes in secretion of hormone from the gland. In some cases, structural changes can result in changes in hormone secretion. Thyroid nodules and goiters in euthyroid patients are common problems. Patients with a goiter who are biochemically euthyroid often require no specific pharmacotherapy unless the goiter is caused by iodine deficiency. In developing countries, iodized salt is the primary therapy in treating goiter. Thyroid nodules, seen in 4% to 7% of adults, may be malignant or may autonomously secrete thyroid hormones. A discussion of thyroid nodules is beyond the scope of this chapter; however, thyroid cancer is discussed briefly in the context of levothyroxine (LT_4) suppressive therapy. Refer to other resources for a more extensive review of thyroid cancer management.

Changes in hormone secretion, often due to an underlying inflammatory disorder (thyroiditis), can result in hormone deficiency or excess. Although patients with overt hypothyroidism and hyperthyroidism may have dramatic signs and symptoms, most patients have subtle signs and symptoms that progress slowly over time. Availability of sensitive and specific biomarkers for diagnosis of thyroid hormone disorders has facilitated screening and earlier case-finding and diagnosis, including in those with mild or subclinical thyroid disorders. Screening of newborns for congenital hypothyroidism has reduced the incidence of mental retardation and neonatal hypothyroidism dramatically in the United States. However, congenital hypothyroidism owing to iodine deficiency remains a significant worldwide public health problem.

PATIENT ASSESSMENT AND MONITORING

Assessment of patients for thyroid disorders entails a history and physical examination. In many patients with mild or subclinical thyroid disease, there may be an absence of specific signs and symptoms, and physical examination findings may be normal. Various diagnostic tests can be used, including levels of serum thyroid hormone(s), TSH, thyroid antibody levels, and imaging techniques (Table 44–1). Laboratory assessment of patients with suspected thyroid disorders must be based on the continuum of disease from subclinical or mild to overt (Figure 44–2).

TSH Levels

KEY CONCEPT In most patients with thyroid hormone disorders, measurement of a serum TSH level is adequate for initial screening and diagnosis of hypothyroidism and hyperthyroidism. Serum free thyroxine (FT_4) and triiodothyronine (FT_3) levels may be helpful in distinguishing mild (subclinical) thyroid disease from overt disease. TSH for most patients being treated for thyroid disorders should be the mean normal value of 1.5 milli international units/L (mIU/L) or 1.5 micro international units/mL (μIU/mL) (target range, 0.5–4 mIU/L or μIU/mL), although patients must be individually titrated based on

Table 44–1

Selected Thyroid Tests for Adults

Test	Reference Range	Comments
TSH	0.5–4.5 mIU/L (μIU/mL)	Gold standard; may be lowered by dopamine, dopamine agonists, glucocorticoids, octreotide, recovery from severe nonthyroidal illness
FT_4	0.7–1.9 ng/dL (9.0–24.5 pmol/L)	May be normal in mild thyroid disease
Anti-TPOAb, Anti-TGAb	Variable[a]	Present in autoimmune hypothyroidism; predicts more rapid progression from subclinical to overt hypothyroidism
TSI (TSHR-SAb)	Undetectable	Confirms Graves disease

[a]Anti-TPOAb reference ranges are highly variable from one laboratory to another depending on the method used. Results greater than the upper cutoff are considered abnormal and are consistent with increased risk for autoimmune thyroid disease.

Anti-TPOAb, antithyroid peroxidase antibody; FT_4, free T_4 (thyroxine); Anti-TGAb, antithyroglobulin antibody; TSH, thyroid-stimulating hormone; TSHR-SAb, TSH receptor-stimulating antibodies; TSI, thyroid-stimulating immunoglobulin.

resolution of signs and symptoms as well as biochemical tests. Target TSH may be different in the elderly and in patients being treated with LT_4 for thyroid cancer.

TSH is a highly sensitive bioassay of the thyroid axis. A twofold change in serum-free T_4 levels will result in a 100-fold change in TSH levels. This biologic magnification by TSH allows it to be used in early diagnosis as well as in closely titrating therapy in hypothyroidism and hyperthyroidism. LO 3 In patients with primary hypothyroidism or hyperthyroidism resulting from gland dysfunction, there is an inverse relationship between the TSH level and thyroid function. High TSH signifies hypothyroidism (or iatrogenic underreplacement), and low TSH signifies hyperthyroidism (or iatrogenic overreplacement). There is controversy regarding the normal or laboratory reference ranges for TSH.[3] NHANES showed the mean TSH level in a normal population was 1.46 mIU/L (μIU/mL) (clinical laboratories use either unit of measurement, usually expressed as mIU/L or μIU/mL), but the values were not normally distributed. Although most laboratories quote the upper limit of normal for TSH between 4 and 5 mIU/L (μIU/mL), 95% of subjects had a TSH level of between 0.5 and 2.5 mIU/L (μIU/mL). The population of subjects whose TSH level was 2.5 to 4.5 mIU/L (μIU/mL) may have had mild hypothyroidism, or the non-normal distribution may reflect different normal ranges in a heterogeneous (age, sex, race) population. The mean normal TSH appears to be higher in the elderly with no clinical evidence of hypothyroidism,[3] and there is some evidence that normal TSH ranges are sex and ethnicity specific.[1] The target TSH for most patients being treated for thyroid disorders is not the same as the reference range. Ideally, TSH should be the mean normal value of 1.5 mIU/L (μIU/mL; target range, 0.5–4 mIU/L [μIU/mL]).[3] The upper limit of the target range may be higher in the elderly. Therapy may be titrated within the target TSH range to maximally improve patient signs and symptoms without causing adverse effects of overtreatment or undertreatment.

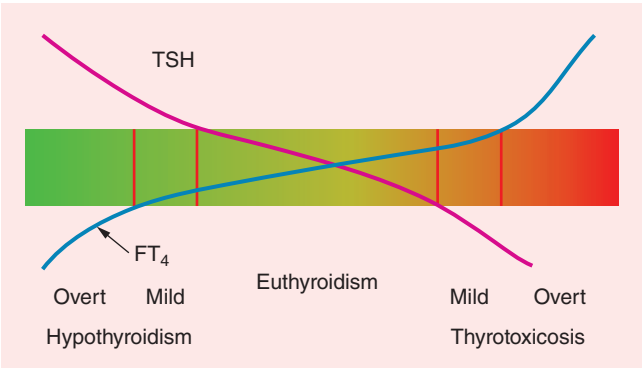

FIGURE 44–2. The continuum of thyroid disorders. (FT_4, free T_4 [thyroxine]; TSH, thyroid-stimulating hormone.)

Serum T_4 and T_3 Levels

Serum T_4 and T_3 levels are used commonly to assess thyroid function. LO 3 Older screening tests of thyroid function measure total serum T_4 or T_3 levels. Because of the high degree of protein binding of these hormones, the free fraction can be altered by changes in the levels of binding proteins or the degree of protein binding. Since a number of factors can alter protein binding, these older assays are very insensitive and should no longer be used. Free or unbound T_4 (FT_4) and T_3 (FT_3) assays are readily available and more sensitive in identifying thyroid dysfunction than older total assays.[3] However, patients with mild hypothyroidism or hyperthyroidism have normal FT_4 levels despite abnormal TSH levels.

Other Diagnostic Tests

Global tests of thyroid gland function can be performed to assess the rate of hormone synthesis. The radioactive iodine uptake (RAIU) is elevated in those with hyperthyroidism and can aid in identifying thyrotoxicosis owing to nonthyroid gland sources. Radionuclide thyroid scans are used in evaluation of thyroid nodules. Because many thyroid disorders are autoimmune, measurement of various serum antithyroid antibodies can be performed. Antithyroid peroxidase antibodies (anti-TPOAb) and antithyroglobulin antibodies (anti-TGAb) are present in many patients with hypothyroidism. Most patients with Graves disease have TSH receptor-stimulating antibodies (TSHR-SAb) as well as elevated anti-TPOAb and antimicrosomal antibodies.

HYPOTHYROIDISM

Hypothyroidism is the most common clinical disorder of thyroid function. It is the clinical syndrome that results from inadequate secretion of thyroid hormones from the thyroid gland. The vast majority of hypothyroid patients have primary gland failure, but occasional patients have pituitary or hypothalamic failure. Most studies define hypothyroidism based on a serum TSH level above the upper limit of the laboratory reference range. LO 1 In adults, 1.4% of women and 0.1% of men are biochemically hypothyroid. However, incidence is highly age dependent. In the Colorado Thyroid Health Study, by age 64 years, 12% of women and 5% of men were hypothyroid, and in the over 74 years age group, incidence in men approached that of women.[2] Most epidemiologic studies of hypothyroidism in the elderly show a prevalence of 6% to 12%.[3] There is a strong correlation between the presence of anti-TPOAb or anti-TGAb and the

risk of developing hypothyroidism. In patients with subclinical hypothyroidism, 2% to 6% per year will progress to overt hypothyroidism, with the risk of progression higher in women, those with higher TSH levels, those with higher levels of anti-TPOAbs and those with low-normal FT_4 levels.[4] Other risk factors for development of hypothyroidism include the postpartum state, family history of autoimmune thyroid disorders, a previous history of head and neck or thyroid surgery, head and neck irradiation, other autoimmune endocrine disorders such as type 1 diabetes and Addison disease, other nonendocrine autoimmune diseases such as celiac disease and pernicious anemia, history of treatment for hyperthyroidism, treatment with certain medications including amiodarone or lithium, and an iodine-deficient diet.[5]

Screening

Because prevalence of hypothyroidism is high in certain populations, screening may be useful. Screening for hypothyroidism in women older than age 35 years may be cost-effective, though some organizations recommend screening of adults after age 50 or 60 years.[6] Others advocate a case-finding approach, defined as performing a TSH determination in patients based on risk factors or presence of signs and symptoms.[3] However, there are no studies that assess the impact of screening for thyroid disease on morbidity and mortality.[7]

Causes

The most common causes of hypothyroidism are listed in Table 44–2.[3,8-11] Up to 90% of patients with autoimmune thyroiditis (Hashimoto disease) have circulating anti-TPOAbs. The autoimmune inflammatory response results in a lymphocytic infiltration of the thyroid gland and its eventual destruction.

Iatrogenic hypothyroidism can occur after thyroid irradiation or surgery and excessive doses of antithyroid drugs. Several drugs can cause hypothyroidism, including iodine-containing drugs such as amiodarone and iodinated radiocontrast media, lithium, interferon-α, multikinase and TKIs (imatinib, sunitinib, sorafenib), *p*-aminosalicylic acid, ethionamide, sulfonylureas, valproic acid and other antiepileptic drugs, and aminoglutethimide.[3,8,11] Iodine deficiency is a common worldwide cause of hypothyroidism, including congenital hypothyroidism in newborns. Patients with hypothalamic or pituitary disease often have other signs of pituitary disease, such as hypogonadism, and their TSH levels are low.

Signs and Symptoms

LO 4

Hypothyroidism can affect virtually any tissue or organ in the body. The most common symptoms, such as fatigue, lethargy, sleepiness, cold intolerance, and dry skin, are nonspecific and can be seen with many other disorders. The classic overt signs, such as myxedema and delayed deep tendon reflexes, are seen uncommonly now because more patients are screened or seek medical attention earlier. Patients with mild (also known as subclinical) hypothyroidism may have subtle symptoms that progress so slowly that they are not noticed easily by the patient or family. The lack of overt or specific signs and symptoms emphasizes the importance of using serum TSH level to identify patients with hypothyroidism.

Table 44–2

Common Causes of Hypothyroidism[3,8-11]

Primary Hypothyroidism
Autoimmune thyroiditis (Hashimoto disease)
Iatrogenic (irradiation, surgery)
Drugs (amiodarone, radiocontrast media, lithium, interferon-α, tyrosine kinase inhibitors, alemtuzumab)
Silent thyroiditis (including postpartum)
Iodine deficiency and excess
Secondary Hypothyroidism
Pituitary disease
Hypothalamic disease

Clinical Presentation and Diagnosis of Hypothyroidism[3,5,8-10]

Symptoms

Fatigue	Cold intolerance
Lethargy	Hoarseness
Sleepiness	Dry skin
Mental impairment	Decreased perspiration
Depression	Decreased appetite
Weight gain	Constipation
Menstrual disturbances	Arthralgia
Paresthesia	

Signs

Slow movements	Dry skin
Goiter	Weight gain
Slow speech	Nonpitting edema (myxedema)
Hoarseness	Hyporeflexia
Bradycardia	Delayed relaxation of reflexes

Screening/Diagnosis

- TSH level of 4.5 to 10 mIU/L (μIU/mL) may constitute mild or subclinical hypothyroidism.
- TSH level greater than 10 mIU/L (μIU/mL) signifies overt hypothyroidism.
- FT_4 level will be normal (0.7–1.9 ng/dL or 9.0–24.5 pmol/L) in mild or subclinical hypothyroidism and low (< 0.7 ng/dL or 9.0 pmol/L) in patients with obvious signs and/or symptoms.

Mild (Subclinical) Hypothyroidism

Mild or subclinical hypothyroidism is present when a patient has a TSH above the upper limit of the laboratory reference range but usually below 10 mIU/L (μIU/mL), normal FT_4, and no overt hypothyroid signs and symptoms.[4,5,9,10] Many of these patients have autoimmune thyroiditis and anti-TPOAbs and some will progress to overt hypothyroidism. Although patients may not express the typical symptoms of hypothyroidism, many patients do have mild, nonspecific symptoms (eg, fatigue, cold intolerance, constipation). Recent studies have shown subclinical hypothyroidism to be a risk factor for cardiovascular mortality and to be associated with decreased myocardial contractility, decreased exercise tolerance, elevated low-density lipoprotein (LDL) cholesterol, and neuropsychiatric symptoms.[4,12-14]

Sequelae of Hypothyroidism

Hypothyroidism is a chronic disease that may result in significant long-term sequelae. Hypercholesterolemia is associated with hypothyroidism, increasing the long-term risk of cardiovascular disease and cardiovascular mortality. Between 4% and 14% of patients with hypercholesterolemia are found to be hypothyroid. The Colorado Thyroid Health Study showed a direct correlation between degree of TSH elevation and rise in serum cholesterol.[2]

Hypothyroidism also may result in increased systemic vascular resistance, decreased cardiac output, and increased diastolic blood pressure. Hypothyroidism can cause significant neuropsychiatric problems, including a dementia-like state in the elderly that is reversible with LT_4 therapy. Maternal hypothyroidism can have dire consequences for developing fetuses. Fetuses are almost completely dependent on maternal thyroid hormones during the first trimester, a time crucial for development of the CNS. Inadequately treated maternal hypothyroidism results in increased risk of miscarriage and developmental impairment in the child.[3,15]

Myxedema coma is seen in advanced hypothyroidism. These patients develop CNS depression, respiratory depression, cardiovascular instability, and fluid and electrolyte disturbances. Myxedema coma often is triggered by an underlying acute medical condition such as infection, stroke, trauma, or administration of CNS depressant drugs.

Treatment

▶ *Desired Outcomes*

KEY CONCEPT There are three major goals in the treatment of hypothyroidism: replace the missing hormones, relieve signs and symptoms, and achieve a stable biochemical euthyroid state. Although these goals should not be difficult to achieve, 20% to 40% of treated patients are not receiving optimal pharmacotherapy.

▶ *Thyroid Hormone Products*

A number of thyroid hormone products are marketed in the United States (Table 44–3). These products include synthetic LT_4 and T_3, combinations of synthetic LT_4 and T_3, and animal-derived products. KEY CONCEPT Despite the availability of a wide array of thyroid hormone products, it is clear that synthetic LT_4 is the treatment of choice for almost all patients with hypothyroidism.[3,8,10,15] LT_4 mimics the normal physiology of the thyroid gland, which secretes mostly T_4 as a prohormone. Peripheral tissues convert T_4 to T_3 as needed based on metabolic demands. If T_3 is used to treat hypothyroidism, the peripheral tissues lose their ability to control local metabolic rates. LT_4 also has distinct pharmacokinetic advantages over T_3. With a 7- to 10-day half-life, LT_4 provides a very smooth dose-response curve with little peak and trough effect. In a small number of patients who have impairment of conversion of T_4 to T_3, addition of T_3 may be warranted. T_3, with a 24-hour half-life, provides a significant peak and trough effect, and many patients have symptoms of thyrotoxicosis after each dose is administered. The use of compounded T_3 or other thyroid hormone products not approved by the Food and Drug Administration (FDA) or dietary supplements marketed for "thyroid health" should be strongly discouraged.[15] For patients who have difficulty adhering to a once-daily regimen, a once-weekly LT_4 regimen is safe and effective.[3,15]

LOS

Animal-derived products such as desiccated thyroid are obtained from pig or cow thyroid and have various degrees of purity. These products contain both LT_4 and T_3, but the amount of T_3 is much higher (T_4:T_3 = 4:1) than what would be found in the human thyroid gland (T_4:T_3 = 14:1). Although some patients want to use desiccated thyroid extract because it is "natural," the products are in no way natural for humans. With strong evidence supporting the safety and efficacy of LT_4 in the treatment of hypothyroidism, there is no rationale for the use of these animal-derived products, and no evidence that desiccated thyroid extract has any benefits over synthetic LT_4.[16] Patients who are treated with these agents should be strongly encouraged to switch to synthetic LT_4. Additionally, patients should be encouraged to not purchase thyroid hormone- or iodine-containing products from health food stores or Internet sites.

Several studies have been published that evaluate use of LT_4 and T_3 combinations in ratios that mimic human physiology. A large number of clinical trials and meta-analyses of studies comparing LT_4 and T_3 combinations with LT_4 monotherapy show no outcome benefit with combination therapy.[15] Except in rare circumstances (eg, patients with impaired T_4-to-T_3 conversion as evidenced by adequate LT_4 dose, continued symptoms and low FT_3 level), there is no rationale for the routine use of LT_4 and T_3 combinations.

Table 44–3

Thyroid Preparations

Drug (Brand Name)	Content	Relative Dose	Comments
Levothyroxine, (Synthroid, Levoxyl, Unithroid), other brands, and generics	Synthetic LT_4; 25-, 50-, 75-, 88-, 100-, 112-, 125-, 137-, 150-, 175-, 200-, and 300-mcg tablets; 100-, 200-, and 500-mcg vial for injection	60 mcg	Gold standard for treating hypothyroidism; products not therapeutically equivalent; full replacement dose, 1–1.6 mcg/kg/day; when switching from animal product, lower calculated daily dose by 25–50 mcg; IV form rarely needed
Liothyronine (Cytomel)	Synthetic T_3; 5-, 25-, and 50-mcg tablets	15 mcg	Rarely needed in treatment of hypothyroidism; rapid absorption and pharmacologic effect; increased toxicity versus LT_4; no outcome benefit to combining with LT_4
Thyroid (desiccated) USP (Armour, others)	Desiccated pork thyroid glands; contains T_3 and T_4; 15-, 16.25-, 30-, 32.5-, 48.75-, 60-, 65-, 90-, 97.5-, 120-, 130-, 162.5-, 180-, 195-, 240-, 260-, 300-, and 325-mg tablets	65 mg	Nonphysiologic T_4:T_3 ratio; T_3 content may cause toxicity; no advantage over LT_4 monotherapy; no role in modern therapy
Liotrix (Thyrolar)	Synthetic T_4, T_3 in fixed 4:1 ratio; ¼-, ½-, 1-, 2-, 3-strength tablets	12.5/50 mcg T_3:T_4 (1 strength)	Nonphysiologic T_4:T_3 ratio; T_3 content may cause toxicity; no role in modern therapy

IV, intravenous; LT_4, levothyroxine; T_3, triiodothyronine; T_4, thyroxine.

▶ Bioequivalence and LT_4 Product Selection

LO 6

LT_4 products have a long history of bioavailability problems.[3,15,17] Over the years, LT_4 bioavailability has increased, so maintenance doses today are significantly lower than those seen before the early 1980s. Currently, the average bioavailability of LT_4 tablet products is about 70% to 80%. Because of long-standing concerns about LT_4 bioequivalence and because LT_4 products had never undergone formal approval by the FDA under the 1938 Food, Drug, and Cosmetics Act, the FDA mandated that all manufacturers of LT_4 products submit an Abbreviated New Drug Application (ANDA) to keep their products on the US market after 2001.[15,17,18] Products approved under this process would have to comply with FDA manufacturing and bioequivalence standards. This action has resulted in many changes in the US LT_4 market, as well as renewed interest in LT_4 bioequivalence. Since 2001, a variety of brand and generic products have been approved by the FDA. Some marketed products carry AB ratings (bioequivalence) to certain other products, using a complex AB1, AB2, AB3, and AB4 system.[18]

For many years, there have been concerns regarding the FDA bioequivalence methodology for LT_4 products. FDA bioequivalence standards allow a –20% to +25% variance in single-dose pharmacokinetic parameters between the test and reference products. Many people believe this degree of allowed variance is not appropriate for a narrow-therapeutic-index (NTI) drug such as LT_4. Furthermore, there are unique challenges to performing bioequivalence studies with an endogenous hormone such as LT_4. Because these single-dose pharmacokinetic studies are done in healthy volunteers, the pharmacokinetic data are a combination of endogenous and exogenous LT_4. Seventy percent of the area under the curve (AUC) in these studies consists of the subjects' endogenous T_4. A study showed the standard FDA bioequivalence methodology would rate 600-, 450-, and 400-mcg LT_4 doses as bioequivalent, and that mathematically removing the subjects' endogenous T_4 level (baseline correction) improves the sensitivity of the analysis.[19] Based on these data, since 2003 the FDA has required that LT_4 bioequivalence data undergo baseline correction. Although this method has improved the ability to identify large differences in LT_4 bioequivalence, small but clinically significant differences will not be identified. In 2008, the FDA adopted stricter criteria for LT_4 tablet shelf-life potency (95%–105% of stated potency vs standard 90%–110%), which may reduce the intrapatient variability seen during long-term LT_4 therapy.

LO 6

More important than bioequivalence is the therapeutic equivalence of LT_4 products. Will patients have the same outcomes if bioequivalent products are used? A study by Dong and colleagues helps to answer this question.[20] Twenty-two well-controlled hypothyroid women were randomly switched to the same dose of four different products every 6 weeks. Non-baseline corrected bioequivalence data showed these products to be bioequivalent. However, as each product switch occurred, more of the subjects had an abnormal TSH level.[21] By the end of the third product switch, 52% had an abnormal TSH level. This is strong evidence that LT_4 products are not therapeutically equivalent even if they are rated as bioequivalent by the FDA.

Evidence does exist that small differences in LT_4 dose can result in large changes in TSH. In one study, when the daily dose was reduced by 25 mcg, 78% had an elevated TSH level.[22] When the daily dose was increased by 25 mcg, 55% had a low TSH level. Clearly, differences in LT_4 dose or bioavailability within the FDA-allowed variance for bioequivalent products can cause significant changes in TSH.

KEY CONCEPT There is no evidence that one LT_4 product is better than another. However, given the evidence that these products do have differences in bioavailability, patients should be maintained on the same LT_4 product. Given the generic substitution regulations of most states, this is best accomplished by prescribing a brand-name product or otherwise ensuring the product remains constant and not allowing substitution.[15] Although practitioners are pressured by insurance companies and employers to substitute LT_4 products as a cost-saving measure, such switching is not in the best interest of the patient and should not be allowed. If patients are switched to a different product, the prescriber should be notified, and a TSH determination should be done in 6 to 8 weeks to allow dose retitration. LT_4 dose changes significantly increase the cost of care.[23]

▶ Therapeutic Use of LT_4

LO 5

LT_4 replacement is indicated for patients with overt hypothyroidism.[3,5,8-10,15,17] However, the need for treatment is controversial in patients with mild or subclinical disease. There are no prospective clinical trials that show an outcome benefit with treating these patients. A retrospective study in elderly patients showed no outcome benefits with LT_4 therapy.[14] In patients without symptoms who have underlying heart disease, high cardiovascular risk, goiter, positive anti-TPOAb and/or are infertile or pregnant, LT_4 replacement may be considered.[3,9,10,12] Patients with mild or subclinical hypothyroidism do not need to be started on the full LT_4 replacement dose because they still have some endogenous hormone production. Start these patients on 25 to 50 mcg/day and titrate every 6 to 8 weeks based on TSH levels. Over time, it is likely the LT_4 dose will need to be increased slowly as the patient's thyroid gland loses residual function.

In patients younger than age 65 years with overt hypothyroidism, the average LT_4 replacement dose is 1.6 to 1.8 mcg/kg/day (use ideal body weight in obese patients[15]). However, there is wide interpatient variability in the optimal replacement dose, so individual dose titration is necessary. If there is no history of cardiac disease, these patients may be started on the full replacement dose.

The full replacement dose in patients older than age 75 years is lower, about 1 mcg/kg/day.[3,15] In the elderly, the starting dose should be 25 to 50 mcg/day, and the dose should then be titrated to the target TSH value. In patients with ischemic heart disease, start with 12.5 to 25 mcg/day and slowly titrate. If the patient develops angina or other forms of myocardial ischemia, lower the dose and titrate more slowly. At the start of therapy and with each change in dose, recheck the TSH in 6- to 8-week intervals. If the TSH is not in the target range (0.5–2.5 mIU/L [μIU/mL]), change the dose by 10% to 20% and then recheck the TSH 6 to 8 weeks later. As the dose is titrated, assess the patient's symptoms. Many patients will improve quickly, and younger patients will feel best if the TSH is titrated to low-normal to middle-normal levels (0.5–1.5 mIU/L [μIU/mL]).

▶ Risks of Overtreatment and Undertreatment

Patients receiving LT_4 therapy who are not maintained in a euthyroid state are at risk for long-term adverse sequelae. In general, overtreatment and a suppressed TSH are more common than undertreatment with an elevated TSH. Patients with long-term overtreatment are at higher risk for atrial fibrillation and other cardiovascular morbidities, anxiety, depression or mental status changes, and osteoporosis. Elderly patients being treated with LT_4 have a dose-related risk of fractures even if the TSH is not suppressed below normal values.[24] However, patients with

Patient Encounter 1, Part 1

A 76-year-old woman comes to the clinic complaining of fatigue, weakness, dry skin, and constipation for the past 6 months. She thought it was because she was getting old but the symptoms have not improved despite her taking some vitamins with iron. She noticed a 2-kg (4.4-lb) weight gain over the past few months. Her friend gave her an herbal product to give her energy, but she is not sure that it helps. Her current medications include the vitamin and herbal product mentioned above, hydrochlorothiazide for hypertension, lansoprazole for gastroesophageal reflux disease, occasional naproxen for headache, and MiraLAX for constipation.

PE:

VS: Wt 86 kg (189 lb); Ht 5′5″ (165 cm); BMI 31.6 kg/m^2

Skin, HEENT, thyroid, pulmonary, and cardiovascular examinations are normal.

Labs

Serum Cholesterol: 205 mg/dL (5.30 mmol/L); LDL cholesterol 96 mg/dL (2.48 mmol/L)

TSH: 7.8 mIU/L (μIU/mL; reference range, 0.5–4.5 mIU/L [μIU/mL])

FT$_4$: 0.96 ng/dL (12.4 pmol/L; reference range, 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L)

Should the patient receive LT$_4$ therapy? Why or why not?

If you think treatment is indicated, what initial dose of LT$_4$ would you choose?

If you think treatment is not indicated, how would you monitor the patient?

What would you tell the patient regarding the significance of her symptoms, elevated TSH level, and risk versus benefits of LT$_4$ therapy?

untreated subclinical hypothyroidism also have an increased risk of fractures.[25] Although studies have not defined a specific TSH target range for the elderly, these patients should receive close monitoring and dose adjustments to prevent over- and undertreatment. Patients who are undertreated are at higher risk for hypercholesterolemia and other cardiovascular problems, depression and/or other mental status changes, and obstetric complications.

▶ *Alterations in LT$_4$ Dose Requirements*

A number of factors can alter LT$_4$ dose requirements (Table 44–4), including time of administration and drug–drug and drug–food interactions.[3,8,15] LT$_4$ has the greatest and most consistent bioavailability when taken in the evening on an empty stomach.[15,17,26] The most common cause of increased dose requirement is coadministration of LT$_4$ with calcium or iron supplements (including prenatal vitamins) or concomitant use of proton pump inhibitors. In patients who have impaired absorption of standard LT$_4$ dosage forms, use of a liquid or gelcap formulation may improve absorption.[27] Counsel patients that they should take the LT$_4$ dose at least 2 hours before or 6 hours after the calcium or iron dose. The most common reason for decreased dose requirement is aging.

Table 44–4

Factors That Alter LT$_4$ Dose Requirements[3,9]

Increased Dose Requirement	Decreased Dose Requirement
Decreased LT$_4$ Absorption	Aging
Malabsorption syndromes	Delivery of pregnancy
H. pylori infection	Withdrawal of interacting substance
Drugs or Diet	
Bile acid binders	
Caffeine	
Calcium	
Charcoal	
Chromium picolinate	
Ciprofloxacin	
Fiber	
Grapefruit juice	
H_2-blockers	
Iron	
Malabsorption syndromes	
Oral bisphosphonates	
Orlistat	
Phosphate binders (sevelamer, aluminum)	
Proton pump inhibitors	
Sodium polystyrene sulfonate	
Soy	
Sucralfate	
Tube feeding	
Increased TBG	
Cirrhosis	
Estrogen therapy	
Hereditary	
Pregnancy	
Tamoxifen, raloxifene therapy	
Increased Clearance	
Carbamazepine	
Growth hormone	
Nevirapine	
Oxcarbazepine	
Phenobarbital	
Phenytoin	
Primidone	
Quetiapine	
Rifampin	
Sertraline	
Stavudine	
Tyrosine kinase inhibitors	
Valproic acid	
Impaired Deiodination	
Amiodarone	
Mechanism Unknown	
Critical illness	

LT$_4$, levothyroxine; TBG, thyroxine-binding globulin.

▶ *Patient Monitoring*

Patients on stable LT$_4$ therapy do not need frequent monitoring. In most patients, measuring TSH every 6 to 12 months along with an assessment of clinical status is adequate (Table 44–5). If the patient's clinical status changes (eg, pregnancy), more frequent monitoring may be necessary. LT$_4$ prescriptions should be written as microgram doses to avoid potential errors when written as milligram doses.

Table 44–5

Monitoring Levothyroxine (LT_4) Therapy

- Serum TSH
  - Every 6–12 months or if change in clinical status
  - 6–8 weeks after any dose or product change
  - As soon as possible in pregnancy; then monthly
- Same product prescribed and dispensed with every refill
- Watch for mg/mcg dosing errors
- Assess patient's understanding of disease, therapy, and need for adherence and tight control
- Assess for signs and symptoms of over- and undertreatment
- Identify potential interactions between LT_4, and foods and/or drugs

TSH, thyroid-stimulating hormone.

Patient education is an important component of care. Treatment adherence rate (at least 80% of doses taken) in hypothyroid patients is 68%, slightly less than adherence rates seen in hypertensive patients.[28] Educate patients about the benefits of proper therapy, importance of adherence, consistency in time and method of administration, and importance of receiving a consistent LT_4 product. Some patients take excessive amounts of LT_4 in an effort to "feel better" or as a weight loss treatment. Explain to patients that excessive amounts of LT_4 will not improve symptoms more than therapeutic doses, can cause serious problems, and is not an effective treatment for obesity.

▶ *Special Populations and Conditions*

LO 7

Hypothyroidism and Pregnancy Hypothyroidism during pregnancy has a variety of maternal and fetal adverse effects.[3,29] During pregnancy, β-human chorionic gonadotropin (β-hCG) acts as a TSH receptor agonist, increasing the amount of thyroid hormone available for fetal growth and development.

Maternal hypothyroidism results in an increased rate of miscarriage and decreased intellectual capacity of the child. Endocrinologists recommend a TSH measurement as soon as pregnancy is confirmed. Most hypothyroid women who become pregnant will quickly need an increased dose of LT_4, typically 25% to 30% or two tablets per week above the prepregnancy dose.[29] The increased dose should be maintained throughout the pregnancy, with monthly TSH monitoring to keep TSH in the middle- to low-normal range. After delivery, LT_4 dose usually can be reduced to prepregnancy levels, although patients with preexisting autoimmune thyroiditis may have increased postpartum dose requirements. Because prenatal vitamins contain significant amounts of calcium and iron, remind patients to take the LT_4 dose at least 2 hours before or 6 hours after the vitamin.

Children Congenital hypothyroidism is uncommon in the United States, and all newborns in the United States undergo screening with a TSH level. As soon as the hypothyroid state is identified, the newborn should receive the full LT_4 replacement dose. The replacement dose of LT_4 in children is age dependent. In newborns, the usual dose is 10 to 15 mcg/kg/day. LT_4 tablets may be crushed and mixed with breast milk or formula, but it is best to administer LT_4 to infants and children on an empty stomach.[30] Serum TSH in the mid-to-lower half and FT_4 levels in the mid-to-upper half of the pediatric reference ranges are used for dose titration. By 6 months of age, the required dose is reduced to 5 to 7 mcg/kg/day, and from ages 1 to 10 years, the dose is 3 to 6 mcg/kg/day. After age 12 years, adult doses can be given. In children with subclinical hypothyroidism, treatment can be considered when the serum TSH is over 10 mIU/L (μIU/mL).

Myxedema Coma This is a life-threatening condition owing to severe, long-standing hypothyroidism and has a mortality rate of 60% to 70%. These patients are given 200 to 400 mcg LT_4 intravenously (IV) initially, using caution in patients with underlying cardiac disease. Although administration of T_3 would provide a more rapid onset of action, there is no evidence that T_3 improves outcomes in patients with myxedema coma. Historically, glucocorticoids, such as hydrocortisone 50 to 100 mg every 6 hours, are administered owing to concern about simultaneous adrenal insufficiency. Although there is no strong evidence for an outcome benefit, the use of glucocorticoids is reasonable because such treatment may be lifesaving, and risks of a short course of corticosteroids at this dose are low. As patients improve, LT_4 dose can be given orally in a typical full replacement dose. Reduce the full replacement dose by 75% if continued IV therapy is needed.[15]

Patient Encounter 1, Part 2

Thirteen months later, the patient comes to you for routine follow-up stating that she has felt progressively worse since her last visit. Her husband passed away 6 months ago, but she doesn't think she is depressed. She feels more fatigued, and gained 2 more kg (4.4 lb). After her husband died, she elected to "go natural," and started taking more supplements purchased at a health food store. Her most recent TSH determination, obtained 2 days ago, was 12.8 mIU/L (μIU/mL; reference range, 0.5–4.5 mIU/L [μIU/mL]).

Why is LT_4 therapy indicated now?

What would you recommend regarding her LT_4 dose and monitoring?

What instructions would you give the patient regarding her LT_4 therapy?

HYPERTHYROIDISM AND THYROTOXICOSIS

Hyperthyroidism is much less common than hypothyroidism. Refer to the Epidemiology section.

Causes of Thyrotoxicosis and Hyperthyroidism

Hyperthyroidism is related to excess thyroid hormone secreted by the thyroid gland. Thyrotoxicosis is any syndrome caused by excess thyroid hormone and can be related to excess hormone production (hyperthyroidism). The common causes of thyrotoxicosis are shown in Table 44–6.[31-33] KEY CONCEPT Graves disease is the most common cause of hyperthyroidism. Thyrotoxicosis in the elderly is more likely caused by toxic thyroid nodules or multinodular goiter than by Graves disease. Excessive intake of thyroid hormone may be caused by overtreatment with prescribed therapy or as a self-remedy for obesity, as thyroid hormones can be obtained easily without a prescription from health food stores or Internet sources. Ingestion of high

Patient Care Process: Hypothyroidism

Collect Information:

- Perform a medication history or medication reconciliation for use of all medications and supplements. Identify adverse drug events, allergies and hypersensitivities.
- Review the medical history and physical assessment findings.
- Speak with the patient and other caregivers as appropriate to identify issues that affect medication access and other aspects of care.

Assess the Information:

- Evaluate for signs and symptoms of hypothyroidism (see Clinical Presentation and Diagnosis of Hypothyroidism). As signs and symptoms of hypothyroidism are nonspecific, clinicians should have a high index of suspicion in higher risk patients including women and the elderly.
- Use serum TSH to identify patients with hypothyroidism (see Clinical Presentation and Diagnosis of Hypothyroidism), and check TSH in pregnant women as soon as pregnancy is determined.
- If patient has been or is already receiving pharmacotherapy to treat thyroid disease, assess efficacy, safety, LT_4 product received (eg, any recent changes in product) and patient adherence. Are there any significant drug interactions?
- If patient is not at desired TSH level and not on therapy, determine if pharmacotherapy is indicated.

Develop a Care Plan:

- Provide synthetic LT_4 replacement to patients with overt hypothyroidism.
- Consider replacement therapy in patients with TSH level of greater than 4.5 but less than 10 mIU/L (µIU/mL) who have nonspecific or subtle symptoms (eg, mild fatigue, lethargy), an elevated cholesterol level, underlying heart disease, or positive anti-TPOAbs.
- Patients with mild hypothyroidism may be started at 25 to 50 mcg/day of LT_4.
- Patients with overt hypothyroidism who are older than 12 and younger than 65 years and do not have cardiac disease may receive the calculated full replacement LT_4 dose of 1.6 mcg/kg/day (based on ideal body weight if obese).
- Elderly patients or those with cardiac disease should be started at a lower LT_4 dose (eg, 12.5–25 mcg/day).
- Provide a brand-name LT_4 product, and do not allow product switches. If the product is switched, check TSH in 6 weeks and retitrate the dose.
- Provide LT_4 prescriptions as microgram, not milligram, doses to avoid errors.
- Make sure patients understand importance of adherence and risks of overuse and underuse of LT_4.
- In pregnant patients, expect to increase LT_4 dose early in first trimester. Maintain TSH in low- to middle-normal range. After delivery, consider reducing LT_4 dose to prepregnancy level, if appropriate.

Implement the Care Plan:

- Educate the patient about any changes in therapy and how to manage and report adverse effects.
- Review proper medication administration with the patient, including issues related to food and concomitant medications.
- Discuss the importance of adherence and risks of over- and undertreatment.
- Determine if the patient has insurance coverage for prescription medications.

Follow-up: Monitor and Evaluate:

- Measure serum TSH 6 to 8 weeks after starting LT_4 or after any dose change. If TSH level is not in target range, alter dose by 10% to 20% increments. Target TSH for patients on LT_4 replacement therapy for hypothyroidism is 0.5 to 2.5 mIU/L (µIU/mL). Younger patients often feel best at a TSH level in the low- to middle-normal range (ie, 0.5–1.5 mIU/L [µIU/mL]).
- Check TSH every 6 to 12 months in stable patients receiving LT_4 replacement.
- Monitor for drug interactions, such as LT_4 absorption problems caused by calcium and iron.
- At each visit, assess for signs and symptoms of overtreatment and undertreatment.
- In pregnant patients, check TSH monthly.

doses of biotin may cause falsely elevated FT_4 levels and a false positive TSHR-SAb assay with subsequent misdiagnosis of Graves disease.[31]

Clinical Manifestations of Thyrotoxicosis

Many of the signs and symptoms seem to be related to autonomic hyperactivity. Clinical manifestations of hyperthyroidism may be subtle and slowly progressive. Screening of patients for thyroid disease may identify patients with subclinical or mild thyrotoxicosis. Patients may seek medical attention only after a long period of thyrotoxicosis or owing to an acute complication such as atrial fibrillation. Clinical manifestations of thyrotoxicosis in the elderly may be blunted or atypical. These patients may present only with atrial fibrillation, depression, or altered mental status or cognition.

Mild (Subclinical) Hyperthyroidism

Mild (subclinical) hyperthyroidism is defined as a low TSH level with a normal FT_4 level.[12,31-33] Although there may be few or no symptoms in these patients, there are several areas of concern.[12,31] Some patients progress to overt thyrotoxicosis. Patients with subclinical hyperthyroidism have been shown to experience long-term cardiovascular[31,34] and bone sequelae.[35] Mild hyperthyroidism appears to increase cardiovascular morbidity and mortality.[34] Prolonged subclinical thyrotoxicosis speeds the loss of bone mineral density and increases fracture rates in postmenopausal

Table 44–6

Causes of Thyrotoxicosis[33-35]

Primary Hyperthyroidism
Graves disease
Toxic multinodular goiter
Toxic adenoma
Thyroid cancer
Struma ovarii
Iodine excess (including radiocontrast, amiodarone)

Thyrotoxicosis Without Hyperthyroidism
Subacute thyroiditis
Silent (painless) thyroiditis
Excess thyroid hormone intake (thyrotoxicosis factitia)
Drug-induced (amiodarone, iodine, lithium, interferons)

Secondary Hyperthyroidism
TSH-secreting pituitary tumors
Trophoblastic (hCG-secreting) tumors
Gestational thyrotoxicosis

hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.

women.[31,35] Treatment of patients with mild hyperthyroidism is controversial but should be considered in patients with TSH levels less than 0.1 mIU/L (μIU/mL), Graves disease, postmenopausal women, and patients with underlying cardiovascular disease.[31,36] Patients who do not have a fully suppressed (below the lower limit of detection) TSH or other risk factors for hyperthyroid complications (eg, osteoporosis, atrial fibrillation, heart failure) may undergo observation, with TSH testing every 6 months to identify progression of the hyperthyroid state.

Graves Disease

Graves disease is an autoimmune syndrome that includes hyperthyroidism, diffuse thyroid enlargement, exophthalmos (abnormal protrusion of the eyeball) and other eye findings, and skin findings.[31-33] The prevalence of Graves disease in the United States is approximately 0.4% in women and 0.1% in men. The peak age of incidence is 20 to 49 years, with a second peak after 80 years of age. Hyperthyroidism results from the production of TSHR-SAbs in at least 80% of patients with clinical Graves disease. These antibodies have TSH agonist activity, thereby stimulating hormone synthesis and release. These antibodies cross-react with orbital and fibroblastic tissue, resulting in ophthalmopathy and dermopathy. Although the underlying cause of Graves disease is not known, heredity seems to play a role. Subclinical Graves disease may become acutely overt in the presence of iodine excess, infection, stress, parturition, smoking, and lithium and cytokine therapy.

LO 1

Several features of Graves disease are distinct from other forms of thyrotoxicosis. Clinically apparent ophthalmopathic changes are seen in 20% to 40% of patients and include exophthalmos, **proptosis**, **chemosis**, **conjunctival injection**, and periorbital edema.[31,32,37] Eyelid retraction causes a typical staring or startled appearance (**Figure 44–3**). Patients may complain of vague eye discomfort and excess tearing. In severe cases, the eyelids are unable to close completely, resulting in corneal damage. In very severe cases, the optic nerve can be compressed, resulting in permanent vision loss. All patients with suspected or known Graves disease must be evaluated and monitored by an ophthalmologist. Treatment of the underlying hyperthyroid state often, but not always, improves the ophthalmopathy.

LO 8

Clinical Presentation and Diagnosis of Hyperthyroidism[31-33]

Symptoms
- Nervousness
- Fatigue
- Weakness
- Increased perspiration
- Heat intolerance
- Tremor
- Hyperactivity, irritability
- Palpitations
- Appetite change (usually increased)
- Weight change (usually weight loss)
- Menstrual disturbances (often oligomenorrhea)
- Frequent bowel movements or diarrhea

Signs
- Hyperactivity
- Tachycardia
- Atrial fibrillation (especially in elderly adults)
- Hyperreflexia
- Warm, moist skin
- Ophthalmopathy, dermopathy (Graves disease)
- Goiter
- Muscle weakness

Screening/Diagnosis
- Low TSH level (< 0.5 mIU/L [μIU/mL]) signifies thyrotoxicosis.
- FT_4 is elevated in overt hyperthyroidism but may be normal in mild hyperthyroidism.
- Increased radioiodine uptake in the thyroid indicates increased hormone production by the thyroid gland.
- Almost all patients with Graves disease will have positive TSHR-SAbs and positive anti-TPOAbs.

LO 8

Dermopathy occurs in 5% to 10% of patients with Graves disease and usually is associated with severe ophthalmopathy. Skin findings include hyperpigmented, nonpitting induration of the skin, typically over the pretibial area (pretibial myxedema), the dorsa of the feet, and the shoulder areas. **Clubbing** of the digits (thyroid acropachy) is associated with long-standing thyrotoxicosis.

Treatment

▶ *Desired Outcomes*

Treatment of thyrotoxicosis caused by hyperthyroidism is similar regardless of the underlying cause.[31-33] KEY CONCEPT Goals of treating hyperthyroidism are to relieve signs and symptoms, reduce thyroid hormone production to normal levels and achieve biochemical euthyroidism, and prevent long-term adverse sequelae.

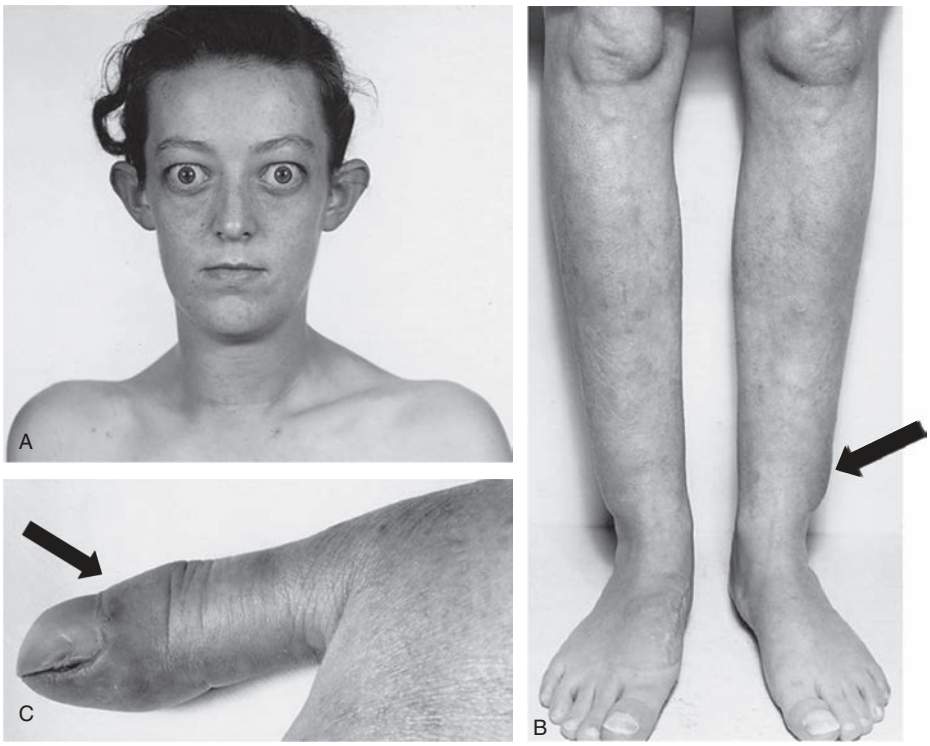

FIGURE 44–3. Features of Graves disease. (**A**) Facial appearance: exophthalmos, eyelid retraction, periorbital edema, and proptosis. (**B**) Thyroid dermopathy over lateral aspects of the shins (*arrow*). (**C**) Thyroid clubbing or acropachy (*arrow*). (From Jameson JL, Weetman AP. Disorders of the thyroid gland. In: Kasper DL, Braunwald E, Fauci AS, et al., eds. Harrison's Principles of Internal Medicine, 16th ed. New York: McGraw-Hill; 2004:2114.)

► *β-Blockers*

Because many manifestations of hyperthyroidism appear to be mediated by the β-adrenergic system, β-adrenergic blockers are used to rapidly relieve palpitations, tremor, anxiety, and heat intolerance. Because β-blockers do not reduce the synthesis of thyroid hormones, they are used only until more specific antithyroid therapy is effective. Because nonselective agents can impair the conversion of T_4 to T_3, propranolol and nadolol are preferred. An initial propranolol dose of 20 to 40 mg four times daily should be titrated to relieve signs (target resting heart rate < 90 beats/min) and symptoms. β-Blockers should not be used in patients with decompensated heart failure or asthma. A more β-1 specific blocker (eg, metoprolol, atenolol) may be used when a relative contraindication to a β-blocker exists; however, when an absolute contraindication to β-blockers exists, clonidine, verapamil, or diltiazem may be used for heart rate control.

► *Methods to Reduce Thyroid Hormone Synthesis*

Excess production of thyroid hormone can be reduced in four ways: iodides, antithyroid drugs, radioactive iodine, and surgery.

Iodide Large doses of iodide inhibit the synthesis and release of thyroid hormones. Serum T_4 levels may be reduced within 24 hours, and the effects may last for 2 to 3 weeks. Iodides are used most commonly in Graves disease patients before surgery and to quickly reduce hormone release in patients with thyroid storm. Potassium iodide is administered either as a saturated solution (SSKI) that contains 38 mg iodide per drop or as Lugol solution, which contains 6.3 mg iodide per drop. The typical starting dose of SSKI is 5 drops every 6 to 8 hours. Iodide therapy should start 7 to 14 days before surgery. Iodide should not be given before radioactive iodine treatment because the iodide will inhibit concentration of the radioactivity in the thyroid. Iodides also are used to protect the thyroid from radioactive iodine fallout after a nuclear accident or attack. Daily administration of 30 to 100 mg iodide markedly reduces thyroid gland uptake of radioactive iodine. The most frequent toxic effects with iodide therapy are hypersensitivity reactions, "iodism" (characterized by palpitations, depression, weight loss, and pustular skin eruptions), and gynecomastia.

LO 9

Antithyroid Drugs The thionamide agents propylthiouracil (PTU) and methimazole (MMI) are used in the United States to treat hyperthyroidism.[31,38] Carbimazole, an MMI prodrug, is used in some countries (10 mg carbimazole = 6 mg MMI). These drugs inhibit thyroid hormone synthesis by interfering with thyroid peroxidase–mediated iodination of tyrosine residues in thyroglobulin. PTU has the added effect of inhibiting conversion of T_4 to T_3. The thionamides also have immunosuppressant effects. In patients with Graves disease treated with thionamides, TSHR-SAb levels and other immune mediators decrease over time. Both drugs are well absorbed from the gastrointestinal (GI) tract. PTU has a half-life of 1 to 2.5 hours, whereas half-life of MMI is 6 to 9 hours.

Antithyroid drugs are used as primary therapy for Graves disease or as preparative therapy before surgery or radioactive iodine administration. The decision to use antithyroid drugs as primary therapy must be weighed against the risks and benefits of radioiodine or surgery. Patient preference must be considered.

In most patients, there is no clear efficacy advantage of one thionamide over the other, but in the United States, MMI use has increased dramatically since the mid-1990s in lieu of

PTU.[39] Although PTU has the advantage of inhibiting T_4-to-T_3 conversion, MMI can be given as a single daily dose and may have a better overall safety profile, particularly less hepatotoxicity. MMI is preferred to normalize thyroid function before radioactive iodine therapy, although both thionamides increase the failure rate of radioactive iodine therapy.[40] The usual starting dose of MMI is 10 to 20 mg/day (range 5–40 mg based on initial FT_4 level), and the usual starting dose of PTU is 50 to 150 mg three times daily. Thyroid hormone levels drop in 2 to 3 weeks, and after 6 weeks, 90% of patients with Graves disease will be euthyroid. Thyroid function testing should be performed every 4 to 6 weeks until stable. After the patient becomes euthyroid, antithyroid drug dose often can be decreased (5–10 mg/day MMI, 100–200 mg/day PTU) to maintain the euthyroid state. Excessive doses of antithyroid drugs will result in hypothyroidism.

LO 9

Remission of Graves disease occurs in 40% to 60% of patients after 1 to 2 years of therapy. Antithyroid therapy may be stopped or tapered after 12 to 24 months. Relapse usually occurs in the first 3 to 6 months after stopping antithyroid therapy. Levels of TSHR-SAb after a course of treatment may have predictive value for the risk of relapse in that antibody-positive patients almost always relapse. However, antibody-negative patients also may relapse after therapy is stopped. About 75% of women in remission who become pregnant will have a postpartum relapse. When therapy is discontinued, a therapeutic strategy should be in place in the event of relapse. Many patients will opt for radioactive iodine as a long-term solution.

LO 9

Antithyroid drugs are associated with an overall low rate of adverse effects, although serious adverse effects can occur. In 2010, the FDA released a boxed warning on severe liver injury with PTU.[41] The warning states that PTU should only be used in patients who cannot tolerate MMI. Skin rash, arthralgias, and GI upset are seen in 5% of patients. Although the drug can be continued in the presence of a minor skin rash, development of arthralgia warrants discontinuation. Hepatotoxicity is an uncommon but potentially serious or fatal adverse effect, occurring in 0.1% to 0.2% of patients. Transient rises in aminotransferase enzyme levels are seen in up to 30% of patients treated with PTU. Severe hepatocellular damage can occur from PTU, whereas MMI is thought to cause cholestatic jaundice. However, a study in an Asian patient population found a higher rate of drug-induced hepatitis in patients who received MMI, implying there may be genetic differences in hepatotoxicity risk.[42] Antineutrophil cytoplasmic antibody (ANCA) vasculitis is another potentially serious but uncommon reaction that is more common with PTU, and patients may develop a drug-induced lupus syndrome.

KEY CONCEPT Agranulocytosis is one of the most serious adverse effects of antithyroid drug therapy. Agranulocytosis must be distinguished from a transient decrease in white blood cell count seen in up to 12% of adults and 25% of children with Graves disease. Agranulocytosis occurs in 0.3% of patients, and the incidence may be the same with PTU and MMI therapy. Lower doses of MMI may be associated with a lower incidence.[31] Agranulocytosis, thought to be autoimmune, almost always occurs within the first 3 months of therapy, and occurs suddenly and unpredictably. Patients will present with fever, malaise, and sore throat, and absolute neutrophil count will be less than 1000/mm^3 (1×10^9/L). Patients may develop sepsis and die rapidly. If agranulocytosis occurs, discontinue the antithyroid drug immediately, administer broad-spectrum antibiotics if the patient is febrile, and consider administration of filgrastim. The white blood cell count should recover in 1 or 2 weeks. Patients who develop agranulocytosis should not be switched to another thionamide drug. Monitoring for agranulocytosis is controversial owing to its sudden and unpredictable nature. Most do not recommend routine monitoring of the complete blood count (CBC), although early detection could improve patient outcomes. Patients initiating thionamide therapy must be informed about the signs and symptoms of agranulocytosis and other serious side effects. Patients should be counseled to report signs and symptoms suggestive of infection, such as fever and sore throat lasting more than 2 or 3 days, bruising, pruritic rash, jaundice, dark urine, arthralgias, abdominal pain, nausea, or fatigue.

Radioactive Iodine Radioactive iodine, typically ^{131}I, produces thyroid ablation without surgery. ^{131}I is well absorbed after oral administration. Iodine is concentrated in the thyroid gland and has a half-life of 8 days. Over a period of weeks, thyroid cells that have taken up the ^{131}I begin to develop abnormalities and necrosis. Eventually, thyroid cells are destroyed, and hormone production is reduced. After a single dose, 40% to 70% of patients will be euthyroid in 6 to 8 weeks, and 80% will be cured. In most patients, hypothyroidism will develop, and long-term LT_4 replacement will be necessary. Because ^{131}I has a slow onset of action and may cause added release of thyroid hormone, most patients are treated initially with β-blockers and antithyroid drugs to prevent ^{131}I-induced thyroid storm. MMI is the preferred agent before administration of ^{131}I. MMI is discontinued 3 to 5 days before administration of ^{131}I and restarted 3 to 7 days later. MMI is then slowly tapered over the next 4 to 6 weeks as thyroid function normalizes. β-Blockers can be continued during ^{131}I therapy. The dose of ^{131}I is based on the estimated weight of the patient's thyroid gland (typical dose, 10–15 mCi [370–555 MBq]). Radioactive iodine therapy is contraindicated during pregnancy and breastfeeding. Radioactive iodine therapy may acutely worsen Graves ophthalmopathy. Patients with prominent eye disease may be started on prednisone 40 mg/day, with the dose tapered over 2 to 3 months. Radioactive iodine also may cause a painful thyroiditis, which may necessitate anti-inflammatory therapy. No long-term carcinogenic effect of ^{131}I has been demonstrated in clinical trials.[31]

LO 9

Surgery Subtotal thyroidectomy is indicated in patients with very large goiters and thyroid malignancies and those who do not respond or cannot tolerate other therapies. Patients must be euthyroid before surgery, and they are often administered iodide preoperatively to reduce gland vascularity. The overall surgical complication rate is 2.7%. Postoperative hypothyroidism occurs in 10% of patients who undergo subtotal thyroidectomy. After thyroidectomy, serum calcium and intact parathyroid hormone levels should be monitored for early identification of postoperative hypoparathyroidism. Postoperative administration of 1250 to 2500 mg/day of calcium and 0.5 mcg/day of calcitriol may be given and then tapered over 1 to 2 weeks if the patient does not develop hypoparathyroidism.

► *Special Conditions and Populations*

Graves Disease and Pregnancy Pregnancy may worsen or precipitate thyrotoxicosis in women with underlying Graves disease owing to the TSH agonist effect of β-hCG.[29] Untreated maternal thyrotoxicosis may result in increased rates of miscarriage, premature delivery, eclampsia, and

LO 7

Patient Encounter 2, Part 1

A 24-year-old woman comes to the clinic stating, "I'm having trouble sleeping." She first noticed these symptoms a few months ago, which haven't improved despite use of OTC sleep aids. She also feels anxious for no reason and has lost a little weight without trying. Sometimes she can feel her heart beating in her chest when she exercises, but denies chest pain or syncope. Her only medications are a multivitamin product, occasional acetaminophen for headaches, and a hormonal contraceptive. She thinks that her mother had some kind of thyroid problem when she was pregnant with her.

PE:

General appearance: Patient appears slightly anxious and responds appropriately to all questions.

VS: Pulse 101 beats/min, BP 108/73 mm Hg, RR 12 breaths/min, T 37°C (98.6°F)

Skin: Warm, moist, and soft

HEENT: Slightly and symmetrically enlarged thyroid, which is nontender and without appreciable nodules; mild exophthalmos

CV: Apical HR: 105/min, RRR

Exts: No tremor

Diagnostic studies

ECG: Sinus tachycardia

Labs: Electrolytes, CBC normal. TSH less than 0.1 mIU/L (μIU/mL; reference range 0.5–2.5 mIU/L [μIU/mL]); FT_4 4.2 ng/dL (54.1 pmol/L; reference range 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L); + TSHR-SAbs. Pregnancy test is negative.

Should this patient be treated for hyperthyroidism?

What therapeutic options exist for this patient's Graves disease?

What pharmacotherapy would you recommend? What if she were pregnant?

How would you initiate and titrate therapy?

What would you tell the patient regarding the cause of her signs and symptoms, significance of her abnormal thyroid function tests, and therapeutic options?

Patient Encounter 2, Part 2

Two years later, the patent is admitted to the hospital for altered mental status and r/o sepsis. For the past year, she had been working in a refugee camp with a non-governmental agency in Jordan. She was unable to obtain her medications and was only taking a local herbal product. Her coworkers in Jordan noticed she was becoming increasingly fatigued, lethargic, and possibly delusional. She was medically evacuated to the United States for further assessment and treatment.

PE:

General appearance: Patient appears sweaty and agitated.

VS: Pulse 144 beats/min, BP 94/68 mm Hg, RR 22 breaths/min, T 40°C (104°F)

Skin: Warm, sweaty, and soft

HEENT: Diffusely enlarged, nontender thyroid without any appreciable nodules; + exophthalmos

CV: Apical HR: 150 beats/min, RRR

Exts: + tremor; Reflexes: biceps, triceps, patellar, and Achilles: 3+/4

GI: Hyperactive bowel sounds

Mental status examination: Patient is only oriented to year and familiar persons. Cannot recall date, time, or location.

Diagnostic studies

ECG: Sinus tachycardia with occasional PACs

Labs: Electrolytes, CBC normal. TSH less than 0.1 mIU/L (μIU/mL; reference range 0.5–2.5 mIU/L [μIU/mL]); FT_4 8.2 ng/dL (105.5 pmol/L; reference range 0.7–1.9 ng/dL, or 9.0–24.5 pmol/L); + TSHR-SAbs. Pregnancy test is negative.

Diagnoses:

1) Thyroid storm.

2) Sepsis: r/o communicable diseases endemic to Jordan such as typhoid.

What are the signs and symptoms of thyroid storm?

How should this patient be treated?

low-birth-weight infants. Fetal and neonatal hyperthyroidism may occur as a result of transplacental passage of TSHR-SAbs. Because radioactive iodine is contraindicated and surgery is best avoided during pregnancy, most patients are treated with antithyroid drugs. PTU is considered the treatment of choice, particularly in the first trimester. While MMI is thought to have greater teratogenic potential versus PTU, the relative safety of these medications in pregnancy is not clear.[43] Patients receiving prepregnancy MMI are switched to PTU as soon as the pregnancy is confirmed. The lowest possible dose of PTU to maintain maternal euthyroidism should be used. Given the potential maternal adverse effects of PTU (eg, hepatotoxicity), it may be preferable to switch from PTU to MMI for the second and third trimesters.[29,41] Antithyroid therapy in excessive doses may suppress fetal thyroid function. Although PTU and MMI are found in breast milk, nursing mothers should be switched to MMI after delivery because of the risk of hepatotoxicity from PTU in the mother and infant.

Pediatric Hyperthyroidism β-Blockers are administered to children who are symptomatic or have a heart rate greater than 100 beats/min.[29] MMI is the preferred antithyroid drug therapy in children at a dose of 0.2 to 0.5 mg/kg/day.[29] Once a euthyroid state is achieved, MMI dose can be reduced by 50% or more to maintain euthyroidism. As in adults, antithyroid drugs are administered to children with Graves disease for 1 to 2 years. If remission does not occur in that time, long-term antithyroid drug therapy, radioactive iodine,

or surgical therapy is offered. Long-term studies with ^{131}I use in children show no increased risk of thyroid cancer or leukemia.[31]

Thyroid Storm Thyroid storm is a life-threatening condition caused by severe thyrotoxicosis.[29,44] Signs and symptoms include high fever, tachycardia, tachypnea, dehydration, delirium, coma, and GI disturbances. Thyroid storm is precipitated in a previously hyperthyroid patient by infection, trauma, surgery, radioactive iodine treatment, and sudden withdrawal from antithyroid drugs. Patients are treated with a short-acting β-blocker such as IV esmolol, IV or oral iodide, and large doses of PTU (500–1000 mg load; then 250 mg every 4 hours) or MMI (60–80 mg/day). Supportive care with acetaminophen to suppress fever, fluid and electrolyte management, and antiarrhythmic agents are important components of therapy. IV hydrocortisone 300 mg initially and then 100 mg every 8 hours is used often because of the potential presence of adrenal insufficiency.

NONTHYROIDAL ILLNESS (EUTHYROID SICK SYNDROME)

A number of changes in the hypothalamic–pituitary–thyroid axis occur during acute illness.[15] These changes are termed *nonthyroidal illness* or *euthyroid sick syndrome*. Type and degree of abnormalities depend on the severity of illness. Mild to moderate medical illness, surgery, or starvation causes a decrease in serum T_3 levels owing to decreased peripheral conversion of T_4 to T_3. Reduced T_3 levels do not correlate with ultimate mortality and are thought to be an adaptive response to stress. Patients with more severe illness, especially those in the intensive care unit, frequently have reduced total T_4 levels, although FT_4 levels often are normal. In critically ill patients, there is a correlation between degree of serum T_4 reduction and mortality. In most acutely ill patients who are euthyroid, TSH level is normal. However, administration of dopamine, octreotide, or high doses of glucocorticoids can reduce TSH levels. During recovery from acute illness, TSH level may become modestly elevated to

Patient Care Process: Hyperthyroidism

Collect Information:

- Perform a medication history or medication reconciliation for use of all medications and supplements. Identify adverse drug events, allergies and hypersensitivities.
- Review the medical history and physical assessment findings.
- Speak with the patient and other caregivers as appropriate to identify issues that affect medication access and other aspects of care.

Assess the Information:

- A low or undetectable TSH level identifies thyrotoxicosis. See Clinical Presentation and Diagnosis of Hyperthyroidism.
- Via a diagnostic assessment, identify the underlying cause (eg, presence of eye and/or skin findings and presence of TSHR-SAbs may be used to identify Graves disease).

Develop a Care Plan:

- Treat severe or troublesome autonomic signs and symptoms with a nonselective β-blocker such as propranolol 20 to 40 mg four times daily. Titrate β-blocker dose based on signs and symptoms.
- Consider reducing excess thyroid hormone production with an antithyroid drug and/or radioactive iodine. If radioactive iodine is given, make sure that antithyroid drugs are stopped 4 to 6 days before treatment.
- MMI is the antithyroid drug of choice in most patients.
- Refer patients with Graves disease to an ophthalmologist for assessment and monitoring.
- Treat pregnant hyperthyroid women with PTU.
- Address any patient concerns regarding therapy.

Implement the Care Plan:

- Educate the patient about any changes in therapy and how to manage and report adverse effects.
- Review proper medication administration with the patient, including issues related to food and concomitant medications.
- Discuss the importance of adherence and risks of over- and undertreatment.
- Determine if the patient has insurance coverage for prescription medications.
- If patient has been or is currently receiving pharmacotherapy to treat hyperthyroidism, assess efficacy, safety, and patient adherence. Are there any significant drug interactions?
- If patient is not at desired TSH level, determine if pharmacotherapy or a change in pharmacotherapy is indicated.

Follow-up: Monitor and Evaluate:

- Monitor patients on antithyroid drugs for signs and symptoms of adverse effects.
- After baseline CBC with differential and liver profile, repeat CBC when patient has a febrile illness and repeat liver panel if signs or symptoms of hepatotoxicity occur (some recommend routine monitoring during the first 6 months of therapy).
- Assess any skin rash or development of arthralgias.
- Antithyroid drugs have a delayed effect. After 2 to 4 weeks of therapy, adjust the dose if TSH is not in target range (0.5–2.5 mIU/L [μIU/mL]). When patient is euthyroid, consider reducing dose of antithyroid drug to avoid hypothyroidism.
- Periodic assessment of TSHR-Sabs.
- Consider stopping antithyroid therapy in patients with Graves disease after 12 to 18 months to see if remission has occurred.
- Several months after radioactive iodine, expect that the patient will require permanent LT_4 replacement; thus, evaluate for such.

renormalize serum T_4 levels. During this time, thyroid function tests may be misinterpreted to indicate hypothyroidism. Despite the sometimes very low T_4 levels, there is no evidence that LT_4 administration has any survival benefit.[3,15,45] Patients with possible thyroid abnormalities during acute illness should be evaluated by an endocrinologist.

THYROID CANCER AND LT_4 SUPPRESSION

KEY CONCEPT The growth and dissemination of thyroid carcinoma are stimulated by TSH. As such, LT_4 is an integral component of thyroid carcinoma management as it suppresses TSH secretion. Early in therapy, patients receive the lowest LT_4 dose sufficient to fully suppress TSH to undetectable levels. Controlled trials show that suppressive LT_4 therapy reduces tumor growth and improves survival. These patients are purposefully "overtreated" with LT_4, sometimes to a fully suppressed TSH level, and rendered subclinically or mildly hyperthyroid. Postmenopausal women and other individuals at high risk for osteoporosis should receive aggressive osteoporosis therapy to prevent LT_4-induced bone loss. Other thyrotoxic complications, such as atrial fibrillation, should be monitored and managed appropriately.

DRUG-INDUCED THYROID ABNORMALITIES

Drugs can affect thyroid function in a number of ways.[3,11] The effects of drugs on thyroid hormone protein binding, LT_4 absorption, and metabolism have been discussed previously. Several commonly used medications can alter thyroid hormone secretion.

Amiodarone

Amiodarone is a commonly prescribed antiarrhythmic drug that contains two iodide atoms, constituting 38% of its mass.[46] Each 200-mg dose of amiodarone provides 75 mg of iodide. Amiodarone deiodination releases about 6 mg of free iodine daily, 20 to 40 times more than the average daily intake of iodine in the United States. Amiodarone blocks conversion of T_4 to T_3, inhibits entry of T_3 into cells, and decreases T_3 receptor binding. Amiodarone causes rapid reduction in serum T_3 levels, increases free and total T_4 levels, and increases TSH level. After 3 months of therapy, TSH levels usually return to normal, although the serum T_3 and T_4 level changes may remain. Most of these patients are euthyroid because the FT_3 levels are in the low-normal range.

LO 10 Amiodarone can frequently cause thyroid abnormalities in previously euthyroid patients. In a study of amiodarone treatment of persistent atrial fibrillation, 25.8% of patients developed subclinical hypothyroidism, and 5% developed overt hypothyroidism.[47] Hyperthyroidism occurred in 5.3%. Thyroid abnormalities, when they occurred, were seen within 6 months of initiation of amiodarone therapy in almost all patients. Amiodarone-induced hypothyroidism is more common in iodine-sufficient areas of the world. Patients with underlying autoimmune thyroiditis are much more likely to develop amiodarone-induced hypothyroidism. Amiodarone-induced hypothyroidism occurs most commonly within the first year of therapy. If amiodarone cannot be discontinued, LT_4 therapy will be effective in most patients. If amiodarone can be stopped, thyroid function will return to normal in 2 to 4 months.

Amiodarone is more likely to cause thyrotoxicosis in iodine-deficient areas. Type 1 amiodarone-induced thyrotoxicosis is caused by iodine excess and typically occurs in patients with preexisting multinodular goiter or subclinical Graves disease. Type 2 amiodarone-induced thyrotoxicosis is a destructive thyroiditis that occurs in patients with no underlying thyroid disease. Amiodarone-induced thyrotoxicosis is more common in men. Because amiodarone has β-blocking activity, palpitations and tachycardia may be absent. In type 1 thyrotoxicosis, amiodarone should be discontinued. If amiodarone therapy cannot be stopped, larger doses of antithyroid drugs may be needed to control thyrotoxicosis. In type 2 thyroiditis, stopping amiodarone may not be necessary because spontaneous resolution may occur. Prednisone 40 to 60 mg/day will quickly improve thyrotoxic symptoms. Prednisone may be tapered after 1 to 2 months of therapy.

KEY CONCEPT Patients receiving amiodarone must receive monitoring for thyroid abnormalities. Baseline measurements of serum TSH, FT_4, FT_3, anti-TPOAbs, and TSHR-SAbs should be performed. TSH, FT_4, and FT_3 should be checked 3 months after initiation of amiodarone and then a TSH at least every 3 to 6 months.

Lithium

LO 10 Lithium is associated with hypothyroidism in up to 34% of patients, and hypothyroidism may occur after years of therapy.[48] Lithium appears to inhibit thyroid hormone synthesis and secretion. Patients with underlying autoimmune thyroiditis are more likely to develop lithium-induced hypothyroidism. Patients may require LT_4 replacement even if lithium is discontinued.

Interferon-α

LO 10 Interferon-α causes hypothyroidism in up to 39% of patients being treated for hepatitis C infection.[3,11] Patients may develop a transient thyroiditis with hyperthyroidism before becoming hypothyroid. The hypothyroidism may be transient as well. Asians and patients with preexisting anti-TPOAbs are more likely to develop interferon-induced hypothyroidism. The mechanism of interferon-induced hypothyroidism is not known. If LT_4 replacement is initiated, it should be stopped after 6 months to reevaluate the need for replacement therapy.

Tyrosine Kinase Inhibitors

LO 10 TKIs are targeted antineoplastic agents used in several types of malignancies, including thyroid cancer.[11,15] Several TKIs have significant effects on thyroid function, both in previously hypothyroid patients on LT_4 replacement and in previously euthyroid patients. Imatinib has been shown to cause a fourfold increase in TSH levels in patients being treated for thyroid cancer. Sunitinib and sorafenib have been associated with primary hypothyroidism in 20% to 40% of treated patients. Some sorafenib patients developed mild hyperthyroidism before becoming hypothyroid. Patients receiving TKI therapy should have baseline and periodic thyroid function monitoring.

OUTCOME EVALUATION

- Desired outcomes include relieving signs and symptoms and achieving a euthyroid state.
- Success of therapy for thyroid disorders must be based not only on short-term improvement of the patient's clinical status and abnormal laboratory values but also on achievement of a long-term, stable euthyroid state. Maintaining TSH level in the normal range improves symptoms and reduces risk of long-term complications.
- Because pharmacotherapy often is lifelong, especially in patients with hypothyroidism, patients must undergo periodic monitoring to avoid long-term complications. In

hypothyroid patients, such monitoring may involve simply asking the patient about signs and symptoms and a yearly measurement of TSH level.

- Any change in the patient's clinical status, such as a new pregnancy or a major change in body weight, necessitates a reevaluation of therapy. Patients at high risk for complications, such as pregnant women, the elderly, and patients with underlying cardiac disease, must be monitored more closely.
- Patients should be educated and periodically reminded about the importance of adherence and long-term tight control, the need for periodic clinical and laboratory monitoring, and the importance of staying on one LT_4 product.
- In hyperthyroid patients, the method of achieving desired outcomes may change over time with the use of antithyroid drugs versus radioactive iodine.
- Patients who receive antithyroid drugs must be monitored for adverse drug events such as hepatotoxicity and agranulocytosis.
- Patients who receive radioactive iodine must be monitored for development of hypothyroidism.
- In patients with thyroid cancer, the desired outcomes with LT_4 therapy are often different from those in hypothyroid patients. LT_4 doses sufficient to suppress tumor growth may result in a suppressed TSH and mild hyperthyroidism. These patients must be monitored closely for complications of the mild hyperthyroid state, such as bone mineral loss and development of atrial fibrillation.

Abbreviations Introduced in This Chapter

ANCA	Antineutrophil cytoplasmic antibody
ANDA	Abbreviated New Drug Application
Anti-TGAb	Antithyroglobulin antibody
Anti-TPOAb	Antithyroid peroxidase antibody
AUC	Area under the (time-concentration) curve
β-hCG	β-Human chorionic gonadotropin
CBC	Complete blood count
CNS	Central nervous system
FDA	Food and Drug Administration
FT_3	Free T_3
FT_4	Free T_4
GI	Gastrointestinal
hCG	Human chorionic gonadotropin
IV	Intravenous
LDL	Low-density lipoprotein
LT_4	Levothyroxine
MMI	Methimazole
NHANES	National Health and Nutrition Examination Survey
NTI	Narrow therapeutic index
PTU	Propylthiouracil
RAIU	Radioactive iodine uptake
SSKI	Saturated solution of potassium iodide
T_3	Triiodothyronine
T_4	Thyroxine
TBG	Thyroxine-binding globulin
TKI	Tyrosine kinase inhibitor
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone (thyrotropin)
TSHR-SAb	Thyroid-stimulating hormone receptor-stimulating antibodies
TSI	Thyroid-stimulating immunoglobulin

REFERENCES

1. Aoki Y, Belin RM, Clickner R, et al. Serum TSH and total T_4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). Thyroid. 2007;17:1211–1223.
2. Canaris GJ, Manowitz NR, Mayor G, Ridgeway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160:526–534.
3. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012;22:1200–1235.
4. Peeters RP. Subclinical hypothyroidism. NEJM. 2017;376: 2556–2565
5. Devdhar M, Ousman YH, Burman KD. Hypothyroidism. Endocrinol Metab Clin North Am. 2007;36:595–615.
6. Danese MD, Powe NR, Sawin CT, Ladenson PW. Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. JAMA. 1996;276:285–292.
7. Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence-based review for the U.S. Preventive Services Task Force. Ann Intern Med. 2015;162:35–45.
8. Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician. 2012;86:244–251.
9. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012;72:17–33.
10. Pearce SHS, Brabant G, Duntas LH, et al. 2013 ETA guideline: management of subclinical hypothyroidism. Eur Thyroid J. 2013;2(4):215–228.
11. Barbesino G. Drugs affecting thyroid function. Thyroid. 2010;20:763–770.
12. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379:1142–1154.
13. Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. Ann Intern Med. 2008;148:832–845.
14. Grossman A, Weiss A, Koren-Morag N, Shimon I, Beloosesky Y, Meyerovitch J. Subclinical thyroid disease and mortality in the elderly: a retrospective cohort study. Amer J Med. 2016;129:423–430.
15. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid. 2014;24:1670–1751.
16. Hoang TD, Olsen CH, Mai VQ, Clyde PW, Shakir MKM. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab. 2013;98:1982–1990.
17. Hennessey JV. The emergence of levothyroxine as a treatment for hypothyroidism. Endocrine. 2017;55:6–18.
18. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Food and Drug Administration Center for Drug Evaluation and Research Electronic. Available from: https://www.accessdata.fda.gov/scripts/cder/ob/. Accessed August 15, 2017.
19. Blakesley V, Awni W, Locke C, Ludden T, Granneman GR, Braverman LE. Are bioequivalence studies of levothyroxine sodium formulations in euthyroid volunteers reliable? Thyroid. 2004;14:191–200.
20. Dong BJ, Hauck WW, Gambertoglio JG, et al. Bio-equivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. JAMA. 1997;277:1205–1213.
21. Mayor GH, Orlando T, Kurtz NM. Limitations of levothyroxine bioequivalence evaluation: an analysis of an attempted study. Am J Ther. 1995;2:417–432.

22. Carr D, McLeod DT, Parry G, Thornes HM. Fine adjustment of thyroxine replacement dosage: comparison of the thyrotrophin releasing hormone test using a sensitive thyrotrophin assay with measurement of free thyroid hormones and clinical assessment. Clin Endocrinol. 1988;28:325–333.
23. Ernst FR, Barr P, Sandulli W, et al. The economic impact of levothyroxine dose adjustments: the CONTROL HE study. Clin Drug Investig. 2017;37:71–83.
24. Turner MR, Camacho X, Fischer HD, et al. Levothyroxine dose and risk of fractures in older adults: nested case-control study. BMJ. 2011;342:d2238.
25. Wirth CD, Blum MR, da Costa BR, et al. Subclinical thyroid dysfunction and the risk for fractures: a systematic review and meta-analysis. Ann Intern Med. 2014;161:189–199.
26. Geer M, Potter DM, Ulrixh H Alternative schedules of levothyroxine administration. Am J Health-Syst Pharm. 2015;72:373–377.
27. Virili C, Trimboli P, Romanelli F, Centanni M. Liquid and softgel levothyroxine use in clinical practice: state of the art. Endocrine. 2016;54:3–14.
28. Briesacher BA, Andrade SE, Fouayzi H, Chan A. Comparison of drug adherence rates among patients with seven different medical conditions. Pharmacotherapy. 2008;28:437–443.
29. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017;27:315–389.
30. Zeitler P, Solberg P. Food and levothyroxine administration in infants and children. J Pediatr. 2010;157:13–15.
31. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343–1421.
32. De Leo S, Braverman L. Hyperthyroidism. Lancet. 2016;388: 906–918.
33. Kravets I. Hyperthyroidism: diagnosis and treatment. Am Fam Physician. 2016;93:363–370.
34. Collet TH, Gussekloo J, Bauer DC, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Int Med. 2012;172:799–809.
35. Wirth CD, Blum MR, da Costa BR, et al. Subclinical thyroid dysfunction and the risk for fractures: a systematic review and meta-analysis. Ann Int Med. 2014;161:189–199.
36. Donangelo I, Suh SY. Subclinical hyperthyroidism: when to consider treatment. Am Fam Physician. 2017;95:710–716.
37. Stan MN, Garrity JA, Bahn RS. The evaluation and treatment of Graves ophthalmopathy. Med Clin N Amer. 2012;96: 311–328.
38. Cooper DS. Drug therapy: antithyroid drugs. New Engl J Med. 2005;352:905–917.
39. Emiliano AB, Governale L, Parks M, Cooper DS. Shifts in propylthiouracil and methimazole prescribing practices: antithyroid drug use in the United States from 1991 to 2008. J Clin Endocrinol Metab. 2010;95:2227–2233.
40. Walker MA, Briel M, Chrit-Crain M, et al. Effects of antithyroid drugs on radioiodine treatment: systematic review and meta-analysis of randomized controlled trials. BMJ. 2007; 335:1–7.
41. FDA drug safety communication: new boxed warning on severe liver injury with propylthiouracil. U.S. Food and Drug Administration. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209023.htm. Accessed August 15, 2017.
42. Wang MT, Lee WJ, Huang TY, Chu CL, Hsieh CH. Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study Br J Clin Pharmacol. 2014;78: 619–629.
43. Rivkees SA. Propylthiouracil versus methimazole during pregnancy: an evolving tale of difficult choices. J Clin Endocrinol Metab. 2013;98:4332–4335.
44. Devereaux D, Tewelde SZ. Hyperthyroidism and thyrotoxicosis. Emerg Med Clin N Am. 2014;32:277–292.
45. Kaptein EM, Sanchez A, Beale E, Chan LS. Thyroid hormone therapy for postoperative nonthyroidal illness: a systematic review and synthesis. J Clin Endocrinol Metab. 2010;95: 4526–4534.
46. Padmanabhan H. Amiodarone and thyroid dysfunction. South Med J. 2010;103:922–930.
47. Batcher EL, Tang C, Singh BN, et al. Thyroid function abnormalities during amiodarone therapy for persistent atrial fibrillation. Am J Med. 2007;120:880–885.
48. Lazarus JH. Lithium and thyroid. Best Pract Res Clin Endocrinol Metab. 2009;23:723–733.

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45 Adrenal Gland Disorders

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LEARNING OBJECTIVES

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

1. Explain the regulation and physiologic roles of hormones produced by the adrenal glands.
2. Recognize the clinical presentation of adrenal insufficiency.
3. Describe the pharmacologic management of acute and chronic adrenal insufficiency.
4. Recommend therapy monitoring parameters for adrenal insufficiency.
5. Recognize the clinical presentation of Cushing syndrome and the physiologic consequences of cortisol excess.
6. Describe the pharmacologic and nonpharmacologic management of Cushing syndrome.
7. Recommend strategies to prevent the development of hypercortisolism and hypocortisolism.
8. Recommend therapy monitoring parameters for Cushing syndrome.

INTRODUCTION

The adrenal glands are important in the synthesis and regulation of key human hormones. They play a crucial role in water and electrolyte homeostasis, as well as regulation of blood pressure, carbohydrate and fat metabolism, physiologic response to stress, and sexual development and differentiation. This chapter focuses on pharmacologic and nonpharmacologic management of the two most common conditions associated with adrenal gland dysfunction: glucocorticoid insufficiency (eg, Addison disease) and glucocorticoid excess (Cushing syndrome). Other adrenal disorders such as **congenital adrenal hyperplasia**, **pheochromocytoma**, hypoaldosteronism, and hyperaldosteronism are beyond the scope of this chapter.

PHYSIOLOGY, ANATOMY, AND BIOCHEMISTRY OF THE ADRENAL GLAND

LO 1

The adrenal gland is located on the upper segment of the kidney. It consists of an outer cortex and an inner medulla. The adrenal medulla secretes the catecholamines epinephrine (also called adrenaline) and norepineprhine (also called noradrenaline), which are involved in the regulation of the sympathetic nervous system. The adrenal cortex consists of three histologically distinct zones: the outer zona glomerulosa, the zona fasciculata, and an innermost layer called the zona reticularis. Each zone is responsible for production of different hormones (**Figure 45–1**).

The zona glomerulosa is responsible for the production of the mineralocorticoids aldosterone, 18-hydroxy-corticosterone, corticosterone, and deoxycorticosterone. Aldosterone promotes renal sodium retention and potassium excretion. Its synthesis and release are regulated by renin in response to decreased vascular volume and renal perfusion. Adrenal aldosterone production is regulated by the **renin-angiotensin-aldosterone system**.

The zona fasciculata is the middle layer and produces the glucocorticoid hormone cortisol. Cortisol is responsible for maintaining homeostasis of carbohydrate, protein, and fat metabolism. Its secretion follows a circadian rhythm, generally beginning to rise at approximately 3 to 4 AM and peaking around 6 to 8 AM. Thereafter, cortisol levels decrease throughout the day, approach 50% of the peak value by 4 PM, and reach their nadir around midnight. The normal rate of cortisol production is approximately 8 to 25 mg/day. Cortisol plays a key role in the body's response to stress. Its production increases markedly during physiologic stress, such as during acute illness, surgery, or trauma. In addition, certain conditions such as alcoholism, depression, anxiety disorder, obsessive-compulsive disorder, poorly controlled diabetes, morbid obesity, starvation, anorexia nervosa, and chronic renal failure are associated with increased cortisol levels. High total cortisol levels are also observed in the presence of increased cortisol binding globulin (the carrier protein for 80% of circulating cortisol molecules), which is seen in pregnancy or other high-estrogen states (eg, exogenous estrogen administration). Cortisol is converted in the liver to an inactive metabolite known as cortisone.[1]

The zona reticularis produces the androgens androstenedione, dehydroepiandrosterone (DHEA), and the sulfated form of dehydroepiandrosterone (DHEA-S). Only a small amount of testosterone and estrogen is produced in the adrenal glands. Androstenedione and DHEA are converted in the periphery, largely to testosterone and estrogen.

Adrenal hormone production is controlled by the hypothalamus and pituitary. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus and stimulates secretion of adrenocorticotropic hormone (ACTH; also known as corticotropin) from the anterior pituitary. ACTH in turn stimulates the adrenal cortex to produce cortisol. When sufficient or excessive cortisol levels are reached, a negative feedback is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production. The control of adrenal androgen synthesis also follows a similar negative feedback mechanism.

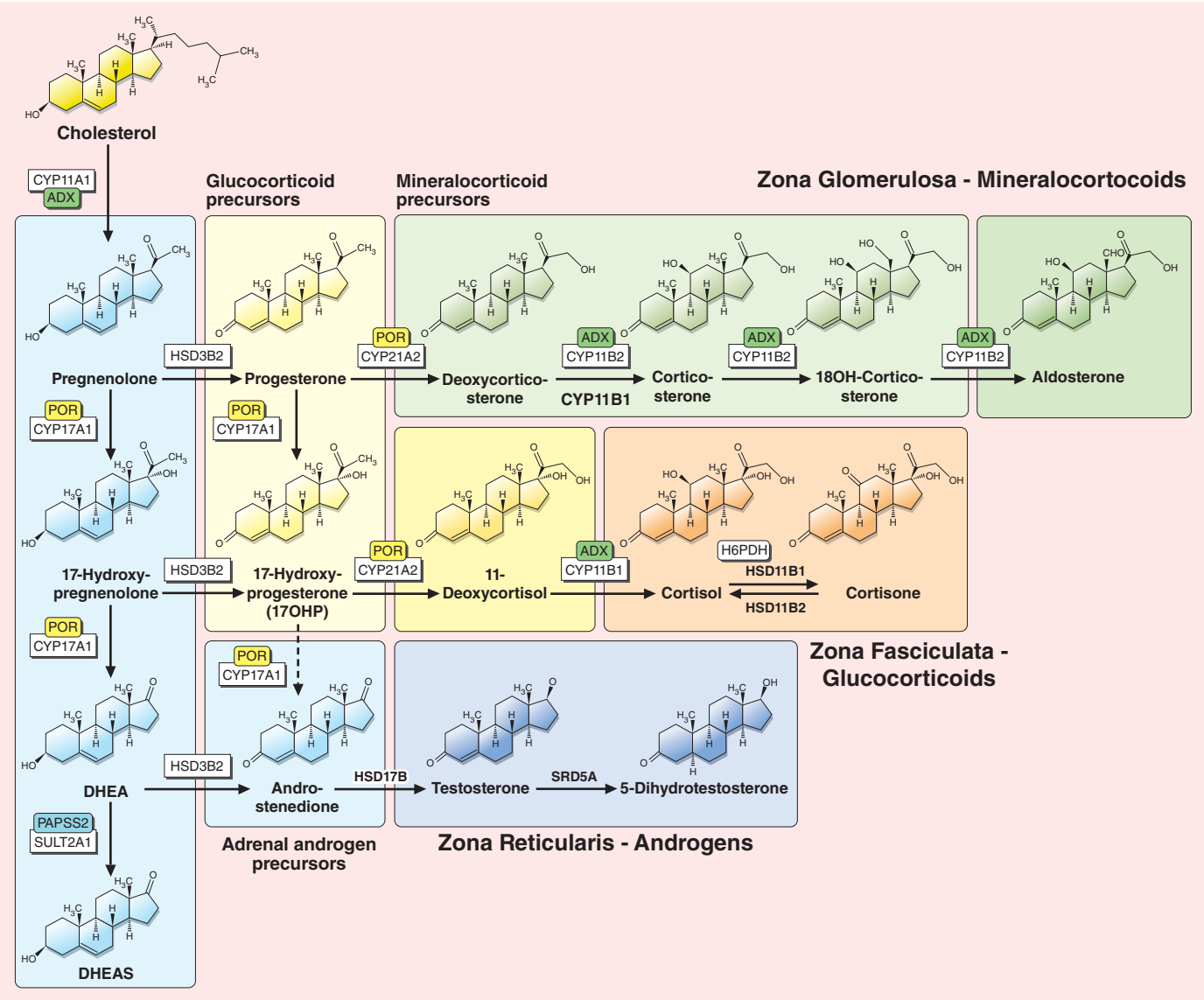

FIGURE 45–1. The adrenal cortex consists of three histologically distinct zones: the outer zona glomerulosa, the middle zona fasciculata, and an innermost layer called the zona reticularis. Each zone is responsible for production of different hormones. The zona glomerulosa is responsible for the production of mineralocorticoids such as aldosterone. The zona fasciculata produces cortisol and the zona reticularis produces androgens. (ADX, adrenodoxin; CYP11A1, side chain cleavage enzyme; CYP17A1, 17-alpha-hydroxylase/17,20 lyase; CYP21A2, 21-hydroxylase; CYP11B1, 11-beta-hydroxylase; CYP11B2, aldosterone synthase; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; H6PDH, hexose-6-phosphate dehydrogenase; HSD11B1, 11-beta-hydroxysteroid dehydrogenase type 1; HSD11B2, 11-beta-hydroxysteroid dehydrogenase type 2; HSD3B2, 3-beta-hydroxysteroid dehydrogenase type 2; HSD17B, 17-beta-hydroxysteroid dehydrogenase; PAPSS2, PAPS synthase type 2; POR, P450 oxidoreductase; SRD5A, 5-alpha-reductase; SULT2A1, DHEA sulfotransferase.) (Adapted, with permission, from Arlt W. Disorders of the adrenal cortex. In: Longo DL, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. New York City: McGraw-Hill, 2011.)

Figure 46–1 in Chapter 46 depicts hormonal regulation with the hypothalamic-pituitary-adrenal (HPA) axis.

ADRENAL INSUFFICIENCY

Epidemiology and Etiology

Adrenal insufficiency generally refers to the inability of the adrenal glands to produce adequate amounts of cortisol for normal physiologic functioning or in times of stress. The condition is usually classified as primary, secondary, or tertiary, depending on the etiology (Table 45–1).[1-5] The estimated prevalence of primary adrenal insufficiency and secondary adrenal insufficiency are approximately 60 to 143 and 150 to 280 cases per 1 million persons, respectively. Whereas primary adrenal insufficiency is usually diagnosed in the third to fifth decade of life, secondary adrenal insufficiency is commonly detected during the sixth decade.[1,6] Adrenal insufficiency is more prevalent in women than in men, with a ratio of 2.6:1.[1] Chronic adrenal insufficiency is rare.

Pathophysiology

Primary adrenal insufficiency, also known as Addison disease, occurs when the adrenal glands are unable to produce cortisol. It occurs from destruction of the adrenal cortex, usually from

Table 45–1

Etiologies of Adrenal Insufficiency[1-5]

Primary Adrenal Insufficiency (Addison disease)
- Autoimmune—accounts for 70%–90% of all cases of primary adrenal insufficiency
- Infectious or granulomatous diseases
  - Cytomegalovirus
  - Fungal (histoplasmosis, coccidioidomycosis, cryptococcosis, *Blastomyces dermatitidis* infection)
  - HIV (human immunodeficiency virus), AIDS (Acquired Immunodeficiency Syndrome)
    - Mycobacterial, cytomegaloviral, *Pneumocystic jiroveci*, and *Toxoplasma gondii* infection
  - Sarcoidosis
  - Tuberculosis
- Bilateral adrenal hemorrhage or infarction—usually due to anticoagulant therapy, coagulopathy, thromboembolic disease, or meningococcal infection. Causes acute adrenal insufficiency.
- Adrenalectomy
- Adrenoleukodystrophy (in men)
- Adrenomyeloneuropathy
- Infiltrative disorders: amyloidosis, hemochromatosis
- Genetic causes
  - Congenital adrenal hyperplasia
  - Familial glucocorticoid deficiency and hypoplasia
- Metastatic malignancy

Secondary Adrenal Insufficiency
- Cushing syndrome
- Panhypopituitarism
- Pituitary tumor
- Transsphenoidal pituitary microsurgery
- Pituitary irradiation
- Traumatic brain injury

Tertiary Adrenal Insufficiency
- Hypothalamic dysfunction

Drug-Induced (Most Common Cause of Secondary and Tertiary Adrenal Insufficiency)
- Chronic glucocorticoid administration at supraphysiologic doses
- Steroidogenesis inhibitors
- Megestrol acetate—has glucocorticoid-like activity
- Mifepristone (RU 486) —antagonizes glucocorticoid receptors
- Tyrosine kinase inhibitors
- Inducers of cytochrome P450 enzymes that increase cortisol metabolism (2B1, 2B2, 3A4)

an autoimmune process. In general, the clinical manifestations are observed when destruction of the cortex exceeds 90%.[4] KEY CONCEPT Signs and symptoms of adrenal insufficiency reflect the disturbance of normal physiologic carbohydrate, fat, and protein homeostasis caused by inadequate cortisol production and inadequate cortisol action. Primary adrenal insufficiency usually develops gradually. Patients may remain asymptomatic in the early stages with signs and symptoms present only during times of physiologic stress. Persistent signs and symptoms of hypocortisolism typically occur with disease progression. Additionally, primary adrenal insufficiency may be accompanied by a reduction in aldosterone and androgen production.

Secondary adrenal insufficiency occurs as a result of pituitary gland dysfunction, whereby decreased production and secretion of ACTH leads to a decrease in cortisol synthesis. Tertiary adrenal insufficiency is a disorder of the hypothalamus that results in decreased production and release of CRH, which in turn decreases pituitary ACTH production and release. In

Clinical Presentation and Diagnosis of Chronic Adrenal Insufficiency[1,3,4,6]

LO 2

General
- Symptoms develop gradually, especially in the early stages, may be vague, and mimic other medical conditions.
- Patients with autoimmune adrenal insufficiency may have other autoimmune disorders such as type 1 diabetes mellitus or autoimmune thyroiditis.

Symptoms (Percent Prevalence)
- Weakness and fatigue (99%).
- Anorexia, nausea, and diarrhea (56%–90%); may range from mild to severe with vomiting and abdominal pain.
- Hypoglycemia may occur.
- Amenorrhea may occur.
- Salt craving occurs in approximately 22% with Addison disease due to aldosterone deficiency.

Signs
- Weight loss (97%).
- Hypotension (< 110/70 mm Hg) and orthostasis (87%).
- Dehydration, hypovolemia, and hyperkalemia (in primary adrenal insufficiency only) due to aldosterone deficiency.
- Hyponatremia and hypochloridemia levels due to aldosterone deficiency. Hyponatremia can also be present in secondary insufficiency due to cortisol deficiency and increased antidiuretic hormone secretion leading to subsequent water retention.
- Increased serum blood urea nitrogen (BUN) and creatinine due to dehydration.
- Hyperpigmentation of skin and mucous membranes (92%). Usually observed around creases, pressure areas, areolas, genitalia, and new scars. Dark freckles and patches of vitiligo may be present. Hyperpigmentation, due to increased ACTH levels, occurs in most patients with primary but not secondary or tertiary insufficiency.
- Personality changes (irritability and restlessness) due to cortisol deficiency.
- Loss of axillary and pubic hair in women due to decreased androgen production.
- Blood count abnormalities (normocytic, normochromic anemia, relative lymphocytosis, neutrophilia, eosinophilia) due to cortisol and androgen deficiency.

Laboratory Tests (Table 45–2[1,3,4,7])
- Decreased basal and stress-induced cortisol levels.
- Decreased aldosterone level (in primary insufficiency only).
- Lack of increase in cortisol and aldosterone level after ACTH stimulation.

Other Diagnostic Tests
- Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the adrenal glands, pituitary, and/or hypothalamus can aid in determining etiology.
- Presence of anti-adrenal antibodies is suggestive of an autoimmune etiology.

Table 45–2

Tests for Diagnosing Adrenal Insufficiency[1,3,4,7]

Test	Procedure	Rationale	Finding in Adrenal Insufficiency	Comments
Screening and Diagnostic Tests for Adrenal Insufficiency				
Unstimulated serum cortisol measurement	Measure serum cortisol at 6–8 AM	Serum cortisol level peaks in the early morning	Serum cortisol < 3 mcg/dL (83 nmol/L)	• Evaluate result in context of those from other test(s) • Can be performed in conjunction with the rapid ACTH stimulation test (measure baseline serum cortisol before administering 250 mcg of cosyntropin)
Rapid ACTH stimulation test (also called cosyntropin stimulation test)	Measure serum cortisol 30–60 minutes after administering cosyntropin 250 mcg IM or IV	Increased cortisol secretion in normal individuals in response to ACTH stimulation but not in adrenal insufficiency	Serum cortisol concentration < 18–20 mcg/dL (497–552 nmol/L)	• Used as gold standard test for diagnosing primary adrenal insufficiency • False negative results may occur if ACTH deficiency is of recent onset (< 1 month) • If measured serum cortisol concentration is low, measure plasma ACTH, aldosterone, and renin concentrations to differentiate between primary and secondary or tertiary adrenal insufficiency (see below) • A normal response does not exclude mild secondary adrenal insufficiency or recent onset ACTH deficiency. Additional testing (eg, insulin tolerance or metyrapone test) may be required
Insulin tolerance test (insulin-induced hypoglycemia test)	Administer insulin IV to induce hypoglycemia then measure serum cortisol during symptomatic hypoglycemia (confirm that blood glucose is < 40 mg/dL [2.2 mmol/L])	Evaluates ability of entire HPA axis to respond to stress (hypoglycemia)	Serum cortisol concentration < 18 mcg/dL (497 nmol/L) is indicative of secondary adrenal insufficiency	• If the result of the rapid ACTH stimulation test is normal, either this or the overnight metyrapone test is still needed to evaluate for secondary adrenal insufficiency. The insulin tolerance test is considered the gold standard • Contraindicated in patients with a seizure history, aged > 60 years, or with cardiovascular or cerebrovascular disease • Requires close medical supervision • Contraindicated in adrenal crisis and primary adrenal insufficiency
Overnight metyrapone test	Administer metyrapone at midnight then measure serum cortisol at 8 AM the next day	Metyrapone inhibits cortisol synthesis. Its administration leads to rise in levels of ACTH and the precursor of cortisol, 11-deoxycortisol. Patients with adrenal insufficiency do not exhibit this	Normal response is a decrease in serum cortisol to < 5 mcg/dL (138 nmol/L) and an increase in 11-deoxycortisol to > 7 mcg/dL (202 nmol/L). Response not seen in secondary adrenal insufficiency	• Distinguishes between normal individuals and patients with secondary adrenal insufficiency • Contraindicated in adrenal crisis and primary adrenal insufficiency
Tests for Differential Diagnosis of Primary, Secondary, and Tertiary Adrenal Insufficiency				
Plasma ACTH concentration	Measure plasma ACTH	In primary adrenal insufficiency, hypocortisolism leads to elevated plasma ACTH concentration via positive HPA axis feedback	• Primary adrenal insufficiency: elevated plasma ACTH • Secondary or tertiary adrenal insufficiency: plasma ACTH low or inappropriately normal	• Evaluate result of test in combination with those from the plasma aldosterone and plasma renin tests

(*Continued*)

Table 45–2

Tests for Diagnosing Adrenal Insufficiency[1,3,4,7] *(Continued)*

Test	Procedure	Rationale	Finding in Adrenal Insufficiency	Comments
Plasma aldosterone concentration	Measure plasma aldosterone from same blood samples as those used in ACTH stimulation test	Patients with primary adrenal insufficiency may experience a reduction in aldosterone production	• Primary adrenal insufficiency: low plasma aldosterone • Secondary or tertiary adrenal insufficiency: aldosterone concentration is usually normal (≥ 5 ng/dL [139 pmol/L])	• Evaluate result of test in combination with those from plasma ACTH and plasma renin tests
Plasma renin concentration or activity	Measure plasma renin concentration or activity	Mineralocorticoid deficiency occurs in primary adrenal insufficiency but is usually not present in secondary or tertiary adrenal insufficiency	• Primary adrenal insufficiency: elevated plasma renin • Secondary or tertiary adrenal insufficiency: plasma renin concentration or activity is usually normal	• Evaluate result of test in combination with those from plasma ACTH and plasma aldosterone concentration tests

ACTH, adrenocorticotropic hormone or corticotropin; HPA, hypothalamic-pituitary-adrenal; IM, intramuscularly; IV, intravenously.

contrast to Addison disease, aldosterone production is unaffected in the secondary and tertiary forms of the disease. Chronic adrenal insufficiency often has a good prognosis if diagnosed early and treated appropriately.

Acute adrenal insufficiency (ie, adrenal crisis) results from the body's inability to sufficiently increase endogenous cortisol during periods of excessive physiologic stress. Adrenal crisis can occur when patients with chronic adrenal insufficiency do not receive adequate glucocorticoid replacement during stressful conditions such as those experienced during surgery, infection, fever, acute illness, invasive medical procedures, or trauma. Acute adrenal insufficiency can also result from bilateral adrenal infarction due to hemorrhage, embolus, sepsis, or adrenal vein thrombosis. Patients who are critically ill may also experience impaired HPA axis function, with an overall prevalence rate of 10% to 20%, and as high as 60% in those experiencing septic shock. These patients are also at risk for the life-threatening consequences of an adrenal crisis. To better recognize this condition, the term *critical illness–related corticosteroid insufficiency* was coined by the

Clinical Presentation and Diagnosis of Acute Adrenal Insufficiency (Adrenal Crisis)[1,4,6]

LO 2

General

- Onset of symptoms is acute and precipitated by excessive physiologic stress or abrupt discontinuation of supraphysiologic doses of chronic glucocorticoid.

Symptoms

- Severe weakness and fatigue.
- Abdominal or flank pain.

Signs

- Severe dehydration leading to hypotension and shock (circulatory collapse). Hypovolemia may not be responsive to intravenous (IV) hydration and may require use of vasopressors.
- Tachycardia
- Nausea, vomiting
- Fever
- Confusion
- Hypoglycemia
- Laboratory abnormalities are similar to those observed in chronic adrenal insufficiency.

Laboratory Tests

- The unstimulated serum cortisol and rapid ACTH stimulation tests are useful in diagnosis (Table 45–2). The insulin tolerance test is contraindicated due to preexisting hypoglycemia. The metyrapone test is also contraindicated since metyrapone inhibits cortisol production.

Note: Due to the life-threatening nature of this condition, empiric treatment should be started before laboratory confirmation in patients who present with the clinical picture of acute adrenal crisis.

American College of Critical Care Medicine Task Force.[8] Additionally, abrupt discontinuation or rapid tapering of glucocorticoids, given chronically in supraphysiologic doses, may lead to adrenal crisis. This condition results from prolonged suppression of the HPA axis and subsequent adrenal gland atrophy and hypocortisolemia. Other drugs associated with adrenal insufficiency include those that inhibit production (eg, ketoconazole) or increase metabolism (eg, the cytochrome P-450 [CYP] 3A4 inducer rifampin) of cortisol.[4] Regardless of the etiology, patients experiencing an adrenal crisis require immediate glucocorticoid treatment since manifestations such as circulatory collapse can lead to life-threatening sequelae.

Treatment

▶ *Chronic Adrenal Insufficiency*

LO 3

The general goals of treatment are to manage symptoms and prevent development of adrenal crisis. KEY CONCEPT Lifelong glucocorticoid replacement therapy may be necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy is usually required for those with Addison disease. Glucocorticoids with sufficient mineralocorticoid activity are generally required. However, the addition of a potent mineralocorticoid such as fludrocortisone, along with adequate salt intake, is sometimes needed to prevent sodium loss, hyperkalemia, and intravascular volume depletion. Mineralocorticoid supplementation typically is not indicated for the treatment of secondary or tertiary adrenal insufficiency because aldosterone production is often unaffected. Moreover, patients with secondary or tertiary adrenal insufficiency may only require replacement therapy until the HPA axis recovers. Hydrocortisone is often prescribed because it most closely resembles endogenous cortisol with its relatively high mineralocorticoid activity and short half-life, and allows the design of regimens that simulate the normal circadian cycle.[3] Other glucocorticoids, however, can be used. Table 45–3 lists the pharmacologic characteristics of commonly used glucocorticoids.[9] Because the primary source of DHEA and androgens is the adrenal cortex, women with adrenal insufficiency may experience decreased libido and energy. Therefore, DHEA supplementation has been advocated as an option for female patients experiencing these effects from adrenal insufficiency. However, a meta-analysis that included 23 randomized controlled trials found that DHEA supplementation was not associated with significant improvement in libido or sexual function.[10] The use of DHEA remains controversial and requires further study. Management strategies for chronic adrenal insufficiency are outlined below:[1-3,6,11,12]

LO 3

- For the treatment of primary adrenal insufficiency (Addison disease) in adults, hydrocortisone (15–25 mg) or cortisone acetate (20–35 mg) in two or three divided oral doses per day is recommended, with the highest dose given in the morning at awakening to mimic the early morning rise in endogenous cortisol. In a two-dose regimen, the second dose is taken in the early afternoon (2 hours after lunch); and in a three-dose regimen, the second dose is taken at lunch and the third dose is taken no closer than 4 to 6 hours before bedtime. This will avoid insomnia and allow for the lowest concentration in the blood at around midnight. In patients with concerns about adherence, oral prednisolone 3 to 5 mg/day, administered once or twice daily, may be given. Dexamethasone, a long-acting glucocorticoid is not recommended due to risk of Cushingoid side effects from difficulty in dose titration.

LO 4

Doses of the glucocorticoid replacement therapy may need to be increased or decreased in patients taking CYP 3A4 inducers or inhibitors, respectively. Glucocorticoid therapy at physiologic replacement doses should not lead to development of Cushing syndrome; however, careful monitoring should still be performed, and the smallest effective dose used. Patients should be educated regarding the need for increased glucocorticoid dosage during excessive physiologic stress. In addition, administer oral fludrocortisone at a starting daily dose of approximately 0.05 to 0.1 mg in the morning, and

Table 45–3

Pharmacologic Characteristics of Major Corticosteroids[9]

Corticosteroid	Glucocorticoid (Anti-Inflammatory) Potency	Mineralocorticoid (Sodium-Retaining) Potency	Duration of Action[a]	Equivalent Dose (mg)[b]
Glucocorticoid				
Cortisol	1	1	S	20
Cortisone	0.8	0.8	S	25
Prednisone	4	0.8	I	5
Prednisolone	4	0.8	I	5
Methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	I	4
Betamethasone	25	0	L	0.75
Dexamethasone	25	0	L	0.75
Mineralocorticoid				
Fludrocortisone	10	125	I	[c]

[a]S, short (ie, 8–12 hour biological $t_{1/2}$); I, intermediate (ie, 12–36 hour biological $t_{1/2}$); L, long (ie, 36–72 hour biological $t_{1/2}$).

[b]These dose relationships apply only to oral or intravenous administration, as glucocorticoid potencies may differ greatly following intramuscular or intraarticular administration.

[c]This agent is not used for glucocorticoid effects.

Adapted, with permission, from Shimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton LL, Chabner BA, Knollmann BC, eds. Pharmacological Basis of Therapeutics, 12th ed. New York City: McGraw-Hill; 2011: Figure 42–2.

Patient Encounter 1, Part 1: Presentation and Medical History

A 52-year-old female presents to the primary care clinic with complaints of fatigue, weakness, and intermittent nausea and diarrhea which have gradually worsened over the past year. She states that despite craving salty foods, she has lost 10 pounds (4.5 kg) in the last 6 months.

PMH:

- Tuberculosis—completed treatment course
- History of candidal vulvovaginitis
- Depression

FH: Father with type 1 diabetes

SH: Denies smoking, alcohol use or illicit drug use

Current Meds:

- Citalopram 20 mg once daily
- Loperamide 2–4 mg as needed for diarrhea (nonprescription)

PE:

VS: Sitting BP 104/66 mm Hg, P 70 beats/min, standing BP 92/64 mm Hg, RR 14 breaths/minute, Wt 139 pounds (63 kg)—10 pound (4.5 kg) loss in last 6 months, Ht 5'3" (160 cm)

Skin: Hyperpigmentation in creases of palms

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Labs (fasting): Serum electrolytes: sodium 132 mEq/L (mmol/L), potassium 5.3 mEq/L (mmol/L), chloride 95 mEq/L (mmol/L), bicarb 30 mEq/L (mmol/L), blood urea nitrogen (BUN) 28 mg/dL (10 mmol/L), creatinine 1.3 mg/dL (115 µmol/L), glucose 63 mg/dL (3.5 mmol/L)

Which signs or symptoms of adrenal insufficiency does the patient exhibit?

Does her presentation offer any clues as to etiology or classification of adrenal insufficiency?

Which tests would be most useful for determining etiology and confirming diagnosis of adrenal insufficiency?

monitor for resolution of postural hypotension, dizziness, salt-craving, dehydration, hyponatremia, and hyperkalemia; increase the dose if needed. Conversely, consider decreasing the dose if adverse reactions from mineralocorticoid administration such as hypertension, hypokalemia, fluid retention and other significant adverse events occur. In patients receiving hydrocortisone, it should be noted that this drug also possesses mineralocorticoid activity; and patients should be educated to avoid licorice and grapefruit juice as they can enhance hydrocortisone's mineralocorticoid effect. Patients taking concurrent phenytoin may need a higher dose as it can induce fludrocortisone's metabolism. All patients with Addison disease should also maintain adequate sodium intake. Lastly, although controversial (as indicated above), consider giving DHEA 25 to 50 mg/day (as a single oral dose in the morning) for a 6-month trial to premenopausal female patients who do not experience an improvement in mood and well-being even with adequate glucocorticoid and mineralocorticoid replacement. In these patients, monitor serum DHEA-S (aim for the middle range of normal levels in healthy young people).

- Patients with secondary and tertiary adrenal insufficiency are treated with oral hydrocortisone or another glucocorticoid as described for primary adrenal insufficiency. However, patients with secondary and tertiary adrenal insufficiency may require a lower dose. Some patients (eg, patients with drug-induced adrenal insufficiency or adrenal insufficiency following treatment for Cushing syndrome) will only require glucocorticoid replacement temporarily, which can be discontinued after recovery of the HPA axis. Fludrocortisone therapy is generally not needed.

► *Acute Adrenal Insufficiency*

LO 3 KEY CONCEPT During an acute adrenal crisis, the immediate treatment goals are to correct volume depletion, manage hypoglycemia, and provide glucocorticoid replacement. The 2016 Endocrine Society's Clinical Practice Guideline on the Diagnosis and Treatment of Primary Adrenal Insufficiency recommends that adults receive a rapid infusion of 1 liter isotonic saline within the first hour or 5% glucose in isotonic saline, followed by continuous IV isotonic saline guided by individual patient needs. For hypoglycemia, dextrose 0.5 to 1 g/kg or 2 to 4 mL/kg of D25W (maximum single dose 25 g) should be infused slowly. Glucocorticoid replacement can be accomplished by hydrocortisone 100 mg IV followed by hydrocortisone 200 mg/day as a continuous infusion for 24 hours, reduced to 100 mg/day the following day.[12] After achieving hemodynamic stability, hydrocortisone can be tapered to a lower maintenance dose by the fourth or fifth day and fludrocortisone can be added if needed. The dose can be increased to 200 to 400 mg/day if there are complications.[1] For the treatment of patients with critical illness-related corticosteroid insufficiency, see the 2017 consensus statements from the Society of Critical Care Medicine and European Society of Intensive Care Medicine.[13]

LO 3 KEY CONCEPT Patients with known adrenal insufficiency should be educated about the need for additional glucocorticoid replacement and prompt medical attention during periods of physiologic stress. Although the dosage of glucocorticoid is generally individualized, a common recommendation is to

Patient Encounter 1, Part 2: Treatment

After appropriate laboratory and diagnostic tests are performed, the patient is diagnosed with Addison disease.

How should her chronic primary adrenal insufficiency be treated?

What monitoring parameters (therapeutic and toxic) should be implemented?

Patient Care Process: Adrenal Insufficiency

Collect Information:

- Perform a medication history of prescription and nonprescription medications.
- Identify allergies.
- Review the medical history and physical assessment findings.
- Identify lifestyle habits, health goals, and socioeconomic factors that affect care.

Assess the Information:

- Evaluate for typical clinical manifestations of chronic or acute adrenal insufficiency.
- Determine if the patient has any etiologies of adrenal insufficiency.
- Assess results from the rapid ACTH stimulation test for presence of adrenal insufficiency (Table 45–2).
- Assess follow-up tests which differentiate between primary, secondary, and tertiary adrenal insufficiency (Table 45–2).

Develop a Care Plan:

- Determine whether patient will require mineralocorticoid replacement therapy in addition to glucocorticoid supplementation.
- Determine if the patient not previously diagnosed with adrenal insufficiency is presenting with acute adrenal crisis, in which case immediate treatment with injectable hydrocortisone and IV saline and dextrose solutions should be initiated prior to confirmation of diagnosis.
- Determine and correct the underlying cause of the acute adrenal crisis (eg, infection).
- Devise a strategy for patients with chronic adrenal insufficiency that includes supplemental doses of glucocorticoid when varying degrees of physiologic stress are experienced (eg, minor infection, pending surgery).
- Monitor patient for signs of an acute adrenal crisis and develop a plan to treat this emergency condition.

Implement the Care Plan:

- Educate patient and caregivers on causes of adrenal insufficiency, how to recognize clinical manifestations, the need to notify all health care providers of condition.
- Inform patients how to prevent an acute adrenal crisis: adhere to therapy, do not abruptly stop glucocorticoid treatment, need to increase the glucocorticoid dose during different severity levels of physiologic stress, including childbirth.
- Discuss when to self-administer parenteral glucocorticoid and seek emergency care.
- Suggest wearing or carrying a medical alert (eg, bracelet, card).
- Review dietary and pharmacologic therapy, including duration of treatment and potential adverse consequences of glucocorticoid and mineralocorticoid replacement.

Follow-up: Monitor and Evaluate:

- Monitor for adequacy of treatment and adverse reactions from glucocorticoid and/or mineralocorticoid therapy.
- Determine duration of treatment for patients with secondary and tertiary adrenal insufficiency.

double the maintenance dose of hydrocortisone if the patient experiences fever, or undergoes invasive dental or diagnostic procedures.[3] Patients who experience vomiting or diarrhea may not adequately absorb oral glucocorticoids and may benefit from parenteral therapy until symptoms resolve. Prior to surgery, additional glucocorticoid replacement (higher dose and parenteral route) must be given to prevent adrenal crisis. The dose and protocol varies depending on the type of surgery (eg, larger doses for major surgery compared to minor surgery).

Outcome Evaluation

LO 4

- Monitor weight, blood pressure, and serum electrolytes, along with symptom resolution and general well-being, in patients with adrenal insufficiency treated with glucocorticoid therapy; adjust dosages accordingly as needed.
- Monitor for adverse drug reactions related to glucocorticoid administration.
- Monitor for progression of the underlying etiology of adrenal insufficiency in patients with secondary or tertiary adrenal insufficiency.

HYPERCORTISOLISM (CUSHING SYNDROME)

Epidemiology and Etiology

Cushing syndrome refers to the pathophysiologic changes associated with exposure to supraphysiologic cortisol concentrations (endogenous hypercortisolism) or pharmacologic doses of glucocorticoids (exogenous hypercortisolism). Cushing syndrome from endogenous causes is a rare condition, with an estimated incidence of two to five cases per 1 million persons per year.[14] Patients receiving chronic supraphysiologic doses of glucocorticoids, such as those with rheumatologic disorders, are at high risk of developing Cushing syndrome.

Pathophysiology

Cushing syndrome can be classified as ACTH-dependent or ACTH-independent (Table 45–4).[1,15-17] ACTH-dependent Cushing syndrome results from ACTH-secreting (or rarely CRH-secreting) adenomas. The term *Cushing disease* refers specifically to Cushing syndrome from an ACTH-secreting pituitary adenoma. ACTH-independent Cushing syndrome is due either to excessive cortisol secretion by the adrenal glands (independent of ACTH stimulation) or to exogenous

Table 45–4

Etiologies of Cushing Syndrome[1,15-17]

ACTH-Dependent
- ACTH-secreting pituitary tumor (Cushing *disease*)—70% of endogenous cases
- ACTH-secreting non-pituitary tumors (ectopic ACTH syndrome)—15% of endogenous cases; usually from small cell lung carcinoma and bronchial carcinoids; also from pheochromocytoma, or from thymus, pancreatic, ovarian, or thyroid tumor. The tumor is usually disseminated (difficult to localize).
- CRH-secreting non-pituitary tumors (ectopic CRH syndrome)—rare

ACTH-Independent—15% of endogenous cases
- Unilateral adrenal adenoma
- Adrenal carcinoma
- Bilateral nodular adrenal hyperplasia—rare (< 1%)

Drug-Induced Cushing Syndrome (ACTH-independent)—most common cause of Cushing syndrome
- Prescription glucocorticoid preparations (most routes of administration)
- Nonprescription and herbal products with glucocorticoid activity (eg, nonprescription anti-itch products with hydrocortisone, herbal products with magnolia bark or those claiming to contain adrenal cortex extracts or other byproducts)
- Other drugs with glucocorticoid activity (eg, megestrol acetate, medroxyprogesterone)

ACTH, adrenocorticotropic hormone or corticotropin; CRH, corticotropin-releasing hormone.

glucocorticoid administration. The plasma ACTH concentration is elevated in ACTH-dependent conditions but not in ACTH-independent conditions because elevated cortisol concentrations suppress pituitary ACTH secretion via negative feedback. ACTH and cortisol concentrations are elevated episodically in ACTH-dependent disease due to random hypersecretion of ACTH.[4] In general, patients with Cushing syndrome due to endogenous or exogenous glucocorticoid excess present with similar clinical manifestations. However, patients with ectopic ACTH syndrome may not exhibit the typical signs and symptoms of hypercortisolism due to the acute onset nature of the underlying disease process.[1,9]

Cushing disease and adrenal **carcinomas** cause adrenal androgen hypersecretion in high enough concentrations to result in signs of androgen excess such as acne, menstrual irregularities, and **hirsutism**, and cause **virilization** in women.[4] Drug-induced Cushing syndrome from glucocorticoid administration occurs most commonly in patients receiving oral therapy, but other routes such as inhalation, dermal, nasal, and intra-articular have also been implicated.[15] Over-the-counter products, including dietary supplements, should also be evaluated since they may contain corticosteroids. Drug-induced Cushing syndrome has been reported with the use of Chinese herbal products adulterated with corticosteroids.[18,19] The risk of glucocorticoid-induced Cushing syndrome appears to increase with higher doses and/or longer treatment durations.[15]

LO 5 Left untreated, patients with Cushing syndrome may experience severe complications of hypercortisolism, resulting in up to a nearly fourfold increase in mortality.[20] Mortality in patients with Cushing is mostly attributed to cardiovascular disease. Hypertension, hyperglycemia, and hyperlipidemia are common findings and can be associated with cardiac hypertrophy, atherosclerosis, and hypercoagulability. Osteopenia, osteoporosis, and increased fractures also have been reported.[20] Prevention and management of these conditions are discussed elsewhere in this text. Children may experience linear growth retardation from reduced growth hormone secretion and inhibition of epiphysial cartilage development in long bones.[14,20]

Treatment

The goal of treatment in patients with Cushing syndrome is reversal of hypercortisolism and management of the associated comorbidities, including the potential for long-term sequelae such as cardiac hypertrophy. KEY CONCEPT Surgical resection is considered the treatment of choice for Cushing syndrome from endogenous causes if the tumor can be localized and if there are no contraindications. The treatment of choice for Cushing syndrome from exogenous causes is gradual discontinuation of the offending agent.

▶ *Nonpharmacologic Therapy*

LO 6 **Transsphenoidal pituitary microsurgery** is the treatment of choice for Cushing disease. Removal of the pituitary tumor can bring about complete remission or cure in 78% to 97% of cases. HPA axis suppression associated with chronic hypercortisolism can result in prolonged adrenal insufficiency lasting for months after surgery and requiring exogenous glucocorticoid administration. Pituitary irradiation or bilateral adrenalectomy is usually reserved for patients who are not surgical candidates or for those who relapse or do not achieve complete remission following pituitary surgery. Because the response to pituitary irradiation can be delayed (several months to years), concomitant treatment with cortisol-lowering medication may be necessary. Bilateral adrenalectomy is also used for management of adrenal carcinoma and in patients with poorly controlled ectopic Cushing disease in whom the ACTH-producing lesion cannot be localized. Bilateral laparoscopic adrenalectomy achieves an immediate and total remission (nearly 100% cure rate), but these patients will require lifelong glucocorticoid and mineralocorticoid supplementation.[5,21] **Nelson syndrome** may develop in nearly 20% to 50% of patients who undergo bilateral adrenalectomy without pituitary irradiation. This condition presumably results from persistent hypersecretion of ACTH by the intact pituitary adenoma, which continues to grow because of the loss of feedback inhibition by cortisol. Treatment of Nelson syndrome may involve pituitary irradiation or surgery.[4]

LO 6 The treatment of choice in patients with adrenal adenomas is unilateral laparoscopic adrenalectomy. These patients require glucocorticoid supplementation during and after surgery due to atrophy of the contralateral adrenal gland and suppression of the HPA axis. Glucocorticoid therapy is continued until recovery of the remaining adrenal gland is achieved. Patients with adrenal carcinomas have a poor prognosis, with a five-year survival of 20% to 58%, because of the advanced nature of the condition (metastatic disease). Surgical resection to reduce tumor burden and size, pharmacologic therapy, or bilateral laparoscopic adrenalectomy are the treatment options commonly utilized to manage this condition.[1,5]

▶ *Pharmacologic Therapy*

LO 6 KEY CONCEPT Pharmacotherapy is indicated when the ectopic ACTH-secreting tumor cannot be localized; to control hypercortisolism to prepare for surgery; and in patients who: (1) are not surgical

Clinical Presentation and Diagnosis of Cushing Syndrome[1,14,15,22]

LO 5

General

- Onset of signs and symptoms range from gradual to rapid, depending on etiology.
- Differential diagnoses include diabetes mellitus and the metabolic syndrome because these conditions share several similar characteristics with Cushing syndrome (eg, obesity, hypertension, hyperlipidemia, hyperglycemia, and insulin resistance). In women, the presentations of hirsutism, menstrual abnormalities, and insulin resistance are similar to those of polycystic ovary syndrome. Cushing syndrome can be differentiated from these conditions by identifying the classic signs and symptoms described below.
- True Cushing syndrome also must be distinguished from other conditions that share some clinical presentations (as well as elevated plasma cortisol concentrations) such as depression, anxiety disorder, obsessive-compulsive disorder, alcoholism, obesity, uncontrolled diabetes, eating disorders, and physiologic stress—the so-called pseudo-Cushing states.

Signs and Symptoms (Percent Prevalence)

General appearance

- Weight gain and obesity, manifesting as truncal obesity (90%)
- Rounded and puffy face ("moon facies") (75%)
- Dorsocervical ("buffalo hump") and supraclavicular fat accumulation
- Hirsutism (75%)

Skin changes from atrophy of dermis and connective tissue

- Thin skin
- Facial plethora (70%)
- Skin striae ("stretch marks" that are usually red or purple in appearance and > 1 cm) (50%)—not common in patients older than 40 years of age
- Acne (35%)
- Easy bruising (40%)
- Hyperpigmentation—typically with ectopic ACTH syndrome

Metabolic

- Hyperglycemia that can range from impaired glucose tolerance (75%) to diabetes mellitus (20%–50%)
- Hyperlipidemia (70%)
- Polyuria (30%)
- Kidney stones (15%–50%)
- Hypokalemic alkalosis (from mineralocorticoid effect of cortisol)

Cardiovascular

- Hypertension (from mineralocorticoid effect of cortisol) (85%)
- Peripheral edema

Genitourinary

- Menstrual irregularities (typically amenorrhea) (70%)
- Erectile dysfunction (85%)

Other

- Psychiatric changes such as depression, emotional lability, psychosis, euphoria, anxiety, and decreased cognition (85%)
- Sleep disturbances
- Osteopenia (80%) and osteoporosis—usually affecting trabecular bone
- Linear growth impairment in children
- Proximal muscle weakness (65%)
- Avascular necrosis (more common in iatrogenic cases)
- Glaucoma, cataracts
- Impaired wound healing and susceptibility to opportunistic infections
- Hypothyroidism

Laboratory Tests

- Diagnosis is often complex and generally requires the involvement of endocrinologists and specialized testing centers.
- Initial screening tests are listed in Table 45–5.[1,22] Typically, a combination of two screening tests is used to establish the preliminary diagnosis.
- After the diagnosis is confirmed, additional tests (eg, midnight serum cortisol or combined dexamethasone suppression plus CRH test) can be performed to determine the etiology or rule out false positive/negative results.

Other Diagnostic Tests

Imaging studies and inferior petrosal sinus sampling may be needed to distinguish between pituitary, ectopic, and adrenal tumors.

candidates; (2) have failed surgery or had a relapse after surgery; or (3) have Cushing disease awaiting the onset of effect of pituitary radiation.[23] The drugs used are classified according to their mechanism and site of action (Table 45–6[21-26]). The most widely used therapeutic class is the adrenal steroidogenesis inhibitors, which can improve hypercortisolism by inhibiting enzymes involved in the biosynthesis of cortisol.[23] Because of their potential to cause adrenal suppression, temporary glucocorticoid replacement, and in some cases mineralocorticoid supplementation, may be needed during and after treatment.

LO 6

KEY CONCEPT In drug-induced Cushing syndrome, discontinuation of the offending agent is the best management option. However, abrupt withdrawal of the glucocorticoid can result in adrenal insufficiency or exacerbation of the underlying disease.[15]

KEY CONCEPT Glucocorticoid doses less than 7.5 mg/day of prednisone or its equivalent for less than 3 weeks generally would not be expected to lead to suppression of the HPA axis.[5,25] However, in patients receiving pharmacologic doses of glucocorticoids for prolonged periods, gradual tapering to near physiologic levels (5–7.5 mg/day of prednisone or its equivalent) should precede drug discontinuation. Administration of a short-acting glucocorticoid in the morning and use of alternate-day dosing may reduce the risk of adrenal suppression. Testing of the HPA axis may be useful in assessing adrenal reserve. In some cases, supplemental glucocorticoid administration during excessive physiologic stress may be needed for up to 1 year after glucocorticoid discontinuation.[15] Table 45–7 lists strategies to prevent the development of hypercortisolism and hypocortisolism.

LO 7

Table 45–5

First-Line Screening Tests in Patients with Characteristics of Cushing Syndrome[1,22]

Test	Test Procedure and Measurement	Rationale	Typical Finding in Cushing Syndrome	Comments
24-hour urinary-free cortisol	Collect urine over 24 hours and measure unbound cortisol excreted by kidneys	Urinary cortisol is elevated in hypercortisolic states	Elevated urinary-free cortisol (value depends on the assay used)	• Easy to perform but should not be used alone since sensitivity and specificity depend on assay used • To exclude periodic hypercortisolism, 2 or more samples should be obtained (with urinary creatinine measurement to assess completeness of collection) • Distinguishes the effects of Cushing syndrome (elevation) from obesity (no elevation). However, false positive in other pseudo-Cushing states, physiologic stress, if fluid intake ≥ 5 liters/day, or taking carbamazepine or fenofibrate (if measured by HPLC) • False negative if moderate to severe renal function, or subclinical hypercortisolism
Overnight dexamethasone suppression test (DST)	Give 1 mg oral dexamethasone at 11 PM, then measure plasma cortisol at 8–9 AM the next morning	Dexamethasone administration suppresses morning plasma cortisol in normal individuals	Plasma cortisol < 1.8 μg/dL (50 nmol/L) is not suggestive of Cushing syndrome	• Simple to perform and inexpensive • Can be used in conjunction with, or instead of, the urinary-free cortisol test • False positive if pseudo-Cushing states, physiologic stress, pregnancy, estrogen treatment (including contraceptives), uremia, taking inducers of dexamethasone metabolism (phenytoin, alcohol, etc.), or decreased dexamethasone absorption • False negative if subclinical hypercortisolism, slow metabolism of dexamethasone (eg, CYP3A4 inhibitors), or liver or renal impairment • In pseudo-Cushing states, the 48-hour 2-mg DST (administer 0.5 mg dexamethasone every 6 hours for 48 hours then measure serum cortisol at 8 or 9 AM after the last dose) is preferred
Late-night salivary cortisol	Collect salivary cortisol concentration at 11 PM	Loss of circadian rhythm of cortisol secretion (no nadir at night) in Cushing syndrome but not in pseudo-Cushing states	Elevated late-night salivary cortisol	• Easiest screening test to perform (sample can be collected at home by patient) • To exclude periodic hypercortisolism, two or more samples (on two separate evenings) should be obtained • False positive possible with cigarette smoking, chewing tobacco, licorice ingestion, in pseudo-Cushing states • Adjust collection time in shift workers and others with bedtime significantly after midnight

CYP, cytochrome P450; HPLC, high-performance liquid chromatography.

Patient Encounter 2

A 32-year-old female presents to a clinical pharmacist for diabetes education. She was recently diagnosed with type 2 diabetes. She also has a diagnosis of hypertension, dyslipidemia, depression, asthma, eczema, and seasonal allergies. She complains of thirst, polyuria, and fatigue. She also reports increased facial acne over the past few months. Physical examination reveals an obese (BMI 38 kg/m^2) woman with truncal obesity, dosocervical fat, and facial plethora. Her current medications include metformin, lisinopril, escitalopram, albuterol inhaler, fluticasone nasal spray, and mometasone 0.1% cream. She has been treated several times this year with methylprednisolone therapy for reoccurring rashes from poison ivy. The clinical pharmacist suggests evaluation for possible Cushing syndrome.

Which findings are suggestive of Cushing syndrome?

Aside from Cushing syndrome, what are some major differential diagnoses for clinical presentation?

The patient is diagnosed with drug-induced Cushing syndrome after evaluation and diagnostic testing by the endocrinologist. What patient education points should be provided?

Table 45–6

Pharmacologic Treatments for Cushing Syndrome[21-26]

Drug	Mechanism of Action	Dosage[a]: Initial, Usual, Maximum, Dosing Adjustment for Renal and/or Hepatic Failure	Common and/or Major Adverse Reactions	Comment
Inhibitors of Adrenal Steroidogenesis				
Ketoconazole[b] (oral administration)	Inhibits several CYP enzymes including 17,20-lyase, 17-hydroxylase, and 11β-hydroxylase. Also inhibits cholesterol synthesis	*Adults*: 400–1600 mg/day; every 6–8 hour dosing Extensively metabolized by liver and dosing adjustment should be considered in severe liver disease. Dosing adjustment not needed in renal disease	Generally well-tolerated. Symptoms of adrenal insufficiency (eg, nausea, vomiting, decreased appetite, fatigue). Gynecomastia, decreased libido, and impotence (due to inhibition of testosterone synthesis). Hepatotoxicity	• Effective in a majority of causes; rapid clinical improvement seen • Monitor efficacy with urinary cortisol • Monitor liver transaminases for hepatotoxicity • Useful in women with hirsutism and patients with hyperlipidemia • Requires gastric acidicity for dissolution and absorption, therefore not useful in patients with achlorhydria and those taking proton pump inhibitors or round-the-clock antacids or histamine-2 receptor blockers • Is a CYP3A4 substrate and a strong CYP3A4 inhibitor. Also has other CYP interaction potential. Coadministration with certain medications can lead to QT prolongation and dysrhythmia
Metyrapone[b] (oral administration)	Inhibits 11β-hydroxylase. Also suppresses aldosterone synthesis	*Adults*: 500 mg/day to 6 g/day; every 6–8 hour dosing Dosages in special populations (liver and kidney disease, elderly patients) have not been established	Generally well-tolerated. Hirsutism, acne, adrenal insufficiency, GI intolerance, rash, hypokalemia, edema, hypertension	• Used in Cushing disease, ectopic ACTH syndrome, and adrenal carcinoma • Also used as a test to diagnose adrenal insufficiency
Etomidate[b] (intravenous infusion administration)	Inhibits 17,20-lyase, 17-hydroxylase, and 11β-hydroxylase	*Adults*: Bolus and titrate Extensively metabolized in the liver to inactive metabolites. Because of changes in protein binding, dosing adjustment may be needed in kidney and liver disease	Injection site pain, nausea, vomiting, myoclonus, hypotension	• Is a general anesthetic • Generally reserved for patients with more severe symptoms and in emergency settings
Adrenolytic Agent				
Mitotane (oral administration)	Inhibits steroidogenesis at lower doses and is adrenolytic at higher doses. Inhibits 11β- hydroxylase and cholesterol side-chain cleavage. Reduces aldosterone synthesis	*Adults*: Starting dose: 250 mg; 500 mg/day to 8 g/d. Elderly patients may require a dose decrease Primarily metabolized by the liver and dosing adjustment may be needed in liver disease	GI intolerance (high incidence), fatigue, dizziness, somnolence, gynecomastia. Hyperlipidemia requiring lipid-lowering treatment. Adrenal insufficiency requiring glucocorticoid replacement therapy	• FDA-approved for treatment of inoperable adrenal cortical carcinoma. Can be used in other types of Cushing syndrome • Efficacy takes several weeks • Lower rate of relapse when used with pituitary radiation. Also enables lower doses and therefore lower rate of adverse reactions • Hypocortisolism (if occurs) may persist several weeks/months after discontinuation as drug is stored in fatty tissues • Strong inducer of CYP3A4

Peripheral Glucocorticoid Antagonist				
Mifepristone (RU 486) (oral administration)	Antagonizes glucocorticoid receptors	*Adults*: 300–1200 mg/day Maximum 300 mg/day with concomitant strong CYP450 inhibitors Do not exceed 600 mg/day in renal impairment or mild-to-moderate hepatic impairment. Do not use in severe hepatic impairment	Nausea, fatigue, headache, hypokalemia, arthralgia, vomiting, peripheral edema, hypertension, dizziness, decreased appetite, endometrial hypertrophy, prolonged QT interval. Has abortifacient and embryotoxic properties	• FDA-approved for control of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery • Increases cortisol and ACTH levels via antagonism of negative feedback of ACTH secretion • Requires cautious use since limited clinical experiences and cannot use cortisol or ACTH levels to monitor efficacy of treatment • Quicker effectiveness compared to other drug treatment options • Is a CYP3A4 substrate. Also inhibits CYP3A and has other CYP interaction potential
Somatostatin Analog				
Pasireotide (subcutaneous injection)	Binds to somatostatin receptor subtype 5 over-expressed in corticotroph tumor cells resulting in inhibition of ACTH secretion	*Adults*: 0.6–0.9 mg twice daily Moderate hepatic impairment (Child Pugh B): initial 0.3 mg twice a day, maximum 0.6 mg twice a day. Avoid in severe hepatic impairment (Child Pugh C). No dosage adjustment needed in renal impairment	Hyperglycemia, GI pain, nausea, diarrhea, headache, fatigue, bradycardia, QT prolongation, liver test elevations, cholelithiasis, pituitary hormone (other than ACTH) inhibition	• FDA-approved for treatment of adult patients with Cushing disease for whom pituitary surgery is not an option or has not been curative • Measure response based on 24-hour urinary-free cortisol level and/or improvement in signs and symptoms

[a]Dosing guidelines (including age ranges) and safety for children have not been definitively established.

[b]These medications do not have FDA-approved indications for the treatment of Cushing syndrome in either adults or children.

ACTH, adrenocorticotropic hormone or corticotropin; CYP, cytochrome P450; FDA, Food and Drug Administration; GI, gastrointestinal.

Table 45–7

Principles of Glucocorticoid Administration to Avoid Hypercortisolism or Hypocortisolism

To Prevent Hypercortisolism and Development of Cushing Syndrome

- Give the lowest glucocorticoid dose that will manage the disease being treated and for the shortest possible duration
- If feasible, give glucocorticoid via administration routes that minimize systemic absorption (such as inhalation or dermal)
- If feasible, administer glucocorticoid treatment every other day (calculate the total 48-hour dose and give as a single dose of intermediate-acting glucocorticoid in the morning)[4]
- Avoid concurrent administration of drugs that can inhibit glucocorticoid metabolism

To Prevent Hypocortisolism and Development of Adrenal Insufficiency or Adrenal Crisis

- If the patient requires discontinuation from chronic treatment with supraphysiologic doses of glucocorticoid, the following discontinuation protocol can be used:[4]
  - Gradually taper the dose to approximately 20 mg of prednisone or equivalent per day, given in the morning, and then
  - Change glucocorticoid to every other day administration, in the morning
  - Stop the glucocorticoid when the equivalent physiologic dose is reached (20 mg/day of hydrocortisone or 5–7.5 mg/day of prednisone or equivalent)
  - Understand that recovery of the HPA axis may take up to a year after glucocorticoid discontinuation during which the patient may require supplementation therapy during periods of physiologic stress
- Evaluate patients at risk for adrenal insufficiency as a result of treatment(s) of Cushing syndrome and initiate glucocorticoid and mineralocorticoid replacement therapy as appropriate
- Avoid concurrent administration of drugs that can induce glucocorticoid metabolism
- Educate patients about:
  - The need for replacement or supplemental glucocorticoid and mineralocorticoid therapy
  - How to administer parenteral glucocorticoid if unable to immediately access medical care during an emergency
  - Need to wear or carry medical identification regarding their condition (eg, card, bracelet)

HPA, hypothalamic-pituitary-adrenal.

Patient Care Process: Cushing Syndrome

Collect Information:

- Perform a medication history of prescription and nonprescription medications.
- Identify allergies.
- Review the medical history and physical assessment findings.
- Identify lifestyle habits, health goals, and socioeconomic factors that affect care.

Assess the Information:

- Determine whether the patient is taking any glucocorticoids (from prescription or herbal/dietary supplement sources) that may have induced Cushing syndrome.
- Review relevant lab tests (eg, 24-hour urinary-free cortisol, overnight dexamethasone suppression test [DST], late-night salivary cortisol).
- Establish diagnosis and etiology based on diagnostic testing.

Develop a Care Plan:

- Evaluate patient for appropriateness of surgery, radiation, and/or pharmacologic therapy depending on etiology.
- If etiology is exogenous administration of glucocorticoid, attempt taper.
- If etiology is endogenous, determine if patient is an appropriate candidate for surgical resection of the tumor or has contraindications to surgical resection such as advanced disease (metastatic adrenal carcinoma).
- Assess response and complications associated with surgery including[21]:
  - Measuring plasma cortisol postsurgery to determine if the patient displays persistent hypercortisolism (surgical treatment failure) or hypocortisolism (adrenal insufficiency requiring steroid replacement therapy).
  - In patients demonstrating hypocortisolism:
    i. Monitor for signs and symptoms of glucocorticoid withdrawal (headache, fatigue, malaise, myalgia).
    ii. Monitor for signs and symptoms of adrenal insufficiency and develop a treatment plan.
    iii. Monitor morning cortisol or response to ACTH stimulation every 3–6 months to assess for HPA axis recovery. Discontinue glucocorticoid replacement therapy when cortisol concentrations are greater than 19 mcg/dL (524 nmol/L) on either test.
    iv. Monitor cortisol, ACTH, low-dose dexamethasone suppression, or other tests to assess for risk of relapse of hypercortisolism.
- If surgical resection does not achieve satisfactory disease control or is not indicated, evaluate the patient for pituitary radiation or bilateral adrenalectomy with concomitant pituitary radiation.

(*Continued*)

Patient Care Process: Cushing Syndrome (*Continued*)

- Evaluate patients with adrenal adenomas for unilateral adrenalectomy.
  - Give glucocorticoid and mineralocorticoid replacement (permanently in the case of bilateral adrenalectomy).

Implement the Care Plan:

- Educate patient and caregivers on causes and possible sequelae of Cushing syndrome, how to recognize clinical manifestations, and the need to notify all health care providers of condition.
- Inform patients on how to reduce modifiable cardiovascular and metabolic complications.
- Review advantages and disadvantages of treatment options including possible adverse consequences.
- Highlight the importance of adherence to therapy.
- Discuss the need for glucocorticoid and mineralocorticoid replacement after treatment, if appropriate.

Follow-up: Monitor and Evaluate:

- Monitor for response to therapy, need for dose adjustments, and presence of adverse drug reactions.
- Once disease control is achieved, continue to monitor biochemical markers and patient for development of complications of Cushing syndrome, as relapse may occur.
- Monitor patients treated with surgery or pituitary radiation for development of pituitary hormone deficiency.

Outcome Evaluation

LO 8

- Monitor patients receiving surgical, medical, or radiation therapy for resolution of the clinical manifestations of hypercortisolism. Symptoms often improve immediately after surgery and soon after initiation of drug therapy. However, it may take months for symptoms to resolve following radiation therapy.
- Monitor for normalization of serum cortisol concentrations.
- Patient Care Process discusses additional evaluation strategies.

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Abbreviations Introduced in This Chapter

ACTH	Adrenocorticotropic hormone or corticotropin
AIDS	Acquired immunodeficiency syndrome
BUN	Blood urea nitrogen
CRH	Corticotropin-releasing hormone
CT	Computed tomography
CYP	Cytochrome P450
DHEA	Dehydroepiandrosterone
DHEA-S	Sulfated form of dehydroepiandrosterone
DST	Dexamethasone suppression test
FDA	Food and Drug Administration
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
HPLC	High performance liquid chromatography
IM	Intramuscular
IV	Intravenous or intravenously
MRI	Magnetic resonance imaging

REFERENCES

1. Carroll TB, Aron DC, Findling JW, Tyrrell JB. Glucocorticoids and adrenal androgens. In: Gardner DG, Shoback D, eds. Basic and Clinical Endocrinology, 9th ed. New York City: McGraw-Hill; 2011.
2. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet. 2014;383:2152–2167.
3. Salvatori R. Adrenal insufficiency. JAMA. 2005;294:2481–2488.
4. Arlt W. Disorders of the adrenal cortex. In: Kasper DL, Fauci A, Hauser S, Longo D, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 19th ed. New York City: McGraw-Hill; 2015.
5. Young WF, Jr., Thompson GB. Laparoscopic adrenalectomy for patients who have Cushing's syndrome. Endocrinol Metab Clin North Am. 2005;34:489–499, xi.
6. Arlt W, Allolio B. Adrenal insufficiency. Lancet. 2003;361:1881–1893.
7. Javorsky BR, Aron DC, Findling JW, Tyrrell JB. Hypothalamus and pituitary gland. In: Gardner DG, Shoback D, eds. Basic and Clinical Endocrinology, 9th ed. New York City: Lange Medical Books/McGraw-Hill; 2011.
8. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36:1937–1949.
9. Shimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton LL, Chabner BA, Knollmann BC, eds. Pharmacological Basis of Therapeutics, 12th ed. New York City: McGraw-Hill; 2011.
10. Elraiyah T, Sonbol MB, Wang Z, et al. The benefits and harms of systemic dehydroepiandrosterone (DHEA) in postmenopausal women with normal adrenal function: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2014;99:3536–3542.
11. Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275:104–115.
12. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2015;101:364–389.
13. Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med. 2017.
14. Findling JW, Raff H. Screening and diagnosis of Cushing's syndrome. Endocrinol Metab Clin North Am. 2005;34:385–402, ix–x.
15. Hopkins RL, Leinung MC. Exogenous Cushing's syndrome and glucocorticoid withdrawal. Endocrinol Metab Clin North Am. 2005;34:371–384, ix.

16. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. Ann Intern Med. 2003;138:980–991.
17. Lacroix A, Bourdeau I. Bilateral adrenal Cushing's syndrome: macronodular adrenal hyperplasia and primary pigmented nodular adrenocortical disease. Endocrinol Metab Clin North Am. 2005;34:441–458, x.
18. Goldman JA, Myerson G. Chinese herbal medicine: camouflaged prescription antiinflammatory drugs, corticosteroids, and lead. Arthritis Rheum. 1991;34:1207.
19. Keane FM, Munn SE, du Vivier AW, Taylor NF, Higgins EM. Analysis of Chinese herbal creams prescribed for dermatological conditions. BMJ. 1999;318:563–564.
20. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab. 2003;88:5593–5602.
21. Utz AL, Swearingen B, Biller BM. Pituitary surgery and postoperative management in Cushing's disease. Endocrinol Metab Clin North Am. 2005;34:459–478, xi.
22. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's Syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100:2807–2831.
23. Nieman LK. Medical therapy of hypercortisolism (Cushing's syndrome). UpToDate, Available from: https://www.uptodate.com/contents/medical-therapy-of-hypercortisolism-cushings-syndrome. Accessed July 6, 2017.
24. Sonino N, Boscaro M. Medical therapy for Cushing's disease. Endocrinol Metab Clin. 1999;28:211–222.
25. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med. 2003;348:727–734.
26. Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR, Feldman D. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). J Clin Endocrinol Metab. 2001;86:3568–3573.

46 Pituitary Gland Disorders

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LEARNING OBJECTIVES

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

1. List the mediators and primary effects of pituitary hormones.
2. Identify clinical features of patients with acromegaly.
3. Discuss the role of surgery and radiation therapy for patients with acromegaly.
4. Select appropriate pharmacotherapy for patients with acromegaly based on patient-specific factors.
5. Identify clinical features of children and adults with growth hormone (GH) deficiency and select appropriate pharmacotherapy for these patients.
6. Recommend monitoring parameters necessary to assess therapeutic outcomes and adverse effects in patients receiving GH therapy.
7. List common etiologies of hyperprolactinemia.
8. Identify clinical features of patients with hyperprolactinemia.
9. Select appropriate pharmacologic and nonpharmacologic treatments for patients with hyperprolactinemia based on patient-specific factors.

PHYSIOLOGY OF THE PITUITARY GLAND

The pituitary, referred to as the "master gland," is a small endocrine gland located at the base of the brain and is responsible for the regulation of many other endocrine glands and body systems. Growth, development, metabolism, reproduction, and stress homeostasis are among the functions influenced by the pituitary. Functionally, the gland consists of two distinct sections: the anterior pituitary lobe and the posterior pituitary lobe. The pituitary receives neural and hormonal input from the inferior hypothalamus via blood vessels and neurons.

The posterior pituitary is innervated by nervous stimulation from the hypothalamus, resulting in the release of specific hormones to exert direct tissue effects. The hypothalamus synthesizes two hormones, oxytocin and vasopressin. These hormones are stored and released from the posterior pituitary lobe. The anterior pituitary lobe is under the control of several releasing and inhibiting hormones secreted from the hypothalamus via a portal vein system. It synthesizes and secretes six major hormones. Figure 46–1 summarizes the physiologic mediators and effects of each of these hormones.

Hormonal Feedback Regulatory Systems

The hypothalamus is responsible for the synthesis and release of hormones that regulate the pituitary gland. Stimulation or inhibition of the pituitary hormones elicits a specific cascade of responses in peripheral target glands. In response, these glands secrete hormones that exert a negative feedback on other hormones in the hypothalamic–pituitary axis (see Figure 46–1). This negative feedback serves to maintain body system homeostasis. In general, high circulating hormone concentrations inhibit the release of hypothalamic and anterior pituitary hormones.

Damage and destruction of the pituitary gland may result in secondary hypothyroidism, hypogonadism, adrenal insufficiency, growth hormone (GH) deficiency, hypoprolactinemia, or panhypopituitarism. A tumor (adenoma) located in the pituitary gland may result in excess secretion of a hormone or may physically compress the gland and suppress adequate hormone release. The type, location, and size of a pituitary tumor often determine a patient's clinical presentation. This chapter discusses the pathophysiology and role of pharmacotherapy in the treatment of acromegaly, GH deficiency, and hyperprolactinemia. The following hormones are discussed elsewhere in this textbook: adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), antidiuretic hormone (or vasopressin; ADH), and oxytocin.

GROWTH HORMONE (SOMATOTROPIN)

Somatotropin or GH, the most abundant hormone produced by the anterior pituitary lobe, is regulated primarily by the hypothalamic–pituitary axis. The hypothalamus releases growth hormone–releasing hormone (GHRH) to stimulate GH synthesis and secretion, whereas somatostatin inhibits it.[1] Release of GH into the circulation stimulates the liver and other peripheral target tissues to produce insulin-like growth factors (IGFs). These IGFs are the peripheral GH targets. There are two types of IGFs, IGF-I and IGF-II. IGF-I is responsible for growth of bone and other tissues, whereas IGF-II is primarily responsible for regulating fetal growth. High concentrations of IGF-I inhibit GH secretion through somatostatin, thereby inhibiting GHRH secretion at the hypothalamus.[1] The hypothalamus also may stimulate the release of somatostatin to inhibit GH secretion.

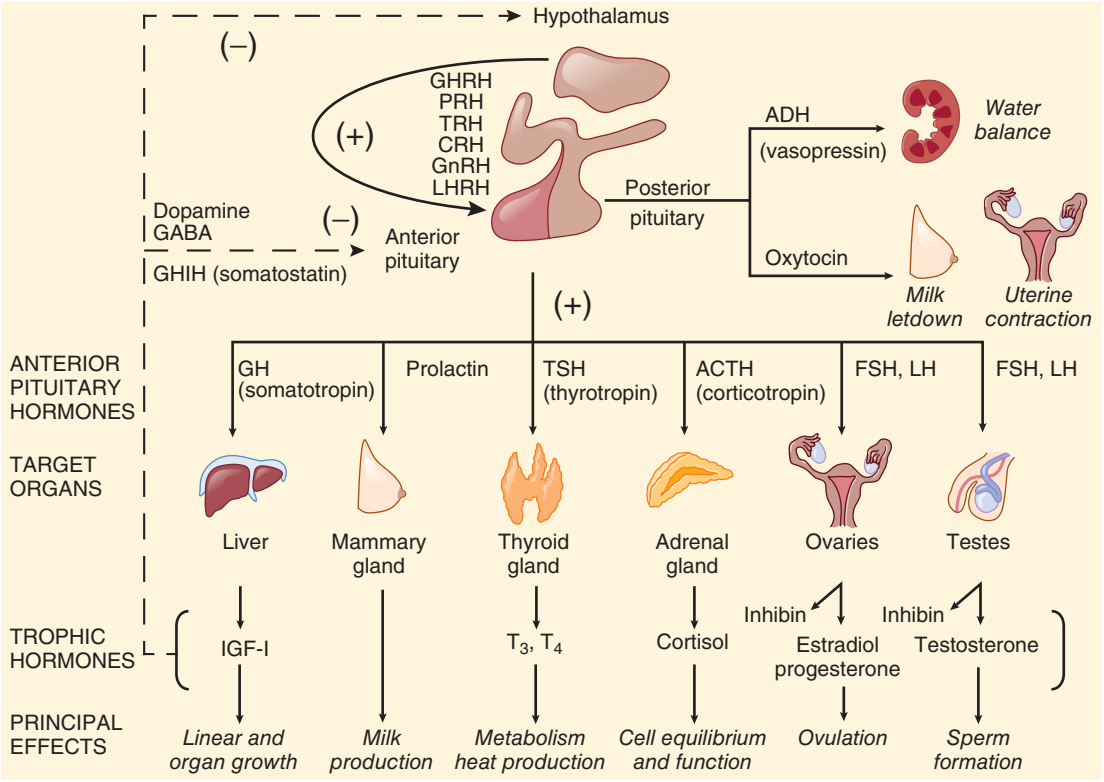

FIGURE 46–1. Hypothalamic–pituitary–target-organ axis. The hypothalamic hormones regulate the biosynthesis and release of eight pituitary hormones. Stimulation of each of these pituitary hormones produces and releases trophic hormones from their associated target organs to exert their principal effects. These trophic hormones regulate the activity of endocrine glands. Subsequently, increased serum concentration of the trophic hormones released from the target organs can inhibit both the hypothalamus and the anterior pituitary gland to maintain homeostasis (negative feedback). Inhibin is produced by the testes in men and the ovaries in women during pregnancy. Inhibin directly inhibits pituitary production of follicle-stimulating hormone (FSH) through a negative feedback mechanism. Melanocyte-stimulating hormone (MSH) produced by the anterior pituitary is not illustrated in the figure. (–), inhibit; (+), stimulate. (ACTH, adrenocorticotropic hormone [corticotropin]; ADH, antidiuretic hormone [vasopressin]; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GABA, γ-aminobutyric acid; GH, growth hormone [somatotropin]; GHIH, growth hormone -inhibiting hormone [somatostatin]; GHRH, growth hormone -releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-I, insulin-like growth factor-I; LH, luteinizing hormone; LHRH, luteinizing hormone -releasing hormone; PRH, prolactin-releasing hormone; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone [thyrotropin].)

The effects of IGF-I in peripheral tissues are both GH dependent and GH independent.[2] GH is an anabolic hormone with direct "anti-insulin" metabolic effects. By stimulating protein synthesis and shifting the body's energy source from carbohydrates to fats, GH promotes a diabetic state (Table 46–1).[2] GH controls somatic growth and has a critical role in the development of normal skeletal muscle, myocardial muscle, and bone.

Table 46–1

Effects of Growth Hormone[2]

	Effect(s)
Lipid metabolism	Increases breakdown of fat (lipolysis) Increases circulating fatty acid concentrations
Protein metabolism	Increases lean body mass Increases muscle mass
Carbohydrate metabolism	Decreases glucose utilization Increases insulin resistance Hyperglycemia Increases hepatic glucose output

In healthy individuals, GH is secreted in a pulsatile manner with several short bursts occurring mostly during the night. The amount of GH secretion fluctuates throughout a person's lifetime. Secretion of GH is lowest during infancy, increases during childhood, peaks during adolescence, and then declines gradually during the middle years.[1] These changes are parallel to an age-related decline in lean muscle mass and bone mineral density.

Growth Hormone Excess

▶ *Epidemiology and Etiology*

Acromegaly affects both genders equally, and the average age of presentation is 44 years. Approximately 125 to 295 people per 1 million are affected, with an estimated annual incidence of five cases per 1 million people.[3] In more than 95% of cases, overproduction of GH is caused by a benign pituitary adenoma, whereas malignant adenomas are rare. Most pituitary adenomas occur spontaneously as a result of a sporadic genetic mutation acquired during life. Depending on tumor size, pituitary adenomas are classified as: (a) microadenomas if they are 10 mm or less in diameter; or (b) macroadenomas if they are greater

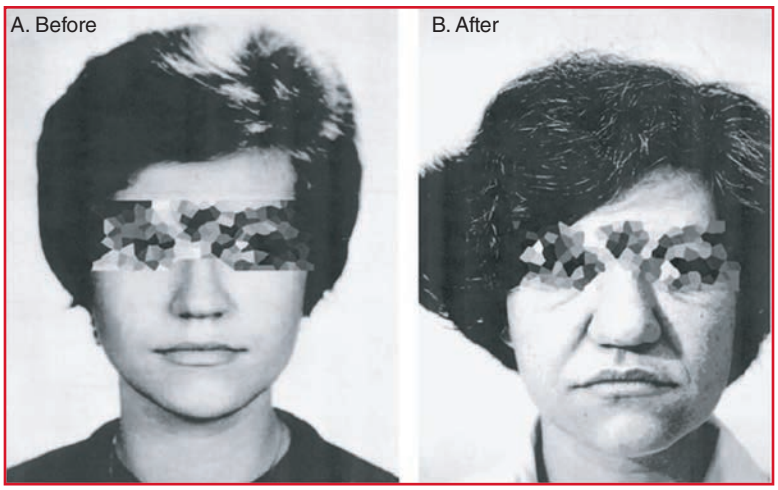

FIGURE 46–2. Before and after photographs of a patient with acromegaly. Compare the photographs **(A)** before the onset of acromegaly and **(B)** after approximately 20 years when the diagnosis was well established. Notice the coarsening of facial features, with an enlarged nose, lips, and forehead.

than 10 mm. Although these tumors can produce GH, they more commonly secrete GHRH, resulting in excessive GH and IGF-I production.

▶ *Pathophysiology*

Acromegaly is a rare disorder that manifests gradually over time and typically occurs after fusion of the epiphyses (growth plates) of the long bones.[4] The facial and hand features of an acromegalic patient are depicted in Figures 46–2 and 46–3. Gigantism refers to GH excess that occurs during childhood before epiphyseal closure and results in excessive linear growth. Because the signs and symptoms of acromegaly are insidious, diagnosis of this disorder is often delayed for up to 10 years after the initial presentation of symptoms.[4] Therefore, it is important for practitioners to be vigilant in identifying this disease in the early stages.

Diagnosis of acromegaly is based on both clinical and biochemical findings. Because GH fluctuates throughout the day, a single random measurement is never a reliable diagnostic tool to evaluate GH excess.[1] GH is suppressed after administration of a 75-g oral glucose challenge because postprandial hyperglycemia inhibits secretion of GH. Therefore, measurement of serum GH secretion in response to an oral glucose tolerance test (OGTT) is the primary biochemical test for diagnosing acromegaly.

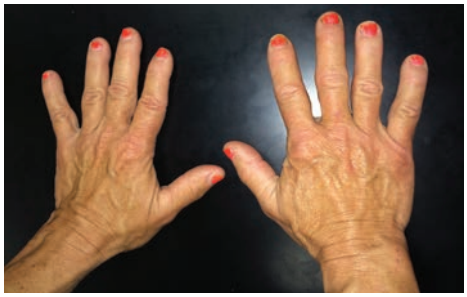

FIGURE 46–3. Photograph of hands from a patient with acromegaly. Soft tissue swelling and enlargement of the hand in a woman with acromegaly resulting in increased ring and glove size.

If the nadir GH concentration is greater than 0.4 ng/mL (mcg/L; 18 pmol/L) 2 hours after the test or the random GH concentration is greater than 1 ng/mL (mcg/L; 45 pmol/L), the patient is diagnosed with acromegaly.[5,6] In addition to clinical presentation, an elevated IGF-I serum concentration helps to confirm the diagnosis. IGF-I concentrations are often represented as age- and sex-matched population values.[5] They are relatively stable and correlate positively with mean GH concentrations,[1] thus making elevations in IGF-I concentrations an ideal and reliable biochemical marker to monitor disease activity and response to therapy.[4,5]

▶ *Treatment*

Desired Outcomes Patients with untreated acromegaly experience a two- to threefold increase in mortality rate primarily because of cardiovascular and pulmonary diseases.[4,6] KEY CONCEPT Prolonged exposure to elevated GH and IGF-I can lead to serious complications in patients with acromegaly. Aggressively manage comorbid conditions such as hypertension, diabetes, dysrhythmias, coronary artery disease, and heart failure to prevent cardiovascular, pulmonary, metabolic, respiratory, and neuropathic complications.[5,6] Normalization of GH and IGF-I concentrations lowers the mortality risk and may improve overall life expectancy. The goals of therapy are as follows.[4,6,8]

- Reduce fasting morning GH and IGF-I concentrations as close to normal as possible
- Reduce tumor size to relieve tumor mass effect
- Prevent tumor recurrence
- Preserve normal pituitary function
- Improve clinical signs and symptoms
- Alleviate significant morbidities
- Reduce mortality rates to those of the general population

LO 3

Surgical Treatment According to the Endocrine Society[6] and the American Association of Clinical Endocrinologists (AACE) treatment guidelines for acromegaly,[4] KEY CONCEPT surgical resection of the pituitary tumor through transsphenoidal pituitary microsurgery is the treatment of choice for most patients with GH-producing pituitary adenomas. When

Clinical Presentation and Diagnosis of Acromegaly[4-7]

LO 2

General

The patient will experience slow development of soft tissue overgrowth affecting many body systems. Signs and symptoms may gradually progress over 7 to 10 years.

Symptoms

- Headache and compromised visual function (loss of peripheral vision and blurred vision) caused by the actual tumor mass and its close proximity to the optic structures.
- Weakness, low blood sugar, or weight loss caused by disruption of adrenal function (ie, ACTH deficiency) by effect of tumor mass on the pituitary.
- Fatigue and weight gain caused by disruption of thyroid function (ie, TSH deficiency) by effect of tumor mass on the pituitary.
- Absence of regular menstrual periods (amenorrhea), impotence, and decreased libido caused by disruption of the gonadotropin secretion (ie, LH and FSH).
- Excessive sweating, joint pain, nerve pain, and abnormal neurologic sensations (paresthesias) related to elevated GH and IGF-I concentrations.

Signs

- Coarsening of facial features
- Increased hand volume
- Increased ring and shoe size
- Increased spacing between teeth
- Increased acne or oily skin
- Enlarged tongue
- Deepening of voice
- Thick, irregular, and patchy skin discoloration
- Enlarged nose, lips, and forehead (frontal bossing)
- Abnormal protrusion of the mandible (prognathia) and bite abnormalities
- Inappropriate secretion of breast milk (galactorrhea)
- Abnormal enlargement of various organs (organomegaly) such as liver, spleen, and heart
- Carpal tunnel syndrome caused by nerve compression from the swollen tissue

Laboratory Tests

- Random GH concentration greater than 1 ng/mL (mcg/L; 45 pmol/L) or nadir GH concentration greater than 0.4 ng/mL (mcg/L; 18 pmol/L) after an OGTT and elevated IGF-I concentration compared with age-matched control values.
- Loss of other hormonal functions caused by tumor mass compression of the anterior pituitary.
- Measure prolactin concentration in all patients because prolactin cosecretion is common.
- Glucose intolerance may be present in up to 50% of patients.

Additional Clinical Sequelae

- Cardiovascular diseases: hypertension, coronary heart disease, cardiomyopathy, left ventricular hypertrophy, and arrhythmia.
- Osteoarthritis and joint damage develop in up to 90% of patients.
- Respiratory disorders and sleep apnea occur in up to 60% of patients.
- Type 2 diabetes mellitus develops in 25% of patients.
- Increased risk for the development of esophageal, colon, and stomach cancer.

Other Diagnostic Tests

- Perform magnetic resonance imaging (MRI) examination of the pituitary to locate the tumor and validate the diagnosis.
- Obtain serum prolactin concentrations to assess for hyperprolactinemia and hypopituitarism.
- Without obvious pituitary tumor but proven acromegaly, measurement of GHRH may be helpful to detect ectopic tumors.

Adapted from Jordan JK, Sheehan AH, Calis KA. Pituitary gland disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy. A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017.

performed by experienced surgeons, greater than 85% of patients with microadenomas and fewer than 50% of patients with macroadenomas achieve remission.[6] Complete resection of a macroadenoma may be difficult if the tumor has already invaded the surrounding nerves and tissues. In such cases, debulking of the tumor along with adjunctive radiation and/or pharmacotherapy may improve treatment outcome. Infrequent surgical complications include meningitis, serious visual impairment, spinal fluid leakage, diabetes insipidus, and hypopituitarism.[6] Relative contraindications to surgery include patient frailty, acromegaly-associated comorbidities, and medically unstable conditions such as airway difficulties, severe hypertension, or uncontrolled diabetes.

Pharmacologic Therapy Pharmacologic therapy is often necessary for patients in whom surgery is not an option (Figure 46–4).[8] Somatostatin analogs, GH receptor antagonists, and dopamine agonists are the primary pharmacologic therapies used for the management of acromegaly (Table 46–2).[4,6,8,9] Pharmacologic therapy avoids hypopituitarism and other surgical risks.

LO 4

Somatostatin Analog (GH-Inhibiting Hormone) KEY CONCEPT

LO 4

Somatostatin analogs are the mainstay of pharmacotherapy for the treatment of acromegaly when surgery is not appropriate, or as an adjuvant therapy until patients achieve a sustained response to radiation therapy.[6,8] These agents mimic endogenous somatostatins and bind to somatostatin receptors in the pituitary to cause potent inhibition of GH, insulin, and glucagon secretion. Long-term treatment can sustain GH suppression, alleviate soft tissue manifestations, and reduce tumor size. The long-acting preparations of somatostatin analogs are considered the cornerstone of therapy because of improved patient adherence and acceptability over the first-generation octreotide. Somatostatin analogs normalize GH and IGF-I concentrations in approximately 55% of patients[4] and modestly reduce pituitary tumor size in more than half of the patients with acromegaly.[6] Optimal dose titration

Patient Encounter 1, Part 1

A 68-year-old Caucasian woman complains of frequent headaches, and she has not seen her primary care provider for years prior due to lack of insurance. The patient has noticeably large facial features, and manly arms, hands, and legs. She states that she has always been somewhat bothered by her more masculine features, but brushed it off because she grew up with several brothers.

PMH: Uncontrolled hypertension for 10 years; uncontrolled type 2 diabetes mellitus for 4 years; sleep apnea for 20 years

FH: Positive for diabetes in patient's mother and four brothers

Allergies: Penicillin (rash)

SH: Unemployed and uninsured, cleans hallways at her apartment building to cover rent and utility; recently quit smoking

Meds: Losartan-hydrochlorothiazide 100-25 mg once daily; metformin 1000 mg twice daily; insulin glargine 40 units once daily; insulin aspart 12 units with dinner; aspirin 81 mg once daily

Based on the information available, what signs and symptoms are suggestive of acromegaly?

What comorbidities are present in this patient as a result of untreated acromegaly?

What diagnostic tests should be performed to confirm the patient's diagnosis of acromegaly?

of somatostatin analogs is important in disease control.[6] Their efficacy and safety have been demonstrated in long-term studies (up to 9 years with octreotide and 4 years with lanreotide).[10-12] The long acting release (LAR) formulation of pasireotide has been demonstrated to provide superior efficacy compared to octreotide or lanreotide in achieving clinical and biochemical control.[9] Because somatostatin analogs can achieve substantial relief of clinical symptoms with significant reduction in tumor size,[13] it is important to monitor patients for tumor recurrence if treatment is discontinued.[4,6] Use of somatostatin analogs before surgery is not routinely recommended due to insufficient data to suggest additional benefits over surgery alone.[14]

Somatostatin analogs are generally well tolerated. Transient gastrointestinal (GI) disturbances are common but usually subside within the first months of therapy.[15] Somatostatin analogs inhibit gallbladder contractility and decrease bile secretion; therefore, their major adverse effect is development of **biliary sludge** and asymptomatic **gallstones (cholelithiasis)**.[15] Somatostatin analog–induced gallstones are generally asymptomatic; therefore, prophylactic therapy or routine abdominal ultrasound monitoring are usually not needed.[6,15] Additionally, somatostatin analogs may alter the balance of counterregulatory hormones (ie, glucagon, insulin, and GH), resulting in either hypoglycemia or hyperglycemia. Higher incidence of hyperglycemia and diabetes has been reported with pasireotide compared to other somatostatin analogs.[9] Somatostatin analogs also may suppress pituitary release of TSH, leading to decreased thyroid hormone secretion and subsequent hypothyroidism. Proactive monitoring of thyroid function and glucose metabolism is recommended.

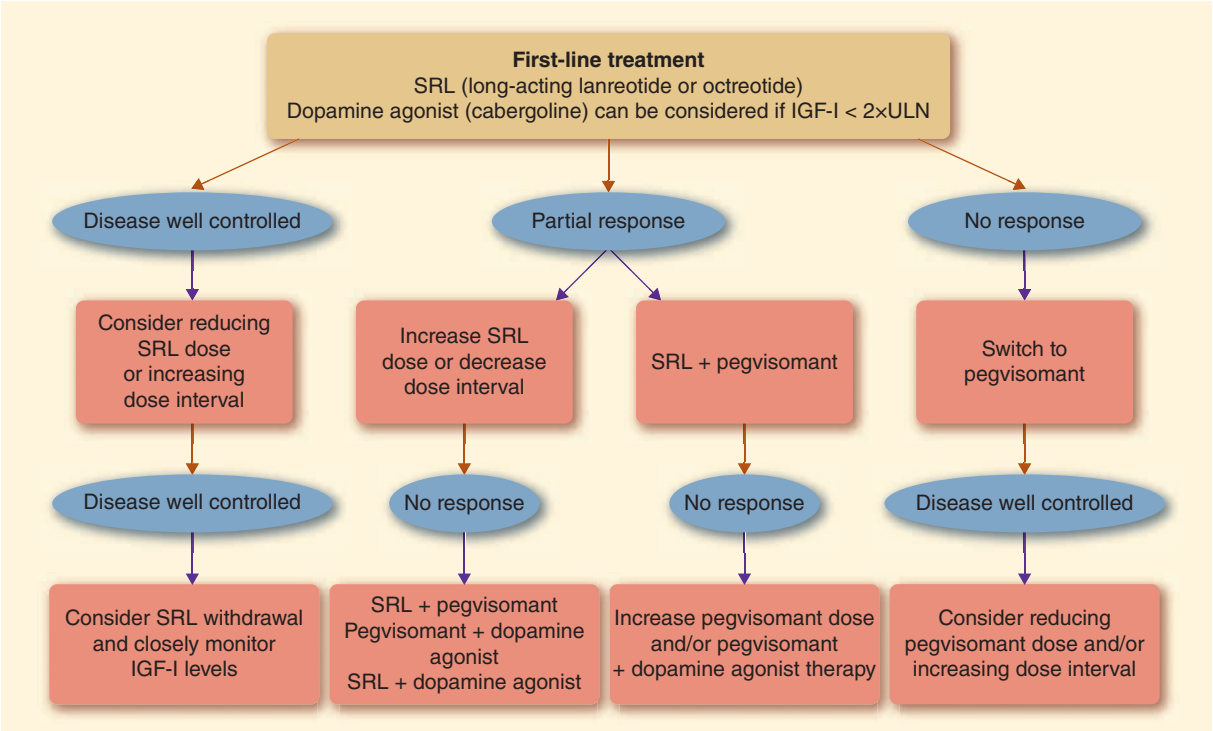

FIGURE 46–4. Medical management of patients with acromegaly.[8] A proposed algorithm for the medical management of acromegaly after surgery or as primary treatment strategy when surgery is inappropriate. Radiation therapy as rescue therapy has not been considered in this algorithm because its use is usually determined by a multidisciplinary management team. IGF-I, insulin-like growth factor I; SRL, somatostatin receptor ligan; ULN, upper limit of normal. (Reprinted by permission from Macmillan Publishers Ltd: Nature Publishing Group, Giustina A, Chanson P, Kleinberg D, et al. Expert consensus document: a consensus on the medical treatment of acromegaly. Nat Rev Endocrinol. 2014;10:243–248.)

Table 46–2

Comparison of Various Drugs Within Drug Classes for Treatment of Acromegaly[4,6,8,9]

	Dopamine Agonist	Somatostatin Analog					GH Receptor Antagonist
Medication	Cabergoline	Octreotide (Sandostatin)	Octreotide LAR (Sandostatin LAR)	Lanreotide SR	Lanreotide Autogel (Somatuline Depot)	Pasireotide (Signifor LAR)	Pegvisomant (Somavert)
Starting dose	1 mg/week orally	50 mcg SC thrice daily	20 mg IM every 4 weeks	60 mg IM every 2 weeks	90 mg deep SC every 4 weeks[a]	40 mg IM every 4 weeks	10 mg SC daily after initial loading dose of 40 mg
Maximal dose	4 mg/week orally	200 mcg SC thrice daily	40 mg IM every 4 weeks[b]	120 mg IM every 7 days	120 mg deep SC every 4 weeks	60 mg IM every 4 weeks	40 mg SC daily[c]
Dosage in hepatic insufficiency	Dosage reduction may be recommended for patients with severe hepatic failure	—	Cirrhosis: 10 mg IM every 4 weeks	Dosage reduction may be necessary; no guidelines available	Moderate to severe impairment: starting dose 60 mg every 4 weeks	Moderate impairment: starting dose 20 mg every 4 weeks, maximal dose of 40 mg every 4 weeks. Severe hepatic impairment: avoid use	Discontinue therapy if liver function tests are elevated at least five times the upper limit of normal or transaminase at least three times the upper limit of normal with any increase in serum total bilirubin
Dosage in renal failure	None	Dialysis dependent: adjustment may be necessary; no guidelines available	Dialysis-dependent renal impairment: 10 mg IM every 4 weeks	Dosage reduction may be necessary; no guidelines available	Moderate to severe impairment: starting dose, 60 mg every 4 weeks	None	None
Side effects	Nausea, GI cramps, headache, drowsiness, dizziness, fatigue	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, flatulence, abdominal pain, constipation, gallstones	Nausea, GI cramps, diarrhea, hyperglycemia, fatigue, gallstones, abdominal pain	Headache, fatigue, GI cramps, abnormal liver enzymes, injection site reactions, sweating
Monitoring suggestions	GH, IGF-I, and prolactin concentration 4–6 weeks after each dose change	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	GH and IGF-I 3 months after dose change, thyroid function tests and blood glucose	Liver function tests (serum transaminase, total bilirubin, alkaline phosphatase) monthly for 6 months, then biannually for the next year; MRI every 6 months, then yearly if no growth; IGF-I (not GH) after first year, then yearly

[a]In the United States, initiate lanreotide at 90 mg every 28 days for 3 months and then titrate accordingly based on response.

Different labeled dosing guidelines exist for the United Kingdom and Canada.

[b]Product labeling recommends a maximum of 30 mg IM every 4 weeks.

[c]Alternative dose administration protocol of twice a week or once a week has been used.[4]

GH, growth hormone; GI, gastrointestinal; IGF-I, insulin-like growth factor-I; IM, intramuscularly; LAR, long-acting release; MRI, magnetic resonance imaging; SC, subcutaneously; SR, slow-release.

Adapted from AACE Medical Guidelines for Clinical Practice for the diagnosis and treatment of acromegaly. Endocr Pract. 2004;10:213–225 by permission of publisher, American Association of Clinical Endocrinologists (AACE) Corp.

Sinus bradycardia, conduction abnormalities, and arrhythmias have been reported with use of somatostatin analogs. Because of the potential adverse effects of the somatostatin analogs, concomitant use with insulin, oral hypoglycemic agents, β-blockers, or calcium channel blockers may require careful dosage adjustment. Somatostatin analogs may also alter the bioavailability and elimination of cyclosporine, and monitoring of cyclosporine serum concentration is necessary.

GH-Receptor Antagonist The advent of a GH-receptor antagonist represents a novel approach to the treatment of acromegaly. Pegvisomant is the only genetically engineered GH-receptor antagonist that blocks the action of GH. Pegvisomant is indicated for treatment of acromegaly in patients who have an inadequate response to surgery or radiation therapy. The effects of pegvisomant work independently of tumor characteristics, somatostatin, and dopamine receptors. To date, pegvisomant is the most effective agent in normalizing IGF-I concentration in acromegaly.[16] Long-term safety and efficacy of pegvisomant (up to 5 years) from an ongoing postmarketing surveillance registry (ACROSTUDY) suggest a reasonable benefit/risk balance.[17] In patients who were relatively unresponsive to other medical or surgical therapies, normal IGF-I concentrations were achieved in 63% of the patients treated with pegvisomant (mean dose of 18 mg/day)[17] and in 69% to 100% of patients treated with pegvisomant and somatostatin analog therapy.[18] Pegvisomant therapy has favorable effects on glucose tolerance and insulin sensitivity and may be considered as a treatment option if patients also present with diabetes as a comorbidity.[6] However, use of pegvisomant is associated with significant dose-dependent increases in GH despite declining IGF-I concentrations. The dose-dependent increase in GH is troubling because it has been suggested that persistent elevation of GH concentration may be indicative of tumor growth. Although the incidence of pituitary tumor enlargement is low (3.2%), careful monitoring with periodic imaging scans is nonetheless warranted.[17] KEY CONCEPT LO 4 Pegvisomant is recommended in patients who have inadequate response to somatostatin analogs, or as an adjuvant for patients who have only a partial response to somatostatin analogs.[4,6,8] Patients at risk of visual damage from large tumors impinging on the optic chiasm may consider alternative pharmacologic therapy.[6]

The long-term use of pegvisomant appears to be well tolerated with a low incidence of adverse effects, including self-limiting injection-site reactions (2.2%) and elevated liver enzymes (2.5%).[17] Although elevations of liver enzymes often are self-limiting and not associated with symptoms,[4,6] hepatotoxicity has been reported in clinical trials, particularly in patients receiving combined pegvisomant and somatostatin analogs.[16] Therefore, serum transaminases, total bilirubin, and alkaline phosphatase should be assessed before initiating therapy and periodically thereafter. Use caution when administering pegvisomant to patients with elevated liver function tests, and therapy should be discontinued in patients who present with clinical signs and symptoms of hepatic injury.

Dopamine Agonists Dopamine is one of the neurotransmitters that can increase GH secretion in healthy adults. However, dopamine agonists administered to patients with acromegaly exert the opposite effect and suppress GH release from the tumor. The first dopamine agonist used for acromegaly, bromocriptine, achieved normal IGF-I concentrations in fewer than 10% of patients.[19] The large doses of bromocriptine required to achieve the desired response are often associated with dose-limiting toxicity such as GI discomfort and orthostatic hypotension. Cabergoline is the preferred dopamine agonist for treatment of acromegaly due to its improved tolerability and extended duration of action. Cabergoline can effectively reduce GH and IGF-I concentrations in approximately 30% of patients but its efficacy appears to decrease over time.[6] Although orally administered dopamine agonists are the least expensive medical therapy for managing acromegaly, the major disadvantage is their relative lack of efficacy compared with existing therapeutic options. KEY CONCEPT LO 4 Cabergoline may be considered for patients with modest elevation of GH and IGF-I concentrations less than two times the upper limit of normal (ULN). It may also be used as adjunctive therapy in patients unresponsive to monotherapy with somatostatin analogs or pegvisomant.[6,8] Although cardiac valvular abnormalities have been observed in patients using higher doses of cabergoline for Parkinson disease, patients receiving treatment for acromegaly do not seem to carry increased risk of cardiac valve disease.[4,6,19,20] Nonetheless, echocardiographic monitoring for potential cardiac abnormalities is reasonable for patients who require prolonged, high-dose (> 2 mg/week) cabergoline therapy.[6]

Combination Therapy For patients who are resistant to monotherapy, combination therapies have been beneficial with improved efficacy and reduced side effects associated with individual medication. Addition of pegvisomant or cabergoline may be considered in patients with inadequate response to somatostatin analog.[6,18]

Radiation Therapy LO 3 Radiation therapy is an important adjunctive therapy in patients with residual GH excess after surgery or pharmacologic therapy.[6] Treatment involves the use of radiation to destroy rapidly growing tumor cells and often results in a reduction in tumor size. A major complication of radiation therapy is hypopituitarism, requiring lifelong hormone replacement.[4] There is also the potential for optic nerve damage if the pituitary tumor is near the optic tracts. Radiation therapy may take 10 to 20 years before its full effects become evident.[4] Owing to this delay in onset of effectiveness, pharmacologic therapy with a somatostatin analog often is indicated as bridge therapy.[4,6] Men and women who desire to have children should be warned that pituitary irradiation therapy may impair fertility because of subsequent gonadotropin deficiency.[4]

Management of Acromegaly in Pregnancy Due to limited safety data, use of pharmacologic therapy during pregnancy is reserved for tumor and headache control. Substitute long-acting formulation of somatostatin analogs and pegvisomant with short-acting octreotide approximately 2 months prior to conception.[6] Monitoring of IGF-I and GH level during pregnancy is limited in patients with acromegaly because conventional assays are not usually able to distinguish between the variant forms of GH.[6]

▶ *Outcome Evaluation*

- Lifelong biochemical assessment is critical for determining therapeutic outcomes. Although some patients may experience a rapid decline in GH concentrations after surgery, stabilization of IGF-I concentrations usually occurs 3 months after surgery but rarely may be delayed for up to 12 months. Fully assess pituitary function at 12 weeks or later after surgery.[4] Monitor random GH and IGF-I concentrations every 3 to 6 months postoperatively to assess treatment response.[4] Obtain IGF-I concentrations annually in all postsurgical patients to monitor for potential pituitary tumor

recurrence.[4,6] Measure nadir GH level after glucose load in patients with GH greater than 1 ng/mL (mcg/L; 45 pmol/L).[6]

- Assess MRI 12 weeks after surgery and 3 to 6 months after starting medical therapy.[21] Because up to 10% of pituitary tumors may recur within 15 years after surgery, continual postoperative monitoring is recommended.[22]
- For patients treated with somatostatin analogs, assess baseline fasting blood glucose, thyroid function tests, and heart rate. Thereafter, periodically monitor patients for adverse reactions such as GI disturbances, glucose intolerance, signs and symptoms of thyroid abnormalities, bradycardia, and arrhythmias in patients receiving long-term somatostatin analogs. Reevaluate IGF-I and GH concentrations at 3-month intervals to determine therapeutic response and inquire about symptoms of gallbladder disease (eg, intermittent pain in the upper right abdomen) during follow-up appointments.[4,6] If normalization of GH and IGF-I concentrations is not fully achieved after 1 year, perform MRI 6 months later and annually thereafter to monitor tumor mass.[4]
- For patients treated with a GH receptor antagonist, GH concentrations are not measured because pegvisomant is a modified GH molecule that is detected in commercial GH assays, resulting in falsely elevated GH concentrations. Therefore, monitor IGF-I concentrations to assess response to pegvisomant therapy. After appropriate dose titration, monitor IGF-I concentrations every 6 months.[4,6] Concern for tumor growth requires careful monitoring of tumor size; therefore, perform MRI every 6 months during the first year of therapy. If there is no evidence of growth, then monitor annually thereafter.[6] Because of the potential for hepatotoxicity with pegvisomant therapy, it is mandatory to monitor liver enzymes prior to initiation of therapy, monthly during the first 6 months, then biannually thereafter.[6] More frequent monitoring of liver enzymes is warranted in patients with elevated liver enzymes at baseline.[4] Discontinue pegvisomant if liver function test (LFT) is more than threefold elevated.[6]
- For patients receiving dopamine agonists, the maximal suppression of GH and IGF-I concentrations may take up to 3 months to achieve. After stable control of biochemical markers is achieved with dopamine agonists or somatostatin analogs, monitor GH and IGF-I concentrations annually.[4] Measure GH, prolactin, and IGF-I level 4 to 6 weeks after dose change.[4]
- Monitor GH and IGF-I annually 1 to 3 months after medication withdrawal to assess efficacy of radiation therapy.[6] Assess for hypopituitarism and replace any hormone deficits.[6]

Growth Hormone Deficiency

▶ *Epidemiology and Etiology*

In the United States, GH deficiency affects approximately 50,000 adults, with around 6000 new cases diagnosed annually.[23] Approximately 10,000 to 15,000 children have growth failure owing to GH deficiency. Children may present with GH deficiency at any time during their developmental stages. The evaluation for GH deficiency in a child of short stature should be deferred until appropriate exclusion of other identifiable causes of growth failure, such as hypothyroidism, chronic illness, malnutrition, genetic syndromes, and skeletal disorders, has occurred. Several medications, such as somatostatin analogs, gonadotropin-releasing hormone (GnRH) agonists, methoxamine, phentolamine, isoproterenol, glucocorticoids, cimetidine, methylphenidate, and amphetamine derivatives, may induce GH insufficiency.[24]

▶ *Pathophysiology*

GH deficiency exists when GH is absent or produced in inadequate amounts. GH deficiency may be congenital, acquired, or result from disruption of the hypothalamus–pituitary axis. GH deficiency may be an isolated condition or occasionally be accompanied by another endocrine disorder

Patient Encounter 1, Part 2

PE:

VS: BP 158/100 mm Hg, P 104 beats/min, RR 18 breaths/min, T 37°C (98.6°F), Ht 168 cm (5'6"), Wt 82 kg (180 lbs), BMI 29.1 kg/m^2

ROS: (+) HA, (+) deepening of voice

HEENT: Visual field defects; head is elongated with bony prominence of the forehead, nose, and lower jaw; large fleshy nose

CV: RRR, normal S_1 and S_2; no murmurs, rubs, or gallops, (–) chest pain, palpitation, orthopnea, and leg swelling

Pulm: (–) SOB, (–) cough

GI: (–) Nausea, vomiting, and abdominal pain

Abd: Soft, nontender, nondistended; (+) bowel sounds, (–) hepatosplenomegaly

Neuro: A & O × 3. Normal reflexes

Psychiatric: Depressed mood. Spacy, sweet, and needs extra help understanding instructions.

Available Labs: Electrolytes and renal function are within normal limits. Fasting blood glucose concentration is 268 mg/dL (14.9 mmol/L), glycated hemoglobin A_{1c} ($HgbA_{1c}$) is 10.4% (0.104; 90 mmol/mol), (+) microalbuminuria. GH concentration 2 hours after an OGTT is 83.6 ng/mL (mcg/L; 3779 pmol/L). Elevated IGF-I concentration at 998 ng/mL (mcg/L; 131 nmol/L). TSH is slightly low at 0.40 µU/mL (mU/L) and free T_4 (FT_4) is within normal range at 1.1 ng/dL (14.2 pmol/L).

MRI: (+) 9 mm benign pituitary adenoma extending toward the optic chiasm; no invasion into the cavernous sinus

Given that the patient doesn't want surgery, what pharmacologic treatment options are available?

Since the patient is uninsured without a source of income, what factors need to be considered when choosing a pharmacologic treatment option?

Provide monitoring parameters to assess efficacy and safety to the patient starting on pegvisomant.

Patient Care Process: Acromegaly

Collect Information:

- Review the available diagnostic data to determine pituitary tumor size and location.
- Perform complete medication history. Identify allergies to medications and other substances.
- Determine treatment options the patient has tried in the past.
- Review the medical history, relevant laboratory tests, and physical assessment findings.
- Speak with patient and review records to identify signs and symptoms of acromegaly, preferences and beliefs, health goals, socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the patient's clinical signs and symptoms and biochemical disease markers to determine the severity of acromegaly.
- Determine if the patient has a coexisting prolactin secreting tumor and impact of the tumor on the optic tract.
- Assess presence of acromegaly complications. Identify any significant comorbidities associated with acromegaly that require immediate treatment or early diagnosis.
- Evaluate patient for presence of surgical contraindications to transsphenoidal microsurgery. Determine if the patient is able or willing to undergo surgical intervention.
- Assess if the patient has any contraindications or allergies to therapies (see Table 46–2).

Develop a Care Plan:

- If surgical intervention does not achieve satisfactory disease control, select subsequent appropriate pharmacologic therapy based on patient-specific factors (see Figure 46–4).
- Determine if selected drug doses are optimal (see Table 46–2). Consider if the patient's therapy requires any dose adjustments.

Implement the Care Plan:

- Discuss potential effectiveness and disadvantages of existing treatment options.
- Address any patient concerns about acromegaly, its management, and possible complications.
- Determine whether the patient has insurance coverage and preferred treatments covered.
- Educate patient about changes in drug therapy, proper medication administration techniques, potential new adverse effects, and how to manage and report adverse effects that occur.
- Discuss importance of medication adherence and how to reduce the modifiable cardiovascular and metabolic risk factors.
- Use motivational interviewing strategies and coping strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Monitor patient's biochemical markers (GH and IGF-I concentrations) and complications to surgical intervention.
- Review adherence to treatment plan using multiple sources of information.
- Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status and complications.
- Evaluate safety and efficacy of pharmacologic therapy and the degree of disease control.
- Determine whether the patient is experiencing any adverse reactions or drug interactions.
- Routinely assess acromegaly complications; include blood pressure, glucose tolerance, fasting lipid profile, cardiac evaluations (if clinically indicated), colonoscopy, dual-energy x-ray absorptiometry (DEXA) scan (hypogonadal only), evaluation of residual pituitary function, and sleep apnea.

Clinical Presentation and Diagnosis of Growth Hormone Deficiency in Children[7,23]

LOS

General

The patient will have a physical height that is greater than two standard deviations below the population mean for a given age and sex.

Signs

- The patient will present with reduced growth velocity and delayed skeletal maturation.
- Children with GH-deficient or GH-insufficient short stature also may present with abdominal obesity, prominence of the forehead, and immaturity of the face.

Laboratory Tests

- Patients will exhibit a peak GH concentration of less than 10 ng/mL (mcg/L; 452 pmol/L) after a GH stimulation test.
- Reduced IGF-I concentration also may be present.
- Because GH deficiency may be accompanied by the loss of other pituitary hormones, hypoglycemia and hypothyroidism also may be noted.

Other Diagnostic Tests

- Perform MRI or computed tomography (CT) scan of the hypothalamic–pituitary region to detect structural or developmental anomaly.
- Perform radiography of the left wrist and hand for children older than 1 year of age to estimate bone age (knee and ankle for children younger than 1 year of age).

Adapted from Jordan JK, Sheehan AH, Calis KA. Pituitary gland disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy. A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017.

Clinical Presentation and Diagnosis of Growth Hormone Deficiency in Adults[25,28,32,34]

LO 5

General

The patient likely will have a history of childhood-onset GH deficiency; hypothalamic or pituitary disorder; or the presence of three or four other pituitary hormone deficiencies caused by head trauma, tumor, infiltrative diseases, surgery, or radiation therapy.

Symptoms

- Reduced strength and exercise capacity
- Defective sweating
- Psychological problems
- Low self-esteem
- Depression
- Fatigue or listlessness
- Sleep disturbance
- Anxiety
- Social isolation
- Emotional lability and impaired self-control
- Poor marital and socioeconomic performance

Signs

- Increased fat mass (especially abdominal obesity)
- Reduced lean body mass
- Reduced muscle strength
- Reduced exercise performance
- Thin, dry skin; cool peripheries; poor venous access
- Depressed affect, labile emotions
- Impaired cardiac function as evidenced by abnormal echocardiography or stress test results

Laboratory Tests

- Patients will exhibit a peak GH concentration of less than 5.1 ng/mL (mcg/L; 231 pmol/L) after a GH stimulation test. ITT is the gold standard stimulation test. Low or low-normal IGF-I concentration also may be present. Presence of three or more pituitary hormone deficiencies with a low IGF-I concentration does not require further stimulation test.
- Increased low-density lipoprotein cholesterol, total cholesterol, triglycerides; decreased high-density lipoprotein cholesterol.
- Reduced bone mineral density associated with an increased risk of fracture.
- Increased insulin resistance and prevalence of impaired glucose tolerance.
- GH deficiency may be accompanied by the loss of other pituitary hormones.

(eg, panhypopituitarism). Because GH is frequently undetectable with random sampling, a stimulation or provocative test usually is performed to confirm the diagnosis. The gold standard for diagnosis of adults with GH deficiency is the insulin tolerance test (ITT), with glucagon as an alternative if GHRH is unavailable.[25] Adults exhibiting a peak GH concentration of less than 5.1 ng/mL (mcg/L; 230 pmol/L) after two ITT simulation tests would warrant treatment.[25] In prepubertal children, measurement of IGF-I concentrations may be useful in evaluating GH deficiency.[26] The diagnosis of GH deficiency in children, often without the need for provocative testing, is established if the child exhibits all three conditions: (1) auxological criteria, (2) hypothalamic-pituitary defect, and (3) deficiency of at least one additional pituitary hormone.[27] Failure of linear growth is an almost universal presenting feature of childhood GH deficiency.

Childhood GH deficiency may or may not continue into adulthood. Most adults with GH deficiency have overt pituitary disease and present with nonspecific clinical disorders distinct from pediatric GH deficiency. Adult GH deficiency presumably is associated with an increased risk of death from cardiovascular diseases.[25]

▶ *Treatment*

Desired Outcomes The goal of treatment for GH deficiency is to correct associated clinical symptoms.[24] In children, prompt diagnosis and early initiation of treatment are important to maximize final adult height. In adults, the goal is to achieve normal physiologic GH concentrations in an attempt to reverse metabolic, functional, and psychological abnormalities.[25,28]

LO 5

Pharmacologic Therapy KEY CONCEPT Recombinant GH therapy is the main pharmacologic treatment for GH deficiency in both children and adults. It promotes skeletal, visceral, and general body growth; stimulates protein anabolism; and affects bone, fat, and mineral metabolism (see Table 46–1).[2] GH therapy requires subcutaneous or intramuscular administrations. Because two-thirds of GH secretion normally occurs during sleep, it is recommended to administer GH injections in the evening.[29] Many preparations of synthetic GH (somatropin) are available with a variety of injection devices to make administration more appealing and easier. Zomacton is only approved for use in children, and other somatropin products such as Humatrope, Norditropin, Genotropin, Omnitrope, and Saizen are approved in both children and adults.

KEY CONCEPT Although comparative trials have not been conducted to date, recombinant GH products appear to have similar efficacy for treating GH deficiency as long as the regimen follows currently approved guidelines. GH secretion decreases with age; therefore, older adults with GH deficiency often require substantially lower replacement doses than younger individuals. The optimal therapeutic approach is to initiate GH therapy at lower doses and titrate according to clinical response, adverse effects, and IGF-I concentrations.[30,31] Table 46–3 lists the recommended GH replacement doses for children and adults.[25,27,30] Conventional weight-based regimens are not recommended in adults due to lack of evidence supporting higher dosages in heavier individuals and greater potential for adverse effects.[25,28,32] For elderly patients, lower GH replacement doses often are adequate because of increased GH sensitivity.[28,32] Women with intact hypothalamic–pituitary–gonadal axis or on estrogen therapy (or oral contraceptives) generally require a higher GH dose than men due to decreased GH concentrations associated with estrogen.[30,32] Carefully monitor patients requiring replacement therapy with estrogens, thyroid hormones, or glucocorticoids because of potential interactions with GH

LO 5

LO 5

Table 46–3

Dose Recommendation for Growth Hormone Deficiency in Children and Adults[25,27,30]

	Growth Hormone Replacement Dose	Dose Titration
Children[27]	**Starting Dose**	• Evaluate every 3–6 months based on height and height velocity. • Monitor IGF-I and IGFBP-3 yearly. • Monitor TSH and T_4 for hypothyroidism. • Reduce dose if serum IGF-I concentration is substantially above normal after 2 years of therapy.
Prepubertal children	22–35 mcg/kg/day with individualization on subsequent dosing	
During puberty	Individualized dosing	• Against routine increase in dose to 700 mcg/kg/week.
Adults[25,30]	**Starting Dose**	• Increase dose by 0.1–0.2 mg/day based on clinical response, serum IGF-I concentrations, and side effects at 1- to 2-month intervals. Longer time intervals and smaller dose titration may be necessary in older adults.
Age < 30 years	0.4–0.5 mg/day[a]	
Age 30–60 years	0.2–0.3 mg/day	
Age > 60 years	0.1–0.2 mg/day	
Diabetes or glucose intolerance (overweight, obese, or history of gestational diabetes)	0.1–0.2 mg/day	
Hepatic impairment	—	• Clearance may be reduced in patients with severe hepatic dysfunction; specific dosing suggestions are not available.
Renal impairment	—	• Patients with chronic renal failure tend to have decreased clearance; specific dosing suggestions are not available.

[a]Might require a higher dose for patients transitioning from pediatric treatment.

IGFBP-3, insulin-like growth factor-bind protein 3; IGF-I, insulin-like growth factor-I; T_4, thyroxine; TSH, thyroid-stimulating hormone.

therapy.[28] The potency of GH products is generally expressed as 3 international units (IU or mU) per 1 milligram of protein.[25] Selection of an injection device depends on patient preference due to lack of differences in clinical outcomes among the various injection systems.[30]

Evidence has suggested that GH treatment in GH-deficient children can increase short-term growth and improve final adult height.[23] Beneficial effects of GH therapy in adults with GH deficiency have been demonstrated to normalize body composition and metabolic process; improve cardiac risk profile, bone mineral density, quality of life, and psychological well-being; and increase muscle strength and exercise capacity.[25,32] However, evidences for reduction in cardiovascular risks and mortality are still lacking with long-term use of GH replacement therapy.[33]

Practitioners should begin GH therapy as soon as possible to optimize long-term growth, especially for young children in whom GH deficiency is complicated by fasting hypoglycemia.[23] Selection of the optimal GH replacement dose will need to be individualized depending on response, financial resources, and product availability. Although the appropriate time to discontinue therapy remains controversial in childhood GH deficiency, it is reasonable to continue GH replacement until the child has reached satisfactory adult height, achieved documented epiphyseal closure, or failed to respond to therapy.[23] It is recommended that the GH dose in pediatric patients does not continue beyond achievement of a growth velocity below 2 to 2.5 cm/year.[27] Management of the transition between pediatric and adult GH replacement remains a challenge because limited data are available.[27] The secretion of GH during adolescence is normally lower than during puberty but higher than during adulthood. Therefore, for patients in a transition phase who may be restarting GH therapy, the initial dose for an adolescent is approximately the average of the pediatric dose required for growth and the adult dose.[30] Starting GH therapy at a low dose and gradually titrating upward may decrease the potential for adverse effects. The optimal duration of treatment with GH therapy remains unclear, but lifelong therapy may be required. However, GH replacement should be discontinued if therapeutic benefit is not achieved after 2 years of therapy.[30]

In both children and adults, treatment with GH may mask underlying central hypothyroidism and adrenal insufficiency.[35] Treatment with GH also may induce insulin resistance and lead to the development of glucose intolerance in patients with preexisting risk factors. Adults are more susceptible to dose-related adverse effects of GH-induced symptoms, such as edema, arthralgia, myalgia, and carpal tunnel syndrome, which may necessitate dose reductions in up to 40% of adults.

Children treated with GH replacement therapy rarely experience significant adverse effects. Benign increases in intracranial pressure related to GH therapy may manifest as headaches, visual changes, or altered concentrations of consciousness. This condition is generally reversible upon discontinuation of treatment. Often, GH therapy can be restarted with smaller doses without symptom recurrence. Presently, there is no compelling evidence that GH replacement therapy is associated with an increased risk of cancers in children without prior history or risk factors.[36,37] It remains unclear if the risk is affected in high-risk patients. Survivors of childhood cancer may have an increased risk of abnormal growth of tissues with GH treatment but it does not appear to increase the risk of cancer reoccurrence.[36] The risk of cancer was unrelated to duration or cumulative dose of GH treatment, but the cancer mortality risk increases significantly with increasing daily dose of GH in previous cancer survivors.[37]

Nevertheless, GH replacement therapy is contraindicated in all patients with active malignancy.[30] In children with a history of malignancies, it would be prudent to wait for a 1-year tumor-free period (5 years for adults) before initiating GH therapy.[23,36] Any patients treated for a prior malignancy should be monitored carefully for tumor recurrence.[23] Because deaths have been reported with use of GH in children with **Prader-Willi syndrome** who are severely obese or suffer from respiratory impairments, use of GH is contraindicated in these individuals.

Evidence from the long-term surveillance study, Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE), remains inconclusive regarding GH therapy and its risk of increased morbidity.[33] Therefore, further surveillance monitoring is warranted.

▶ *Outcome Evaluation*

LO 6

- Children with GH deficiency should be evaluated by a pediatric endocrinologist every 3 to 6 months. Monitor for an increase in height and change in height velocity to assess response to GH therapy.[23,38] Every effort should be made to maximize height before the onset of puberty. After final adult height is reached and GH is discontinued for at least 1 month, retest and reevaluate the patient using the adult GH-deficiency diagnostic criteria.[25,30,38]
- Although GH and IGF-I concentrations do not always correlate with growth response, measure IGF-I concentrations yearly to assess adherence to therapy and patient response. If the IGF-I concentrations are substantially above the normal range 2 years after GH replacement therapy, the dose should be reduced.[38] IGF-I concentration may be used as a guide to gradually reduce replacement dose after epiphyseal closure.
- Routine monitoring of fasting lipid profile, bone mineral density, and body composition in children is not typically required during GH replacement but should be done before and after discontinuation of therapy.[23,38]
- In adults, measurement of serum IGF-I, along with careful clinical evaluation, appears to be the most reliable way to assess the appropriateness of the GH dose. Measure IGF-I serum concentrations 1 to 2 months during dose titration and semiannually thereafter.[25] If therapy is not observed after at least 1 year of treatment, therapy may be discontinued.[25,28,30]
- Continuously monitor for dose-related adverse effects such as edema, arthralgia, myalgia, and carpal tunnel syndrome.
- Evaluate psychological well-being.
- Assess patients' bone mineral density every 2 to 3 years.[30]
- When maintenance therapy is achieved, assess body composition (body mass index [BMI], waist circumference, waist-to-hip ratio), metabolic status (fasting glucose concentration, free thyroxine serum, hemoglobin A_{1c}), cardiac risk factors (eg, fasting lipid profile), hypothalamic–pituitary–adrenal axis function (eg, morning serum cortisol response to ACTH stimulation), and testosterone concentrations at 6- to 12-month intervals.[28,30]

PROLACTIN

Prolactin is an essential hormone for normal production of breast milk after childbirth. It also plays a pivotal role in a variety of reproductive functions. Prolactin is regulated primarily by the hypothalamus–pituitary axis and secreted solely by the lactotroph cells of the anterior pituitary gland. Under normal conditions, secretion of prolactin is predominantly under inhibitory control by dopamine. Increases of hypothalamic thyrotropin-releasing hormone in primary hypothyroidism can stimulate the release of prolactin.

Patient Care Process: GH Deficiency in Children

Collect Information:

- Obtain a thorough history and physical examination (weight and height) that may indicate the possible presence of GH deficiency.
- Obtain GH and IGF-I concentrations.
- Review imaging tests of the hypothalamic–pituitary region to detect any anomalies.
- Speak with caregivers to identify signs and symptoms of GH deficiency, preferences and beliefs, health goals, socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the child's growth characteristics and compare the physical height with a population standard (eg, Centers for Disease Control and Prevention Growth Charts).
- Exclude other identifiable causes of growth failure.
- Assess presence of other pituitary hormone deficiency.
- Assess risk factor for development of malignancy (history of cancer or active cancer).
- Assess if the patient has any contraindications, allergies, or drug interactions to GH therapy.

Develop a Care Plan:

- Calculate the appropriate GH therapy at the lower dosing range based on patient weight (see Table 46–3).

Implement the Care Plan:

- Initiate GH therapy based on patient preference (see Table 46–3).
- Discuss with caregivers and child the potential effectiveness and disadvantages of existing GH treatment options.
- Address any patient concerns about long-term complications of GH deficiency, its management, and possible adverse effects of GH therapy.
- Educate regarding potential for lifelong replacement therapy.
- Use motivational interviewing strategies and coping strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Review child's medication adherence.
- Monitor response (increase in height and change in height velocity) and adverse effects of GH therapy (intracranial hypertension, slipped capital femoral epiphysis, and scoliosis progression). Individualized dose based on child's response.
- Continue GH therapy until child reaches satisfactory adult height, achieves documented epiphyseal closure, or fails to respond to treatment.
- Review and retest the child using adult GH deficiency diagnostic criteria when the child reaches final adult height.

Patient Care Process: GH Deficiency in Adults

Collect Information:

- Obtain a thorough history and physical examination that may indicate the possible presence of GH deficiency, history of childhood GH deficiency, or presence of other pituitary hormone deficiencies.
- Obtain GH and IGF-I concentrations after appropriate provocative testing.
- Review imaging tests of the hypothalamic–pituitary region to detect any anomalies.
- Perform complete medication history. Identify allergies to medications and other substances.
- Speak with patient to identify sign and symptoms of GH deficiency, preferences and beliefs, health goals, socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the patient's clinical signs and symptoms to determine the severity of GH deficiency.
- Assess presence of other pituitary hormone deficiency.
- Assess presence of metabolic abnormalities and cardiovascular and fracture risks.
- Assess risk factor for development of malignancy (history of cancer or active cancer).
- Assess if the patient has any contraindications, allergies, or drug interactions to GH therapy.

Develop a Care Plan:

- Determine if GH therapy is indicated. Initiate the appropriate GH therapy at the lower dosing range based on patient characteristics (see Table 46–3).

Implement the Care Plan:

- Initiate GH therapy based on patient preference and characteristics (see Table 46–3).
- Discuss with patient the potential effectiveness and disadvantages of existing GH treatment options.
- Address any patient concerns about long-term complications of GH deficiency, its management, and possible adverse effects of GH therapy.
- Discuss with patient how to reduce the modifiable cardiovascular, metabolic, and fracture risk factors.
- Educate regarding potential for lifelong replacement therapy.
- Use motivational interviewing strategies and coping strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Review medication adherence.
- Assess the efficacy and adverse effects of GH therapy and consider if the patient's therapy requires any dose adjustments based on IGF-I concentration, patient response, and adverse effects.
- Monitor for improvement of metabolic, cardiovascular, bone mineral density, mood, and body composition parameters to assess response to GH therapy.

Hyperprolactinemia

▶ *Epidemiology and Etiology*

LO 7

Hyperprolactinemia affects women of reproductive age more than men, and the estimated prevalence in women treated with hyperprolactinemia is 90 cases per 100,000 person years.[39] The etiologies of hyperprolactinemia are presented in Table 46–4.[7,24,39] Any medications that antagonize dopamine or stimulate prolactin release can induce hyperprolactinemia.[7,24] Therefore, it is important to exclude medication-induced hyperprolactinemia from other common causes such as pregnancy, primary hypothyroidism, benign prolactin-secreting pituitary adenoma (prolactinoma), and renal insufficiency. Prolactinomas are the most common pituitary tumors. They are classified as microprolactinomas if they are less than 10 mm in diameter and as macroprolactinomas if they are 10 mm or larger in diameter.[39] In general, microprolactinomas rarely increase in size, but macroprolactinomas have the potential to enlarge and invade the surrounding tissues.[40]

▶ *Pathophysiology*

LO 8

Hyperprolactinemia is a condition of elevated serum prolactin. It is the most common endocrine disorder of the hypothalamic–pituitary axis. High prolactin concentrations inhibit the release of gonadotropin-releasing hormone by the hypothalamus and subsequently suppress secretion of LH and FSH from the anterior pituitary (see Figure 46–1). High prolactin concentrations result in reduced gonadal hormone concentrations, often leading to reproductive dysfunction and galactorrhea (inappropriate breast milk production).

In combination with clinical symptoms, one or more serum prolactin concentrations greater than 25 ng/mL (mcg/L; 1087 pmol/L) will confirm the diagnosis of hyperprolactinemia in women.[39] A number of physiologic factors such as eating, exercise, and stress can transiently elevate prolactin concentrations.[7] If an intravenous line is present or planned, it is prudent to wait at least 2 hours after line insertion before measuring serum prolactin to decrease detecting transient physiologic increases in prolactin concentration.[7,24,39] Although medication-induced hyperprolactinemia is typically associated with prolactin concentrations of 25 to 100 ng/mL (mcg/L; 1087–4348 pmol/L), metoclopramide, risperidone, and phenothiazines have been associated with concentrations greater than 200 ng/mL (mcg/L; 8696 pmol/L). However, prolactin concentrations greater than 500 ng/mL (mcg/L; 21739 pmol/L) are almost always associated with the presence of a macroprolactinoma.[39]

▶ *Treatment*

Desired Outcomes Because hyperprolactinemia is often associated with hypogonadism, the goals for management of hyperprolactinemia are as follows[39]:

- Normalize prolactin concentration
- Restore normal gonadal function and fertility
- Prevent development of osteoporosis
- If a pituitary tumor is present:
  - Ablate or reduce tumor size to relieve tumor mass effect
  - Preserve normal pituitary function
  - Prevent progression of pituitary tumor or hypothalamic disease

General Approaches to Treatment Management of drug-induced hyperprolactinemia is to discontinue the offending

LO 7

Table 46–4

Causes of Hyperprolactinemia[7,24,39]

Physiologic Causes
Pregnancy
Stress (including exercise and hypoglycemia)
Breast stimulation
Breastfeeding
Coitus
Sleep
Meal
Increased prolactin production
Ovarian: Polycystic Ovarian Syndrome
Oophorectomy (removal of an ovary)
Pituitary tumors
Adenomas
Microprolactinoma (< 10 mm diameter)
Macroprolactinoma (≥ 10 mm diameter)
Hypothalamic stalk interruption (prevent dopamine from reaching the pituitary)
Hypophysitis (inflammation)
Ectopic tumors
Hypothalamic Prolactin Stimulation
Primary hypothyroidism
Adrenal insufficiency
Reduced Prolactin Elimination
Chronic renal failure
Hepatic cirrhosis
Neurogenic Causes
Chest wall injury (eg, surgery, herpes zoster)
Spinal cord lesions
Abnormal Molecules
Macroprolactinemia
Medications
Dopamine antagonists: antipsychotics,[a] phenothiazines, metoclopramide, domperidone
Dopamine-depleting agents: reserpine, α-methyldopa
Prolactin stimulators: serotonin reuptake inhibitors, dexfenfluramine, estrogens, progestins, antiandrogens, gonadotropin-releasing hormone analogs, benzodiazepines, tricyclic antidepressants, monoamine oxidase inhibitors, protease inhibitors, histamine$_2$ receptor antagonists
Other: isoniazid, cocaine, opioids, verapamil
Seizures
Idiopathic (Unknown)

[a]Atypicals (olanzapine and clozapine) other than risperidone may cause an early but transient elevation in prolactin.

Data from Jordan JK, Sheehan AH, Calis KA. Pituitary gland disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy. A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017.

agent, if clinically feasible, and replace it with an appropriate alternative that does not cause hyperprolactinemia.[39] When the offending agent cannot be discontinued or dosage cannot be reduced, cautious use of hormone replacement, oral contraceptives, pharmacologic treatment for osteoporosis, aripiprazole, or dopamine agonists may be considered depending on the patient's clinical circumstances.[41] Treatment options for the management of hyperprolactinemia include: (a) clinical observation, (b) pharmacologic therapy with dopamine agonists, (c) transsphenoidal pituitary adenomectomy, and (d) radiation therapy. Clinical observation and close monitoring are justifiable in patients with asymptomatic elevation of prolactin.[39] KEY CONCEPT

LO 9

Dopamine agonists are the first-line treatment of choice for all patients with symptomatic hyperprolactinemia; transsphenoidal surgery and radiation therapy are reserved for patients who are resistant to or severely intolerant of pharmacologic therapy.[39] However, in patients with underlying psychiatric symptoms, use of dopamine agonists in addition to an antipsychotic therapy may exacerbate the underlying psychosis and should be used with caution in consultation with a mental health clinician.[41]

Pharmacologic Therapy Dopamine is the principal neurotransmitter responsible for the inhibition of prolactin secretion from the anterior pituitary. Thus, dopamine agonists are the main pharmacologic therapy used for management of hyperprolactinemia. Treatment with dopamine agonists has proven to be extremely effective in normalizing serum prolactin concentration, restoring gonadal function, decreasing tumor size, and improving visual fields.[39,42] Patients with macroprolactinomas generally require a higher dose to normalize prolactin concentrations compared with patients with microprolactinomas.[43]

LO 9

Two dopamine agonists—bromocriptine and cabergoline—are used for the management of hyperprolactinemia (Table 46–5).[44] Because these two dopamine agonists are ergot derivatives, they are contraindicated in combination with potent cytochrome P-450 subfamily IIIA polypeptide 4 (CYP3A4) inhibitors, including protease inhibitors, azole antifungals, and some macrolide antibiotics. Furthermore, ergot derivatives can cause constriction of peripheral and cranial blood vessels. These medications are also contraindicated in patients with uncontrolled hypertension, severe ischemic heart disease, or peripheral vascular disorders.

Bromocriptine Bromocriptine directly binds to the D_2 dopamine receptors. It normalizes prolactin concentration in 68% of patients and reduces tumor size in 62% of patients.[42] Treatment with bromocriptine may also restore menses and fertility in women and improve testosterone secretion, sperm count, and erectile function in men. It may also improve visual field defects associated with macroadenomas.[42] Adverse effects such as nausea, dizziness, and orthostatic hypotension often limit 5% to 10% of patients from continuing treatment. To reduce risk of adverse effects and improve patient adherence, bromocriptine may be initiated at bedtime or be administered vaginally (2.5 mg/day) at low dose.[40,45]

Cabergoline Cabergoline has a higher affinity for D_2 dopamine receptors than bromocriptine and possesses a long half-life, allowing for once- or twice-weekly administration. Cabergoline appears to be better tolerated than bromocriptine, and may be more effective in normalizing prolactin concentrations and restoring menses.[46] It is also effective in treating hyperprolactinemia in patients who are resistant to or intolerant of bromocriptine and in men and women with microprolactinomas and macroprolactinomas.[39,46] Given its favorable safety and efficacy profile and ease of administration, cabergoline has replaced bromocriptine as first-line therapy for the management of hyperprolactinemia.[39] Withdrawal of pergolide from the US market due to increased risk for valvular heart disease raised concerns about the safety of cabergoline. However, to date, cabergoline use in patients with hyperprolactinemia[47] or prolactinoma[48] has not been associated with clinically significant valvular heart disease.

Clinical Presentation and Diagnosis of Hyperprolactinemia[7,39]

LO 8

General

Hyperprolactinemia most commonly affects women of reproductive age and is very rare in men.

Signs and Symptoms

Premenopausal women

- Headache and compromised or loss of vision caused by the prolactin-secreting tumor and its close proximity to the optic structures.
- Clinical presentation is associated with the degree of prolactin elevation:
  - Prolactin greater than 100 ng/mL (mcg/L; 4348 pmol/L): hypogonadism, galactorrhea, and amenorrhea
  - Prolactin 51 to 75 ng/mL (mcg/L; 2217–3261 pmol/L): oligomenorrhea (infrequent menstruation)
  - Prolactin 31 to 50 ng/mL (mcg/L; 1348–2174 pmol/L): decreased libido and infertility
- Increased body weight may be associated with a prolactin-secreting pituitary tumor.
- The degree of hypogonadism generally is proportionate to the degree of prolactin elevation.
- Excessive hair growth (hirsutism) and acne also may be present owing to relative androgen excess compared with low estrogen concentrations.

Men

- Decreased libido, decreased energy, erectile dysfunction, impotence, decreased sperm production, infertility, gynecomastia, and rarely, galactorrhea.
- Impotence is unresponsive to treatment and is associated with reduced muscle mass, loss of pubic hair, and osteoporosis.

Laboratory Tests

- Prolactin serum concentrations at rest will be greater than 20 ng/mL (mcg/L; 870 pmol/L) in men or 25 ng/mL (mcg/L; 1087 pmol/L) in women with at least three measurements.
- Obtain β-human chorionic gonadotropin (β-hCG) concentration to exclude pregnancy.
- Obtain TSH concentration to exclude primary hypothyroidism.
- Obtain blood urea nitrogen and serum creatinine tests to exclude renal failure.

Other Diagnostic Tests

- Perform MRI to locate the tumor, exclude a pseudo-prolactinoma, and validate the diagnosis.
- Consider a bone mineral density test in patients with long-term hypogonadism.

Additional Clinical Sequelae

- The prolonged suppression of estrogen in premenopausal women with hyperprolactinemia leads to decreases in bone mineral density and significant risk for the development of osteoporosis.
- Risk for ischemic heart disease may be increased with untreated hyperprolactinemia.

Adapted, with permission, from Jordan JK, Sheehan AH, Calis KA. Pituitary gland disorders. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy. A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017.

LO 9

Nonpharmacologic Therapy In a small number of patients who have failed or are intolerant of dopamine agonists, transsphenoidal adenomectomy may be necessary.[39] Surgical treatment is also considered in patients with nonprolactin-secreting tumors or macroprolactinomas that jeopardize the optic chiasm.[43] Nonetheless, surgical intervention does not reliably lead to long-term cure and may cause permanent complications.[42] Radiation therapy is reserved for failures of both pharmacologic therapy and surgery.[39] However, normalization of prolactin concentration with radiation therapy may take 20 years to show full benefit, and

Table 46–5

Comparison of Dopamine Agonists for Treatment of Hyperprolactemia[44]

	Bromocriptine (Parlodel)	Cabergoline
Starting dose	0.625–1.25 mg/day at bedtime	0.5 mg/week or 0.25 mg twice/week
Titrating dose	1.25 mg increments at 1-week interval	0.25 mg twice weekly increment, up to 1 mg twice weekly every 2 to 4 months
Usually effective dose	2.5–15 mg/day	1–2 mg/week
Maximal dose	20 mg/day	4.5 mg/week
Dosing frequency	Two to three divided doses per day	Once or twice weekly
Dosage in hepatic insufficiency	May be required in acute hepatitis or cirrhosis; no guidelines are available	Dose reductions may be recommended for patients with severe hepatic failure (Child-Pugh scores of 10 or higher)
Dosage in renal failure	None	None
Adverse effects	Dizziness, headache, syncope, nausea, vomiting, gastrointestinal cramps, orthostatic hypotension, nasal congestion	Similar but orthostatic hypotension less common
Cost	Moderately expensive	More expensive

Patient Encounter 2, Part 1

A 27-year-old woman presented to primary care clinic 8 months ago with complaints of infrequent menstruation and infertility. Since she started cabergoline for hyperprolactinemia 6 months ago, she was excited to see return of her regular menses for several months until she realized her last menstrual period was 5 weeks ago.

PMH: Depression for 5 years

FM: Mother has depression, post-traumatic stress disorder, hypertension; father with high cholesterol and coronary artery disease.

SH: Married, dental assistant; sexually active (occasional use of condoms)

Meds: Prenatal vitamin one tablet daily; cabergoline 1-mg tablet weekly; naproxen 220 mg one to two tablets as needed for menstrual cramps and headache

ROS: Negative, other than in history of present illness

PE:

HEENT: Ophthalmic examination reveals normal visual acuity and fields. (–) goiter

VS: BP 128/78 mm Hg, P 76 beats/min, RR 19 breaths/min, T 37.1°C (98.8°F)

CV: RRR, normal S1, S2; no murmurs, rubs, or gallops

Breasts: (–) Galactorrhea with no abnormalities

Abd: Soft, nontender, nondistended; (+) bowel sounds; (–) hepatosplenomegaly

Rectal: Heme (–) stool

Prolactin: Elevated prolactin at 79 ng/mL (mcg/L; 3434 pmol/L) 7 months ago; prolactin at 30 ng/mL (mcg/L; 1304 pmol/L) today.

Imaging: MRI revealed a 4-mm pituitary tumor (7 months ago)

What signs and symptoms were suggestive of hyperprolactinemia in this patient?

What other tests would also be appropriate to obtain based on patient's history and diagnosis?

radiation-induced hypopituitarism may require lifelong hormone replacement.

Management of Hyperprolactinemia in Pregnancy Most women with hyperprolactinemia require dopamine agonist therapy to achieve regular ovulatory cycles and pregnancy. Because restoration of the ovulatory cycle may occur immediately after initiation of therapy, it is necessary to caution patients regarding their potential to become pregnant and ensure adequate contraception when beginning therapy.[43]

Overall, there is reassuring evidence that bromocriptine use during pregnancy does not increase fetal malformations, spontaneous abortions, preterm deliveries, or multiple births.[39,49] Although experience during pregnancy is limited, cabergoline does not appear to be teratogenic.[44] Despite these data, continuation of dopamine agonists during pregnancy is generally not recommended. KEY CONCEPT Women who become pregnant while taking a dopamine agonist should discontinue treatment to minimize fetal exposure.[39]

LO 9

Patient Encounter 2, Part 2

Labs: Electrolytes, renal and thyroid functions are within normal limits.

β-human chorionic gonadotropin (β-hCG): 7800 mIU/mL (U/L)

Given this additional information, what nonpharmacologic and pharmacologic treatment options are available for the patient at this time?

Microadenomas rarely cause complications during pregnancy. However, untreated macroprolactinomas carry about a 31% risk of tumor enlargement and potentially can jeopardize vision.[39] Therefore, monitor female patients with macroprolactinomas closely for the development of headache and visual impairments. Baseline and routine visual field examinations are essential. Evidence of abnormal visual fields may indicate tumor growth and should be followed by an MRI. If tumors enlarge, bromocriptine is the preferred choice over cabergoline because of greater experience with this drug during pregnancy.[39]

▶ *Outcome Evaluation*

- Assess patients for tolerability to dopamine agonists.
- Monitor clinical symptoms associated with hyperprolactinemia every month for the first 3 months to assess therapeutic efficacy and assist with dose titration.
- Evaluate the patient for symptoms, such as headache, visual disturbances, menstrual cycles in women, and sexual function in men, to assess clinical response to therapy.[39]
- When the prolactin concentration is normalized and clinical symptoms of hyperprolactinemia have resolved, monitor prolactin concentration every 6 to 12 months.
- If the prolactin concentration is well controlled with dopamine agonist therapy for 2 years with significant tumor reduction, gradually taper therapy to the lowest effective dose or consider discontinuing therapy.[39] Check prolactin concentration after each dose reduction.
- If the prolactin concentrations remain unchanged for 1 year at the reduced dose, dopamine agonist therapy may be discontinued.
- In patients with macroprolactinomas, monitor visual field at baseline and repeat the test 1 month after initiation of a dopamine agonist.
- Repeat the MRI in 1 year after initiating therapy or in 3 months in patient with macroprolactinoma or if an increase in symptoms or rise in prolactin concentration suggests the presence of tumor growth.[39]
- Discontinuation of therapy in patients with macroprolactinomas usually leads to tumor regrowth and recurrence of hyperprolactinemia. This decision warrants careful consideration.

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Patient Care Process: Hyperprolactinemia

Collect Information:

- Review the available diagnostic data to determine tumor size and location.
- Perform complete medication history. Identify allergies to medications and other substances.
- Review the medical history, relevant laboratory tests, and physical assessment findings.
- Speak with patient and review records to identify signs and symptoms of hyperprolactinemia, preferences and beliefs, health goals, socioeconomic factors or barriers that affect medication access and other aspects of care.

Assess the Information:

- Assess the patient's clinical signs and symptoms and prolactin level to determine the severity of hyperprolactinemia.
- Exclude other common causes of hyperprolactinemia (Table 46–4).
- Review patient's medication list to exclude medication-induced hyperprolactinemia (Table 46–4).
- Determine if the patient has a coexisting prolactin secreting tumor and impact of the tumor.
- Assess presence of hyperprolactinemia complications.
- Assess if the patient has any contraindications, allergies, or drug interactions to dopamine agonists.
- Determine the patient's plan regarding pregnancy because this influences treatment selection.

Develop a Care Plan:

- Initiate the appropriate dopamine agonist at the lowest effective dose for management of hyperprolactinemia (see Table 46–5). Consider if the patient's therapy requires any dose adjustments.

Implement the Care Plan:

- Discuss potential effectiveness and disadvantages of existing treatment options.
- Address any patient concerns about long-term complications of hyperprolactinemia, its management, and possible adverse effects of existing dopamine agonists.
- Educate patient about risks associated with hyperprolactinemia.
- Use motivational interviewing and coaching strategies to maximize adherence.

Follow-up: Monitor and Evaluate:

- Evaluate safety and efficacy of dopamine agonist. When appropriate, be sure to make dose adjustments (Table 46–5).
- Monitor patient adherence to treatment plan using multiple sources of information.
- Monitor patient prolactin level. If the prolactin concentration remains normal for 2 years, reassess the need to continue treatment.
- Consider bone mineral density tests in patient with long-term hypogonadism.

Abbreviations Introduced in This Chapter

AACE	American Association of Clinical Endocrinologists
ACTH	Adrenocorticotropic hormone or corticotropin
ADH	Antidiuretic hormone or vasopressin
β-hCG	β-Human chorionic gonadotropin
BMI	Body mass index
CRH	Corticotropin-releasing hormone
CT	Computed tomography
CYP3A4	Cytochrome P-450 subfamily IIIA polypeptide 4
DEXA	Dual-energy x-ray absorptiometry
FSH	Follicle-stimulating hormone
FT_4	Free T_4
GABA	γ-Aminobutyric acid
GH	Growth hormone or somatotropin
GHIH	Growth hormone–inhibiting hormone or somatostatin
GHRH	Growth hormone–releasing hormone
GI	Gastrointestinal
GnRH	Gonadotropin-releasing hormone
$HgbA_{1c}$	Glycated hemoglobin A_{1c}
IGF	Insulin-like growth factor
IGF-I	Insulin-like growth factor-I
IGF-II	Insulin-like growth factor-II
IGFBP-3	Insulin-like growth factor-binding protein-3
IM	Intramuscular
ITT	Insulin tolerance test
LAR	Long-acting release
LFT	Liver function test
LH	Luteinizing hormone
LHRH	Luteinizing hormone–releasing hormone
MRI	Magnetic resonance imaging
MSH	Melanocyte-stimulating hormone
OGTT	Oral glucose tolerance test
PRH	Prolactin-releasing hormone
SAGhE	Safety and Appropriateness of Growth hormone treatments in Europe
SC	Subcutaneous
SR	Slow release
SRL	Somatostatin receptor ligan
T_3	Triiodothyronine
T_4	Thyroxine
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone or thyrotropin
ULN	Upper limit of normal

REFERENCES

1. Muller EE, Locatelli V, Cocchi D. Neuroendocrine control of growth hormone secretion. Physiol Rev. 1999;79(2):511–607.
2. Le Roith D, Bondy C, Yakar S, Liu JL, Butler A. The somatomedin hypothesis: 2001. Endocr Rev. 2001;22(1):53–74.
3. Melmed S, Kleinberg DL, Bonert V, Fleseriu M. Acromegaly: assessing the disorder and navigating therapeutic options for treatment. Endocr Pract. 2014;20(suppl 1):7–17; quiz 18–20.

4. Katznelson L, Atkinson JL, Cook DM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update. Endocr Pract. 2011;17(suppl 4):1–44.
5. Melmed S, Casanueva FF, Klibanski A, et al. A consensus on the diagnosis and treatment of acromegaly complications. Pituitary. 2013;16(3):294–302.
6. Katznelson L, Laws ER, Jr., Melmed S, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–3951.
7. Jordan JK, Sheehan AH, Calis KA. Pituitary gland disorders. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York City: McGraw-Hill; 2017:1227.
8. Giustina A, Chanson P, Kleinberg D, et al. Expert consensus document: a consensus on the medical treatment of acromegaly. Nat Rev Endocrinol. April 2014;10(4):243–248.
9. Wildemberg LE, Gadelha MR. Pasireotide for the treatment of acromegaly. Expert Opin Pharmacother. 2016;17(4):579–588.
10. Carmichael JD, Bonert VS, Nuno M, Ly D, Melmed S. Acromegaly clinical trial methodology impact on reported biochemical efficacy rates of somatostatin receptor ligand treatments: a meta-analysis. J Clin Endocrinol Metab. 2014;99(5): 1825–1833.
11. Cozzi R, Montini M, Attanasio R, et al. Primary treatment of acromegaly with octreotide LAR: a long-term (up to nine years) prospective study of its efficacy in the control of disease activity and tumor shrinkage. J Clin Endocrinol Metab. 2006;91(4):1397–1403.
12. Ronchi CL, Varca V, Beck-Peccoz P, et al. Comparison between six-year therapy with long-acting somatostatin analogs and successful surgery in acromegaly: effects on cardiovascular risk factors. J Clin Endocrinol Metab. 2006;91(1):121–128.
13. Caron PJ, Bevan JS, Petersenn S, et al. Tumor shrinkage with lanreotide Autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. J Clin Endocrinol Metab. 2014;99(4):1282–1290.
14. Fleseriu M, Hoffman AR, Katznelson L, AACE Neuroendocrine and Pituitary Scientific Committee. American Association of Clinical Endocrinologists and American College of Endocrinology disease state clinical review: management of acromegaly patients: what is the role of pre-operative medical therapy? Endocr Pract. 2015;21(6):668–673.
15. Grasso LF, Auriemma RS, Pivonello R, Colao A. Adverse events associated with somatostatin analogs in acromegaly. Expert Opin Drug Saf. 2015;14(8):1213–1226.
16. Giustina A, Arnaldi G, Bogazzi F, et al. Pegvisomant in acromegaly: an update. J Endocrinol Invest. 2017;40(6): 577–589.
17. van der Lely AJ, Biller BM, Brue T, et al. Long-term safety of pegvisomant in patients with acromegaly: comprehensive review of 1288 subjects in ACROSTUDY. J Clin Endocrinol Metab. 2012;97(5):1589–1597.
18. Lim DS, Fleseriu M. The role of combination medical therapy in the treatment of acromegaly. Pituitary. 2017;20(1):136–148.
19. Kuhn E, Chanson P. Cabergoline in acromegaly. Pituitary. 2017;20(1):121–128.
20. Maione L, Garcia C, Bouchachi A, et al. No evidence of a detrimental effect of cabergoline therapy on cardiac valves in patients with acromegaly. J Clin Endocrinol Metab. 2012;97(9):E1714–E1719.
21. Giustina A, Chanson P, Bronstein MD, et al. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab. 2010;95(7):3141–3148.
22. Biochemical assessment and long-term monitoring in patients with acromegaly: statement from a joint consensus conference of the Growth Hormone Research Society and the Pituitary Society. J Clin Endocrinol Metab. 2004;89(7):3099–3102.
23. Gharib H, Cook DM, Saenger PH, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in adults and children—2003 update. Endocr Pract. 2003;9(1):64–76.
24. Gums JG, Anderson SD. Hypothalamic, pituitary, and adrenal disorders. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases: Prevention, Detection, and Management. 2nd ed. Bethesda, Maryland: American Society of Health-System Pharmacists; 2010:605–628.
25. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML, Endocrine S. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(6):1587–1609.
26. Federico G, Street ME, Maghnie M, et al. Assessment of serum IGF-I concentrations in the diagnosis of isolated childhood-onset GH deficiency: a proposal of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED). J Endocrinol Invest. 2006;29(8):732–737.
27. Grimberg A, DiVall SA, Polychronakos C, et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr. 2016;86(6):361–397.
28. Ho KK. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol. 2007;157(6):695–700.
29. Cummings DE, Merriam GR. Growth hormone therapy in adults. Annu Rev Med. 2003;54:513–533.
30. Cook DM, Yuen KC, Biller BM, Kemp SF, Vance ML, American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients—2009 update. Endocr Pract. 2009;15(suppl 2):1–29.
31. Gasco V, Prodam F, Grottoli S, et al. GH therapy in adult GH deficiency: a review of treatment schedules and the evidence for low starting doses. Eur J Endocrinol. 2013;168(3):R55–R66.
32. Gasco V, Caputo M, Lanfranco F, Ghigo E, Grottoli S. Management of GH treatment in adult GH deficiency. Best Pract Res Clin Endocrinol Metab. 2017;31(1):13–24.
33. Allen DB, Backeljauw P, Bidlingmaier M, et al. GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol. 2016;174(2):P1–P9.
34. Casanueva FF, Castro AI, Micic D, Kelestimur F, Dieguez C. New guidelines for the diagnosis of growth hormone deficiency in adults. Horm Res. 2009;71(suppl 1):112–115.
35. Filipsson H, Johannsson G. GH replacement in adults: interactions with other pituitary hormone deficiencies and replacement therapies. Eur J Endocrinol. 2009;161(suppl 1):S85–S95.
36. Raman S, Grimberg A, Waguespack SG, et al. Risk of neoplasia in pediatric patients receiving growth hormone therapy—a report from the Pediatric Endocrine Society Drug and Therapeutics Committee. J Clin Endocrinol Metab. 2015;100(6):2192–2203.
37. Swerdlow AJ, Cooke R, Beckers D, et al. Cancer risks in patients treated with growth hormone in childhood: the SAGhE European cohort study. J Clin Endocrinol Metab. 2017;102(5):1661–1672.
38. Wilson TA, Rose SR, Cohen P, et al. Update of guidelines for the use of growth hormone in children: the Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr. 2003;143(4):415–421.

39. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(2):273–288.
40. Faje A, Nachtigall L. Current treatment options for hyperprolactinemia. Expert Opin Pharmacother. 2013;14(12): 1611–1625.
41. Montejo AL, Arango C, Bernardo M, et al. Multidisciplinary consensus on the therapeutic recommendations for iatrogenic hyperprolactinemia secondary to antipsychotics. Front Neuroendocrinol. 2017;45:25–34.
42. Wang AT, Mullan RJ, Lane MA, et al. Treatment of hyperprolactinemia: a systematic review and meta-analysis. Syst Rev. 24 2012;1:33.
43. Mann WA. Treatment for prolactinomas and hyperprolactinaemia: a lifetime approach. Eur J Clin Invest. 2011;41(3): 334–342.
44. Capozzi A, Scambia G, Pontecorvi A, Lello S. Hyperprolactinemia: pathophysiology and therapeutic approach. Gynecol Endocrinol. 2015;31(7):506–510.
45. Darwish AM, Farah E, Gadallah WA, Mohammad, II. Superiority of newly developed vaginal suppositories over vaginal use of commercial bromocriptine tablets: a randomized controlled clinical trial. Reprod Sci. 2007;14(3):280–285.
46. dos Santos Nunes V, El Dib R, Boguszewski CL, Nogueira CR. Cabergoline versus bromocriptine in the treatment of hyperprolactinemia: a systematic review of randomized controlled trials and meta-analysis. Pituitary. 2011;14(3):259–265.
47. Steffensen C, Maegbaek ML, Laurberg P, et al. Heart valve disease among patients with hyperprolactinemia: a nationwide population-based cohort study. J Clin Endocrinol Metab. May 2012;97(5):1629–1634.
48. Auriemma RS, Pivonello R, Perone Y, et al. Safety of long-term treatment with cabergoline on cardiac valve disease in patients with prolactinomas. Eur J Endocrinol. 2013;169(3):359–366.
49. Molitch ME. Prolactinoma in pregnancy. Best Pract Res Clin Endocrinol Metab. 2011;25(6):885–896.

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47 Pregnancy and Lactation: Therapeutic Considerations

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LEARNING OBJECTIVES

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

1. Explain the principles of embryology and teratology.
2. Identify known teratogens and drugs of concern during lactation.
3. Compare the main sources of drug information relevant to pregnancy and lactation.
4. Evaluate and communicate the risks of a drug when taken during pregnancy or lactation.
5. Apply a systematic approach to counseling on the use of drugs during pregnancy and lactation.
6. Recommend the appropriate dose of folic acid to prevent congenital anomalies.
7. Describe physiologic changes during pregnancy and their impact on pharmacokinetics.
8. Choose an appropriate treatment for common conditions in a pregnant or lactating woman.

INTRODUCTION

This chapter will provide general principles to understand the scientific data on medication use during pregnancy and lactation, to choose appropriate treatment and adjust their dosage for a variety of conditions prevalent during pregnancy, and to counsel women in a helpful and supportive way.

EPIDEMIOLOGY AND ETIOLOGY

Background Risks of Anomalies in Pregnancy

Table 47–1 describes the baseline risks of congenital anomalies and some obstetrical complications. This information is essential to evaluate risks associated with medication use and to counsel pregnant women.

Causes of Congenital Anomalies

Although the risk of drug-induced teratogenicity is of concern, the actual risk of birth defects from most drug exposures is small. Medications are associated with less than 1% of all congenital anomalies, although they may also interact with genetic factors.[3,4] It is important to evaluate and optimize drug use in pregnant women and women planning a pregnancy.

Other causes of anomalies include genetic causes in 25% of cases (inherited disease, gene mutation, chromosomal disorder), maternal infections (1%), maternal conditions (1%–3%; eg, pregestational diabetes, obesity), multifactorial heredity (23%–50%), and unknown causes (34%–43%).[3] Theoretical concerns regarding paternal exposure to genotoxic medication are reported, but currently no medication taken by a man has been proven teratogenic.[4]

PATHOPHYSIOLOGY

Age of Pregnancy

LO 1

The age of pregnancy can be defined as gestational or postconceptional age (PCA).[4] Gestational age (GA) is the term used in clinical practice. It is calculated from the first day of the last menstruation or by ultrasound dating.

PCA, calculated from the day of conception, is 14 days shorter than GA if the menstrual cycle is 28 days. Some references in

Table 47–1

Occurrence of Some Obstetrical Complications and Risk of Congenital Anomalies in the General Population[1-3]

	Risk of Occurrence in Population (%)
Spontaneous abortion/miscarriage (pregnancy loss that occurs after the pregnancy is known and before 20 weeks of GA; risk increases with higher maternal age)	10–15
Congenital anomalies (percentage of live births):	
• Minor malformations	14
• Major malformations at birth	3
• Major malformations at 2 years old	6
Preterm birth (< 37 completed weeks gestation)[a]	9.6
Low birth weight (< 2500 g)[a]	8.0

[a]United States data from 2014.

GA, gestational age.

Table 47–2

Phases of Embryonic and Fetal Development[3,4]

Phase of Development	Stage of Pregnancy[a]	Development Description	Potential Complications
Implantation and predifferentiation	0–14 days after conception (14–28 days after LMP)	Very little contact between the blastocyst and mother's blood Pluripotent cells, capacity to repair a damage Cells are fragile, miscarriage before pregnancy is detected if too many are destroyed	Spontaneous abortion; even if stopped during this period, long half-life drugs could affect organogenesis
Organogenesis (embryogenesis)	From day 14 until the 9th week after conception (From day 28 until the 11th week after LMP)	Organs are being formed; most critical period for structural anomalies Organs are being formed at different times; sensitivity for each organ differs Refer to Figure 47–1 for the time frame of organ formation	Major or minor structural anomalies; Spontaneous abortion; neurologic impairment
Fetogenesis	After the organogenesis and until birth	The fetus grows Organs begin to function (eg, glomerular filtration) Active cell growth, proliferation, and migration (eg, CNS)	Fetal growth retardation; functional deficit (eg, renal insufficiency), neurologic impairment; spontaneous abortion, stillbirth; neonatal complications

[a]Stage of pregnancy based on a menstrual cycle of 28 days.

LMP, last menstrual period; CNS, central nervous system.

the field of teratology and embryology refer to PCA to describe stages of pregnancy.

Principles of Embryology

Pregnancy is divided into three development phases: implantation and predifferentiation, organogenesis (or embryogenesis), and fetogenesis. Table 47–2 describes these phases and possible drug effects if taken during these phases, and Figure 47–1 illustrates the critical periods of human in utero development. KEY CONCEPT The risk of birth defects is usually higher during organogenesis.

▶ *Teratogens*

LO 2

KEY CONCEPT Health professionals should know which medications have teratogenic risk. A teratogen is an exogenous agent that can modify normal embryonic or fetal development.[3] Teratogenicity can manifest as structural anomalies, functional deficit, cancer, growth restriction, neurologic impairment, or death (spontaneous abortion, stillbirth).

In utero exposure to medication near delivery can also lead to transient neonatal complications, such as withdrawal or side effects (eg, opioids, selective serotonin reuptake inhibitors, antipsychotics, lithium).[4,5]

Teratogenic exposure is a term preferred over *teratogen* as it considers level (dose) and timing of exposure during pregnancy to determine whether it could lead to a higher risk of a specific malformation.[6]

Criteria have been proposed to determine whether a causal relationship between congenital anomalies and a medication is plausible when analyzing scientific documentation (teratogenic effect).[6] Exposure to the medication must have happened during the critical period of development of the organ for which a malformation is noticed (Figure 47–1). Also, a pattern of anomaly or a specific syndrome must be reproducible in at least two studies conducted in different populations. A rare anomaly associated with a rare exposure is also indicative of a teratogenic effect (eg, ear anomalies and isotretinoin).

Other criteria, listed below, are considered:

- Strength of the association
- Same effects observed in animal studies

Patient Encounter Part 1

A 35-year-old woman comes to your office after a positive urine pregnancy test. You collect the following data:

Estimated Gestational Age: 5 weeks, regular menstrual cycles of 28 days

PMH: Type 2 diabetes mellitus (T2DM) diagnosed 3 years ago, hypercholesterolemia, obesity (BMI 37 kg/m^2)

FH: T2DM, hypertension

SH: Afro-American origin. Nursing assistant. No use of alcohol, tobacco, or illicit substances. Not very active, but tries to respect low-carb diet

Meds: Metformin 1 g orally twice daily with meals, linagliptin 5 mg orally daily in the morning, glargine insulin 10 units subcutaneously at night

Allergy: None

ROS: Morning nausea; tiredness

VS: Wt 209 lb (95 kg), Ht 63 in (160 cm), BP 110/72 mm Hg with large cuff, pulse 70 beats/min, RR 12 breaths/min

How will you confirm gestational age?

What prenatal workup would you perform at this time?

What is the appropriate counseling at this time?

What are the risks of drugs taken in the first weeks of pregnancy? What resources will you use to find the appropriate information?

What do you recommend for her pharmacologic treatment?

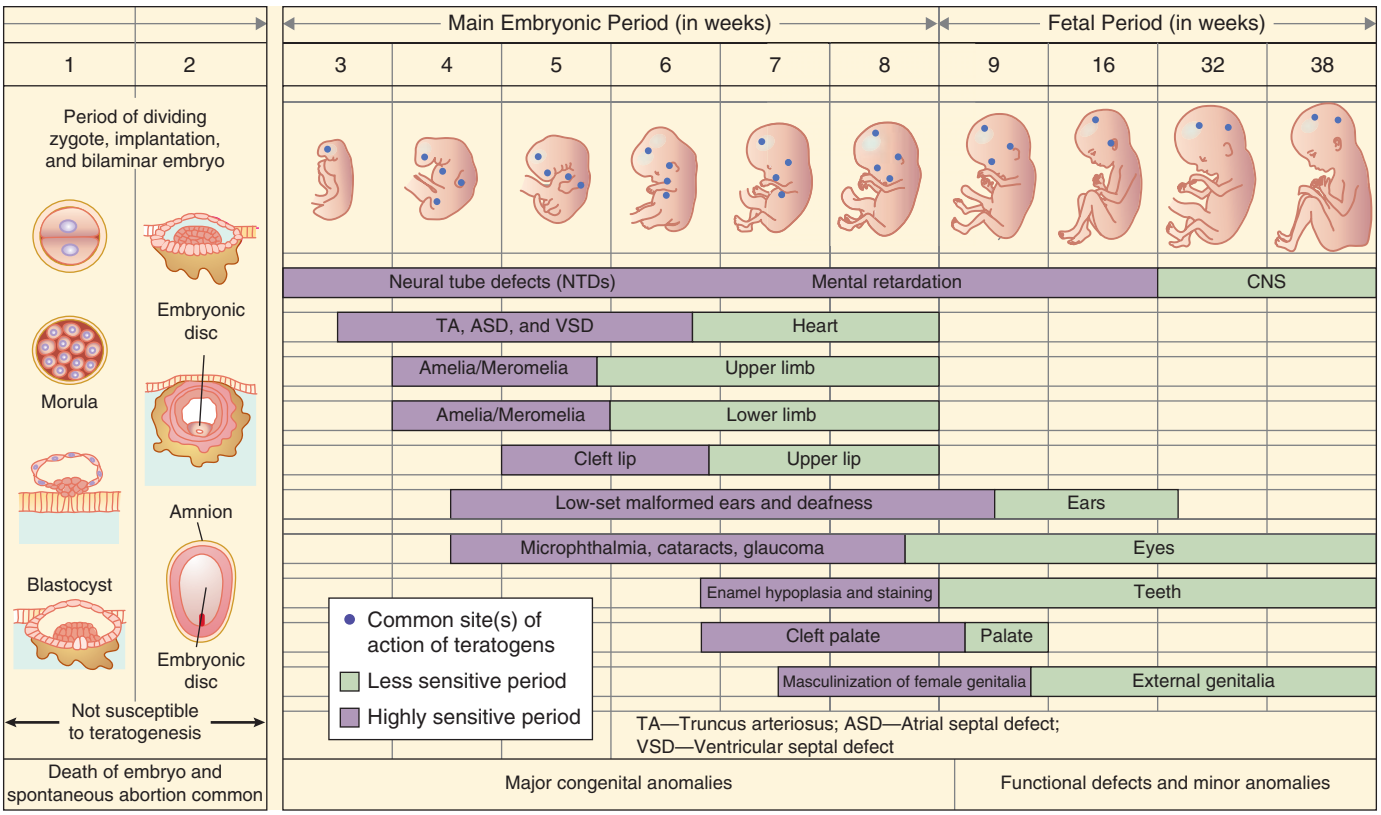

FIGURE 47–1. Embryonic and fetal development. The horizontal bars represent potential sensitivity to teratogens. The colored areas represent the more critical times. Embryonic period is in postconceptional weeks. (Reprinted with permission from Moore KL. The Developing Human. New York: Elsevier, p. 976: copyright 1974.)

- Biological plausibility based on pharmacologic effect
- Higher incidence of the anomaly in the population with the period of use of the medication (eg, thalidomide and limb anomalies)
- Dose–response relationship

LO 1 LO 2 With these criteria, there are approximately 30 medications or classes of medications that are considered teratogens (Table 47–3). Others are not necessarily safe: we must be careful not to interpret a lack of data as an absence of risk. A medication on this list is not necessarily contraindicated as severity and occurrence of malformations vary from one agent to another. Some can be used when benefits outweigh potential risks.

RISK EVALUATION

Desired Outcomes

The goal of drug use during pregnancy and lactation is to treat conditions effectively when necessary while minimizing risk to the developing embryo/fetus or the neonate.

Medication and Pregnancy

▶ *Data Published on Medication Safety During Pregnancy*

Most available data on drug safety during pregnancy come from postmarketing reports: case reports or case series, epidemiological research using population/prescription databases or using questionnaires, manufacturer registries, or specialized pregnancy registries. Clinicians are encouraged to refer their patients taking medication to a pregnancy registry; a list of pregnancy registries is available on the Food and Drug Administration (FDA) website (www.fda.gov/pregnancyregistries).

Animal studies, now mandatory before marketing a medication, can identify high-risk medications and prevent congenital anomalies. However, they have limitations; different species do not share the same pharmacodynamics and pharmacokinetics, and usually much higher doses than those used in clinical settings are tested.[8]

▶ *Sources of Information on the Use of Drugs During Pregnancy and Lactation*

KEY CONCEPT Health care professionals should be able to compare the main sources of drug information relevant to pregnancy and lactation. Some specialized information sources provide data on the use of medications during pregnancy and lactation (Table 47–4).

LO 3

The new FDA regulation, the Pregnancy and Lactation Labeling Rule (PLLR), has been effective since June 30, 2015.[9] This rule requires that the labels of all prescription drugs and biologic products approved after June 30, 2001 include narrative summaries of the risk of using them during pregnancy and lactation, with presentation of data supporting the summaries, and asks for an update of the information presented when it is outdated. It replaces the categories A, B, C, D, and X that were proposed before. Letters have long been criticized by experts because it is much too simplistic and can lead to a misinterpretation of risk.

Drugs that were approved before June 30, 2001 do not have to include in their label the information requested by the PLLR, but they have to remove the categories A, B, C, D, and X.

Table 47–3

Medications with Proven Teratogenic Effects in Humans[4-7]

Drug or Drug Class	Teratogenic Effects	Critical Period[a]
Alkylating agents	Malformations of many different organs	Organogenesis
Amiodarone	Transitory hypothyroidism (risk of 17%, goiter in some cases) or transitory hyperthyroidism	From 12th week after LMP
Androgens (danazol, testosterone)	Masculinization of genital organs in female fetus	From 9th week after LMP
Angiotensin converting enzyme inhibitors; angiotensin II receptor antagonists	Renal failure, anuria, oligohydramnios, pulmonary hypoplasia, intrauterine growth restriction, limbs contracture, skull hypoplasia	After the first trimester
Anticonvulsants (first generation)	NTD (carbamazepine and valproic acid); oral cleft, skeletal, urogenital, craniofacial, digital, and cardiac malformations	Organogenesis for structural anomalies
• Carbamazepine • Phenytoin • Phenobarbital • Valproic acid, divalproex	Major malformations: up to 5%–10% depending on the agent used, with variation with dosage used (10%–15% or more for valproic acid). Valproic acid: abnormal neurologic development	Valproic acid: whole pregnancy for neurologic impairment
Corticosteroids (systemic)	Oral cleft (risk of 3–4/1000 vs 1/1000 in general population)	Organogenesis (most critical period for palate formation: 8 and 11 weeks after LMP)
Diethylstilbestrol	Girls: cervical or vaginal adenocarcinoma, incidence: 1/1000. Structural genital anomalies (eg, of cervix, vagina) Boys: genital anomalies, spermatogenesis anomalies	First and second trimesters
Fluconazole high doses	Skeletal and craniofacial malformations, cleft palate, cardiac anomaly (with chronic dose ≥ 400 mg/day; not reported with 150 mg single dose)	Not defined, but cases are reported where exposure was throughout pregnancy
Iodine (supraphysiologic dosage)	Hypothyroidism, goiter	From 12th week after LMP
Isotretinoin, other systemic retinoids (acitretin, bexarotene, etretinate), and high dose of vitamin A (vitamin A > 10,000 IU/day not recommended)	Spontaneous abortion, CNS, skull, eyes and ears malformations, micrognathia, oral cleft, cardiac malformations, thymus anomalies, mental retardation: estimated risk at 25%–30% (may be higher for neurologic development impairment) Isotretinoin and bexarotene: discontinue 1 month before pregnancy, isotretinoin prescribed under a special program called iPLEDGE Acitretin: discontinue 3 years before pregnancy	Organogenesis (risk of teratogenic effect after organogenesis not excluded)
Lithium	Cardiac malformations: risk of 0.9%–6.8% (higher risks in small studies) (baseline risk ~1%) Includes Ebstein anomaly: risk estimated at 0.05%–0.1%	Cardiac organogenesis (5–10 weeks after LMP)
Methimazole/propylthiouracil	Methimazole: aplasia cutis, choanal atresia, esophageal atresia, omphalocele, minor facial anomalies, growth delay; risk of 2%–4% Methimazole/propylthiouracil: fetal hypothyroidism in 1%–5% of newborns, goiter	Organogenesis Second and third trimesters
Methotrexate	Spontaneous abortion, CNS, and cranial malformations (large fontanelles, hydrocephalia, incomplete cranial ossification, craniosynostosis), oral cleft, ear, skeletal and limb malformations, mental retardation; discontinue at least one ovulatory cycle before pregnancy	Organogenesis (8–10 weeks after LMP for structural anomalies but some exceptions reported)
Misoprostol	Moebius syndrome ± limb anomalies ± CNS anomalies Abortion, preterm birth	Organogenesis Throughout pregnancy for abortion/preterm birth
Mycophenolate mofetil, mycophenolic acid	Anomalies including ear anomalies, oral cleft, micrognathia, ophthalmic, cardiac, and digital anomalies (risk of structural anomalies estimated from 20%–25%); spontaneous abortion (30%–50%)	Organogenesis (risk unknown after)
Nonsteroidal anti-inflammatory drugs	In utero closure of ductus arteriosus (constriction is rare before 27 weeks, 50%–70% at 32 weeks [GA]) and neonatal pulmonary hypertension Renal toxicity and oligohydramnios possible after prolonged use from second half of second trimester from 20 weeks of gestational age	Third trimester
Penicillamine	Cutis laxa Joints and CNS anomalies Risk probably low	Not defined
Tetracyclines	Teeth discoloration	From 16 weeks after LMP

(*Continued*)

Table 47–3

Medications with Proven Teratogenic Effects in Humans[4-7] (*Continued*)

Thalidomide	Limb anomalies (amelia, phocomelia) Cardiac, urogenital, gastrointestinal, and ear malformations Risk of 20%–50% Prescribed under a special program called STEPS (System for Thalidomide Education and Prescribing Safety)	34–50 days after LMP
Trimethoprim	Cardiac and urogenital malformations, NTD, oral cleft; overall risk probably < 6%	Organogenesis
Warfarin/acenocoumarol	Before 6 weeks: baseline risk of anomalies Taken between 6 and 12 weeks: nasal hypoplasia, epiphysis dysplasia, vertebral malformations, rarely ophthalmic anomalies, scoliosis, hearing loss; risk estimated of 6%–10% and possibly dose-dependent 12 weeks after LMP: rarely, heterogeneous CNS anomalies	Between weeks 6 and 12 after LMP; some risks persist after

[a]Stages of pregnancy in this table are calculated after last menstrual period (gestational age) and not after conception to be more clinically useful.
CNS, central nervous system; LMP, last menstrual period; NTD, neural tube defect.

Manufacturers of medication approved between June 30, 2001 and June 30, 2015 have a 3- to 5-year period to comply with the PLLR.[9]

▶ *Communication of Information*

Communication of data on medication use during pregnancy can be challenging[10]:

- Data may be limited or contradictory.
- Taking medications during pregnancy is a source of anxiety.
- Pregnant women tend to overestimate their risk of an anomaly associated with medication use and to underestimate their risk associated with undertreating their condition.

Table 47–4

Examples of Sources of Information on Drug Use in Pregnancy and Lactation

Books
- Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 11th ed. Philadelphia: Lippincott Williams & Wilkins, 2017.
- Schaefer C, Peters PWJ, Miller RK. Drugs During Pregnancy and Lactation, Treatment Options and Risk Assessment, 3rd ed. Amsterdam: Elsevier, 2014.
- Hale TW. Medications and Mother's Milk, 17th ed. New York: Springer Publishing Company, LLC, 2017.

Databases
- Reprotox: www.reprotox.org
- Teris (Teratogen Information System): http://depts.washington.edu/terisweb/teris/

Websites/Applications
- www.mothertobaby.org
- www.motherisk.org
- www.marchofdimes.org
- www.cdc.gov
- www.fda.gov
- https://www.ncbi.nlm.nih.gov/pubmed/
- List of pregnancy registries: http://www.fda.gov/pregnancyregistries
- Lactmed: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Teratology Information Service
- MotherToBaby, a service of Organization of Teratology Information Specialists (OTIS): Go to *www.mothertobaby.org* to find your local Teratogen Information Service, or call National Toll-Free Number: (866) 626-6847

LO 4 LO 5

KEY CONCEPT Health care professionals should be able to evaluate and communicate the risks of a drug when taken during pregnancy or lactation. The objective is to give precise data that will help the patient make an informed decision for her health and baby's health. Information should include a well-grounded assessment of risks, including baseline risks in the general population, risks associated with the medication, and risks of not treating the disease during pregnancy.[10]

When discussing risks[10]:

- Use absolute numbers instead of relative numbers.
- Use negatively and positively framed information at the same time (eg, 3% chance of having a malformed child; 97% chance of having a child without malformation).
- Use the same denominator when discussing probabilities.

To determine a woman's risk of birth defects, obtain good medical, obstetrical, and pharmacotherapeutic histories (including over-the-counter medications and natural health products) and exposures to alcohol, tobacco, and other recreational drugs.[13]

KEY CONCEPT With all this information, the health care professional should be able to apply a systematic approach to counseling on the use of drugs during pregnancy and lactation.

▶ *Preconception Care*

Adverse pregnancy outcomes, including prematurity, low birth weight, and birth defects, are major health concerns. Late start in prenatal care can delay the identification and modification of risk factors that can affect pregnancy outcomes. Strategies to improve pregnancy outcomes include treating nutritional deficiencies, adequate folic acid, avoiding alcohol, substance and smoking, optimizing the management of chronic illnesses and genetic disorders, screening for infections, vaccination, pregnancy planning, and reaching a healthy weight.[11]

▶ *Folic Acid*

Anencephaly and spina bifida, with an estimated annual prevalence of 6.5 cases per 10 000, are the most common neural tube defects (NTDs) from an inadequate closure of the embryonic neural tube early in pregnancy.[12] Multivitamins containing folic acid reduce NTD and other congenital anomalies including oral clefts and cardiovascular, limb, and urinary tract malformations.[13]

KEY CONCEPT All women of childbearing age should be counseled on the appropriate dose of folic acid to prevent congenital anomalies.

LO 6 The American College of Obstetricians and Gynecologists (ACOG) and the US Preventive Services Task Force recommend that all women capable of pregnancy take 0.4 to 0.8 mg of folic acid daily, beginning 1 month before pregnancy and through the first 2 to 3 months, to prevent NTD.[12] Women at higher risk of NTD (eg, personal or family history of NTDs, use of antiseizure medications [valproic acid and carbamazepine], maternal diabetes, obesity, and mutations in folate-related enzymes) should take higher daily doses of folic acid (eg, 1–5 mg).[12]

► *Impact of Physiologic Changes During Pregnancy on Pharmacokinetics*

KEY CONCEPT Several physiologic changes during pregnancy have an impact on pharmacokinetics.

Absorption Decreased gastrointestinal transit can delay drug peak effect, prolonging the time of contact of drugs with the intestinal mucosa, and possibly enhancing absorption of certain drugs. Higher gastric pH may affect absorption of weak bases or acids. Pregnancy physiologic changes may also increase skin, tissue, and lung absorption.[14]

Distribution Volume of distribution increases for most drugs during pregnancy due to plasma volume expansion and the presence of amniotic fluid, the placenta, and the fetus, thus decreasing maximal drug concentrations. In addition, hypoalbuminemia and decreased protein binding increase free fraction (active portion) of some medications.[14]

Metabolism During pregnancy, the activity of some isoenzymes is increased (eg, CYP3A4, CYP2A6, CYP2D6, CYP2C9), while activity of others is decreased (eg, CYP1A2, CYP2C19). Net impact on drug effect is often unpredictable since there is a wide interindividual variability, and some drugs are metabolized by several isoenzymes.[14]

Renal Elimination Renal blood flow and glomerular filtration increase significantly during pregnancy. The impact of this is more important for drugs that are eliminated in the urine, which results in a decrease in their half-lives.

LO 7 Table 47–5 shows clinical recommendations based on pharmacokinetic changes during pregnancy for several drugs.[4,14]

Medication and Lactation

According to the latest policy statement from the American Academy of Pediatrics (AAP), mothers should breast-feed exclusively for 6 months and continue for 1 year if possible.[15]

► *Drug Transfer into Breast Milk*

To study drug effects, breast-fed infant's serum drug levels could be measured to evaluate safety; however, these data are often unavailable. In most instances, the approximate quantity of drug ingested by the breast-fed infant is estimated using published measured drug concentrations in breast milk. With these data, the percentage of pediatric dose or, if a pediatric dose is not available, the relative infant dose (percentage of weight-adjusted

Table 47–5

Altered Pharmacokinetics During Pregnancy: Clinical Implications and Management[4,14]

Drugs	Pharmacokinetic Changes	Recommendations and Monitoring[a]
Aminoglycosides	↑ V_d, ↑Cl, ↓ $t_{1/2}$	Monitor peaks and troughs; increase doses if necessary
Antiretrovirals	Variable Cl and C_{max}	Monitor clinical response; drug levels can be useful to adjust some drug dosages
Caffeine	↑ $t_{1/2}$ ↓ Cl (T_1, T_2, T_3)	Risk of more frequent and prolonged side effects; decrease caffeine consumption
Carbamazepine	↑ Cl ↓ $t_{1/2}$	Measure free fraction (preferably); increase dose according to clinical response and levels
Digoxin	↑ Cl ↓ C_{max}	Adjust according to clinical response and plasma levels; digoxin-like immunoreactive substance might interfere with measurement
Fluoxetine and other SSRIs	↑ Cl (T_3)	Increase dose according to clinical response
Heparin LMWH	↑ Cl (T_1, T_2, T_3)	For high-risk women (mechanical valves, new clot on therapeutic dosing) or CKD, follow anti-XA levels. Use twice daily administration for high-risk women.
Lamotrigine	↑ Cl (T_1, T_2, T_3)	For epilepsy: measure drug levels at least every trimester; increase dose according to clinical response and levels
Levothyroxine (T_4)	↓ff	Increase dose at the beginning of pregnancy; follow TSH levels every 4–6 weeks until 20 weeks and once in early T3
Lithium	↑ Cl (T_1, T_2, T_3) ↓ $t_{1/2}$	Measure drug levels every trimester and monthly in T3; increase dose according to levels if necessary
Nicotine	↓ $t_{1/2}$ ↑ Cl (T_2, T_3)	Higher doses might be required (smoking cessation) at T2 and T3; however, higher nicotine plasma levels possible (increased transdermal absorption)
Nifedipine	↑ Cl (T_3)	Monitor clinical effect; increase doses/frequency if necessary. Use twice daily for extended release formulation if > 40 mg/day
Phenytoin	↓ C_{total}, ff ↑ Cl (T_3) ↓ $t_{1/2}$	Measure free fraction; adjust dose according to clinical response, levels and signs of toxicity.
Valproic acid	↓ C_{total} ↑ ff	Measure free fraction if prepregnancy reference level available; dose will remain the same in most cases. Increase dose according to clinical response and levels

[a]Resume prepregnancy dosage after delivery in case of dosage adjustment for altered pharmacokinetics.

↑, increase; ↓, decrease; ↔, unchanged; C_{max}, maximum serum concentration; CKD, chronic kidney disease; Cl, clearance; ff, free fraction; T, trimester; $t_{1/2}$, elimination half-life; LMWH, low-molecular-weight heparin; C_{total}, total concentration; SSRI: selective serotonin reuptake inhibitor.

maternal dose) can be calculated, assuming an average of 150 mL/kg/day of milk ingested by a breast-fed infant.

$$\text{Percentage of pediatric dosage} = \frac{\text{Quantity of medication taken from milk by the baby (mg/kg/day)}}{\text{Usual initial pediatric dose (mg/kg/day)}} \times 100$$

$$\text{Weight adjusted maternal dose or relative infant dose} = \frac{\text{Quantity of medication taken from milk by the baby (mg/kg/day)}}{\text{Maternal dose adjusted by weight (mg/kg/day)}} \times 100$$

In the latter equation, maternal dose refers to the dose used by patients in a published study or a case report, not to the dose of your actual patient.

Usually, a percentage of less than 10% of the pediatric dose or, when a pediatric dose is not available, a percentage of less than 10% of weight adjusted maternal dose is generally accepted as safe in full-term healthy infants unless a drug has a toxic side-effect profile.[16]

▶ *Drug Pharmacokinetics*

If clinical data are unavailable on drug transfer into breast milk, drugs that are highly protein bound, have a high molecular weight, have a short half-life, have no active metabolites, and are well tolerated by children could be preferred.[16] In addition, drugs that are not orally absorbed should not cause systemic adverse effects in the breast-fed infant.

▶ *Drugs of Concern During Breast-Feeding*

LO 2

KEY CONCEPT Most drugs are safe during breast-feeding. However, some drugs are of concern and require a more thorough assessment by the clinician (Table 47–6). One should also consider additive side effects of several medications.

LO 8 CONDITIONS PREVALENT IN PREGNANCY AND LACTATION

KEY CONCEPT When possible, treat conditions occurring during pregnancy with nonpharmacologic treatments instead of drug therapy.

KEY CONCEPT Evaluate the need for treatment, including benefits and risks, and possibility of delaying treatment after pregnancy or breast-feeding.

For chronic diseases, please refer to the relevant chapter under "Special populations."

Iron-Deficiency Anemia

Anemia during pregnancy is defined as a hemoglobin level less than 11 g/dL (110 g/L; 6.83 mmol/L).[17] Maternal symptoms include fatigue, palpitations, and decreased resistance to exercise and infections. Fetal risks are prematurity, low birth weight, and perinatal death. All pregnant women should be screened for anemia, and those with iron deficiency should be treated with oral iron preparations in addition to prenatal vitamins.[17] Iron supplementation decreases the prevalence of maternal anemia at delivery and reduce transfusion requirements. It is unclear whether supplementing nonanemic pregnant women will improve perinatal outcomes but it reduces maternal fatigue.[17]

Nausea and Vomiting of Pregnancy (NVP)

As many as 80% of pregnant women suffer from nausea or vomiting.[18] Taking prenatal vitamin for 3 months before pregnancy may reduce the incidence and severity of NVP. Nonpharmacologic measures, such as lifestyle (rest, avoidance of nausea triggers) and

Table 47–6

Drugs of Concern During Breast-Feeding[4,5,16]

Drug or Class	Comments
Drugs that can decrease the breast milk production	
Clomiphene	Has been used to suppress lactation
Ergot derivatives (bromocriptine, cabergoline, ergotamine)	Have been used to suppress lactation
Estrogens	Contraceptives with ethinylestradiol should be delayed for 3–6 weeks postpartum to decrease effect on lactation and to prevent thrombosis
Pseudoephedrine	Do not use in women with low milk production; a few doses will probably not have effect
Drugs for which use during breast-feeding may expose the neonate to a significant quantity and may necessitate a strict follow-up	
β-Blocking agents (acebutolol, atenolol, sotalol)	Neonatal β-blockade reported Concern for acebutolol, atenolol, and sotalol, but other β-blocking agents such as metoprolol, propranolol, and labetalol are safe
Amiodarone	May accumulate (long half-life); possible neonatal thyroid and cardiovascular toxicity
Antineoplastics	Neonatal myelosuppression possible
Chloramphenicol	Severe adverse effects reported when used to treat babies (blood dyscrasia, grey baby syndrome)
Ergotamine	Symptoms of ergotism (vomiting and diarrhea) reported
Illicit drugs	Unknown contents and effects
Lamotrigine	A breast-fed infant could have blood concentrations between 10% and 50% of maternal blood concentrations (variable but can be in therapeutic range); monitor for CNS side effects (sedation, hypotonia, weight gain, and poor sucking) and rash
Lithium	Up to 50% of maternal serum levels have been measured in infants; cases of infant toxicity (lethargy, cyanosis, electrocardiogram anomalies, dysthyroidism, tremors) reported; if breast-feeding, monitor infant serum lithium, creatinine, urea, and TSH levels every 4–12 weeks and other side effects (jitteriness, feeding problems, signs of dehydration)
Phenobarbital/ primidone	Drowsiness and reduced weight gain reported; up to 25% of a pediatric dose can be ingested via breast milk; monitor for CNS adverse effects (sedation, hypotonia, weight gain, and poor sucking)
Radioactive iodine-131	No breast-feeding for days to weeks to achieve nonsignificant radiation levels (long radioactive half-life); monitor radioactive levels in milk before allowing breast-feeding; for diagnostic purposes, prefer Tc99m or iodine-123
Tetracyclines	Chronic use may lead to dental staining or decreased epiphyseal bone growth (theoretical)

CNS, central nervous system.

dietary changes (small/frequent meals, fluid restriction during meals, avoiding spicy/fatty foods, consuming crackers upon rising, high protein snacks) should be used as first-line management. Acupuncture and acupressure also can be helpful.[18]

Early treatment with pyridoxine (vitamin B6) or a combination of pyridoxine and doxylamine is recommended to prevent progression to more severe NVP such as *hyperemesis gravidarum*. When insufficient, metoclopramide, diphenhydramine, or ondansetron can be prescribed (Table 47–7).[18]

Pain

Pregnant or lactating women experience pain from preexisting conditions or from temporary pathologies (eg, musculoskeletal conditions, fibromas, migraine, etc).

The general principles of treatment are[4,5,19]

- Maximize nonpharmacological measures
- Acetaminophen is the safest analgesic during pregnancy
- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs) during the third trimester; short-term (< 72 hours) courses can be used under medical supervision during the first and second trimesters.
- Opiates are not associated with a higher risk of malformations. However, close neonatal monitoring is necessary due to possible withdrawal if opiates are taken regularly near delivery.
- Pregnancy and lactation safety data are limited for some medications (eg, pregabalin, gabapentin) and their use should be evaluated on a case-by-case basis
- For migraine, sumatriptan can be used when other medications are not sufficient or indicated.

Urinary Tract Infections

Urinary tract infections, even asymptomatic, are associated with preterm birth, low birth weight, and preeclampsia, and treatment reduces these risks.[20] Untreated bacteriuria leads more often to pyelonephritis due to physiologic changes of the urinary tract.[20] Screening for asymptomatic bacteriuria is performed in the first trimester,[20] but may be repeated in high-risk women (eg. preexistant diabetes mellitus [DM], sickle cell disease, and neurogenic bladder). Uropathogens are the same for nonpregnant women,[20] including multidrug-resistant strains; antibiograms are warrant. Differential diagnosis of dysuria includes sexually transmitted infections.

Antimicrobial therapy is considered for asymptomatic women with ≥ 10^8 colony forming unit (cfu)/L or symptomatic women with ≥ 10^5 cfu/L of a uropathogen on a clean-catch mid-stream specimen. Treatment options include β-lactams and nitrofurantoin (Table 47–7). Trimethoprim-sulfamethoxazole should be avoided during organogenesis (congenital malformations) and near term (theoretical risk of **kernicterus**).[5] Quinolones are reserved for resistant infections due to theoretical concerns of arthropathy.[5] Initiate in-hospital intravenous (IV) antibiotics for pyelonephritis.

Repeat urine culture 7 days after treatment then monthly. Suppressive prophylaxis (Table 47–7) up to 6 weeks after delivery is indicated for persistent bacteriuria despite two treatment courses, recurrent cystitis, or after a single pyelonephritis episode.[20]

Preterm labor

Preterm birth is defined as a delivery before 37 completed weeks (< 259 days). Preterm birth, especially before 32 weeks of pregnancy, is the major cause of short- and long-term neonatal mortality and morbidity. In case of a premature delivery threat, depending on the gestational age, start: antenatal corticosteroids for fetal pulmonary maturation, antibiotic to lower the risk of neonatal group B streptococcal disease, and magnesium sulfate for fetal neuroprotection. **Tocolytics** can be administered in preterm labor and antibiotic in preterm premature rupture of membranes (PPROM) to prolong pregnancy.

► *Antenatal Corticosteroids*

Administration of antepartum corticosteroids to the mother to accelerate the maturation of the fetal lungs decreases incidence and severity of neonatal respiratory distress syndrome, intraventricular hemorrhage, **necrotizing enterocolitis**, and death.[21] Provide a single course of antenatal corticosteroids (betamethasone or dexamethasone) to women between 24 0/7 weeks and 33 6/7 weeks of gestation at risk of delivery within 7 days (Table 47–7).[21] It may also be considered starting at 23 0/7 weeks or between 34 0/7 weeks and 36 6/7 weeks if they did not receive a previous course. A single repeat course can be considered after 7 to 14 days if at less than 34 0/7 weeks and, at risk of delivery within 7 days.[21]

► *Tocolytic Agents*

Tocolytics are used when preterm labor occurs before 33 6/7 weeks to delay delivery in order to complete a course of corticosteroids and allow transfer of the mother to a center with neonatal intensive care facilities. Tocolytics include magnesium sulfate, β-mimetics (terbutaline), prostaglandin inhibitors (indomethacin), oxytocin receptor blockers (atosiban, not available in the United States), and calcium channel blockers (nifedipine) (Table 47–7).[22,23] Tocolytic agents can prolong pregnancy for up to 48 hours. Magnesium sulfate is associated with significant maternal adverse effects, and indomethacin cannot be used after 32 weeks of pregnancy.[22]

FDA issued a warning regarding the use of terbutaline for tocolysis due to the risk of serious maternal adverse effects. Accordingly, its use should be limited to short-term inpatient use.[22]

► *Neuroprotection*

Magnesium sulfate given to women at imminent risk of delivery before 32 0/7 weeks gestation decreases the incidence of subsequent neurologic morbidities like cerebral palsy (Table 47–7).[22,24,25]

► *Antibiotics for PPROM*

In the presence of PPROM, 2 days of parenteral ampicillin/erythromycin followed by 5 days of oral amoxicillin and erythromycin are associated with a delay of delivery and reduction in maternal and neonatal morbidity (Table 47–7).[25] Women with PPROM should receive an adequate intrapartum Group B *Streptococcus* (GBS) prophylaxis for the first 48 hours to prevent neonatal infection (refer to section on GBS infection).[25,26]

► *Progesterone*

Progesterone is used to reduce the risk of preterm birth in women with singleton gestation and a prior spontaneous singleton preterm delivery. Administration of progesterone is also recommended in women with a very short cervix (≤ 20 mm) by transvaginal ultrasound before or at 24 weeks of gestation (Table 47–7).[27]

Group B *Streptococcus* Infection

Ten percent to 30% of pregnant women are colonized by GBS at term. IV antibiotics are effective in reducing the incidence

Table 47–7

Medication Dosing Recommendations During Pregnancy and Lactation[4,12,17,19-22,24–42]

Drug	Dosage	Comments
Micronutrients and Vitamins		
Folic acid	0.4–0.8 mg po daily 1–5 mg po daily	Dosage necessary to reach RDA: 0.6 mg (pregnancy), 0.5 mg (breast-feeding) If higher risk of having a child with NTD
Iron	60–200 mg (elemental iron) po per day (divided doses if > 60–100 mg of elemental iron)	Doses to treat iron-deficiency anemia
Nausea and Vomiting		
Diphenhydramine or dimenhydrinate	25–50 mg po four times daily as needed	Will likely cause sedation. Do not drive under the effect of these medications
Doxylamine	12.5 mg po three to four times daily as needed	
Pyridoxine	25 mg po three times daily as needed	Dose up to 200 mg daily have been used
Doxylamine + pyridoxine	Two pills at bedtime, one pill in the morning, and one pill in the afternoon (up to eight pills daily)	
Metoclopramide	5–15 mg po three to four times daily as needed	
Ondansetron	4–8 mg po three times daily as needed	
Urinary Tract Infections		
Asymptomatic bacteriuria and uncomplicated acute cystitis		
Nitrofurantoin	100 mg po four times daily for 3–7 days (Furadantin, Macrodantin) 100 mg po twice daily (macrocrystalline—Macrobid) for 3–7 days	
Cefadroxil	1000 mg po twice daily for 3–7 days	
Cefprozil	500 mg po twice daily for 3–7 days	
Cephalexin	500 mg po twice daily for 3–7 days	
Amoxicillin	500 mg po three times daily for 3–7 days	Check for local resistance before prescribing
Acute pyelonephritis		
Ampicillin + gentamicin	1–2 g IV every 6 hours + 1.5 mg/kg/dose IV every 8 hours	Switch to oral antibiotic after 48 hours afebrile and treat for a total of 10–14 days, for example: • Cephalexin 500 mg po four times daily • Cefprozil 500 mg po twice daily • Amoxicillin clavulanate 875/125 mg po twice daily
Cefazolin	1–2 g IV every 8 hours	
Cefuroxime	0.75–1.5 g IV every 8 hours	
Ceftriaxone	1–2 g IV or IM every 24 hours	
Prophylaxis		
Nitrofurantoin	50–100 mg po at bedtime	Start after the end of the treatment for pyelonephritis and continue until 4–6 weeks after delivery
Cephalexin	250 mg po at bedtime	Nitrofurantoin should be preferred to prevent resistance to cephalosporins
Fetal Lung Maturation		
Betamethasone	12 mg IM every 24 hours for two doses	A single rescue course may be considered after at least 1 or 2 weeks of treatment if gestational age is < 34 0/7 weeks and the woman is likely to give birth within the next week
Dexamethasone	6 mg IM every 12 hours for four doses	
Tocolytic agents		
Indomethacin	50 mg oral load, then 25–50 mg po every 6 hours up to 48 hours	Avoid after 32 weeks of pregnancy; reports of increased risk of maternal postpartum hemorrhage, and neonatal complications (eg, premature closure of the ductus arteriosus, renal insufficiency, patent ductus arteriosus, necrotizing enterocolitis) are worrisome
Magnesium sulfate	4 g IV over 30 minutes, then continuous IV infusion of 2 g/hour up to 48 hours	Contraindicated in women with myasthenia gravis; maternal pulmonary edema and cardiac arrest have been reported Monitor blood magnesium levels Use with caution if renal impairment, contraindicated if renal failure
Nifedipine (short acting)	10–30 mg oral load (divided over at least 1 hour if > 10 mg used), then 10–20 mg every 4–8 hours up to 48 hours	Avoid in women with hypotension and preload-dependent cardiac lesions such as aortic insufficiency

(*Continued*)

Table 47–7

Medication Dosing Recommendations During Pregnancy and Lactation[4,12,17,19-22,24-42] (*Continued*)

Drug	Dosage	Comments
Magnesium sulfate For neuroprotection or prevention of eclampsia.	4 g IV over 30 minutes, then continuous IV infusion of 1 g/hour	Contraindicated in women with myasthenia gravis; maternal pulmonary edema and cardiac arrest have been reported; treatment limited to 24 hours for neuroprotection Monitor blood magnesium levels Use with caution if renal impairment; contraindicated if renal failure
Preterm Premature Rupture of Membranes		
Ampicillin	2 g IV every 6 hours for 48 hours followed by amoxicillin	Ampicillin/amoxicillin are used with erythromycin
Amoxicillin	250 mg po three times daily for 5 days	
Erythromycin base	250 mg IV every 6 hours for 48 hours followed by 333 mg three times daily for 5 days	
Preterm Labor Prevention		
17-α-hydroxyprogesterone	250 mg IM each week	Start at 16–24 weeks' gestation if previous preterm delivery
Progesterone (micronized)	100 mg (capsules) or 90 mg (8% gel) intravaginally daily (previous preterm delivery) 200 mg intravaginally daily (short cervix)	Start at 16–24 weeks' gestation if previous preterm delivery and before 24 weeks if short cervix
Group B *Streptococcus*		
Penicillin G	5 million units IV initially, then 2.5–3 million units IV every 4 hours until delivery	First choice
Ampicillin	2 g IV initially, then 1 g IV every 4 hours until delivery	
Cefazolin	2 g IV initially, then 1 g IV every 8 hours until delivery	
Clindamycin	900 mg IV every 8 hours until delivery	Only if isolate proven sensitive to clindamycin and erythromycin, or sensitive to clindamycin and testing for inducible clindamycin resistance is negative
Vancomycin	1 g IV every 12 hours until delivery	If other options are inappropriate
Cervical ripening/ Induction of labor		
Misoprostol	25 mcg (1/4 of 100 mcg tablet) vaginally every 3–6 hours	Check for uterine tachysystole with or without fetal heart rate changes
Dinoprostone	0.5 mg gel in cervical canal, or 1–2 mg gel vaginal	Do not use if previous uterine surgery including cesarean section
	10 mg extended-release vaginal insert in posterior fornix	Check for uterine tachysystole with or without fetal heart rate changes
Oxytocin	Low-dose regimen: 0.5–2 mU/min, with 1–2 mU/min increase every 15–40 minutes according to contractions High-dose regimen: 6 mU/min with 3–6 mU/min increases every 15–40 minutes according to contractions	Check for uterine tachysystole and water intoxication
Postpartum hemorrhage treatment		
Oxytocin	10 units IM or 10–40 units per 500–1000 mL as continuous intravenous infusion	Use normal saline or lactated Ringer; cautious with bolus if cardiac disease
Carbetocin (prophylaxis)	100 mcg IM or IV over 1 minute	
Methylergonovine	0.2 mg IM every 2–4 hours	Do not use in women with hypertension, preeclampsia or cardiovascular disease
Carboprost tromethamine	0.25 mg IM or intramyometrial every 15–90 minutes up to eight doses	Use with caution if asthma
Misoprostol	600–1000 mcg PO or PR	
Tranexamic acid	1g IV over 10 minutes (repeat once if bleeding persists)	
Hyperthyroidism		
Methimazole	5–15 mg po once or twice daily (total daily dose: 10–30 mg)	Second and third trimesters
Propylthiouracil	50–100 mg po one to three times daily (100–600 mg divided in three daily doses)	First trimester; risk of hepatotoxicity
Severe Hypertension		
Labetalol	Start with 10–20 mg IV over 2 minutes; repeated 20–80 mg every 15–30 minutes (max 300 mg/24 hours) Or 1–2 mg/min IV drip Oral formulation can be acceptable if woman is asymptomatic and no other option is available	Can exacerbate asthma symptoms May cause fetal bradycardia

(*Continued*)

Table 47–7

Medication Dosing Recommendations During Pregnancy and Lactation[4,12,17,19-22,24–42] (*Continued*)

Drug	Dosage	Comments
Nifedipine (short acting)	5–10 mg po; could be repeated after 30 minutes	May cause headache, flushing, dizziness, reflex tachycardia, and maternal pulmonary edema
Hydralazine	5 mg IV or IM; repeated 5–10 mg IV every 30 minutes (max 20 mg IV or 30 mg IM) Or 0.5–10 mg/hour IV drip	May cause reflex tachycardia, headaches
Nonsevere Hypertension		
First choices		
Methyldopa	500–3000 mg in 2–4 daily doses—max 750 mg per dose	May cause drowsiness, depression, hemolytic anemia, positive antinuclear antibodies
Labetalol	100–1200 mg divided in two to four daily doses	Can exacerbate asthma symptoms. May cause tiredness, headaches, hepatotoxicity
Nifedipine extended release	20–120 mg po in one to two daily doses (twice daily if > 40 mg daily)	May cause tachycardia, headaches, lower limb edema
Second choices		
Hydralazine	10–50 mg po two to four times daily	May cause reflex tachycardia, headaches, lupus-like syndrome; avoid monotherapy
Metoprolol	50–200 mg dived in two daily doses	Can exacerbate asthma; may cause fetal bradycardia
Clonidine	0.05–0.2 mg po (maximum: 0.8 mg daily divided in two daily doses)	May cause drowsiness
Hydrochlorothiazide	12.5–50 mg po once daily	May cause hypokalemia, dehydration
Bacterial Vaginosis		
Metronidazole	250 mg po three times daily for 7 days or 500 mg orally twice a day for 7 days 0.75% vaginal gel, once or twice daily for 5 days	Can be used in all trimesters For metronidazole and clindamycin, use oral formulation during pregnancy if treatment aim is to prevent PTB
Clindamycin	300 mg po twice daily for 7 days 2% cream, 5 g intravaginally at bedtime for 7 days 100-mg ovules intravaginally at bedtime for 3 days	
Vulvovaginal Candidiasis: refer to Chapter 83		
6–7 days treatments for intravaginal antifungical azoles are recommended during pregnancy to prevent recurrent episodes; shorter courses are appropriate during breast-feeding. Fluconazole is an acceptable alternative if intravaginal azoles cannot be used or during lactation.		
Mastitis		
Outpatient Treatment		
Dicloxacillin	500 mg po four times daily	Treat for 10–14 days
Cephalexin	500 mg po four times daily	
Amoxicillin 875 mg + clavulanate 125 mg	One tablet po twice daily	
Inpatient Treatment for More Severe Cases		
Oxacillin	2 g IV every 4 hours	Treat IV for 24–48 hours until afebrile then continue with outpatient treatment
Nafcillin	2 g IV every 4 hours	
Clindamycin	600–900 mg IV every 8 hours	
Vancomycin	1 g IV every 8–12 hours	If MRSA suspected or proven
Breast Candidiasis		
Mother		
Clotrimazole, miconazole, or nystatin	Topical cream	After each feeding and for 1 week after symptoms have resolved; also treat infant even if asymptomatic
Fluconazole	200–400 mg po for one dose followed by 100–200 mg po daily	If topical treatment not efficacious, add fluconazole; use until 1 week after symptoms have resolved (minimum of 2 weeks); also treat infant even if asymptomatic
Infant		
Nystatin oral solution	100,000–200,000 units (1–2 mL) to be swabbed into infant's mouth four times daily, after feedings	
Clotrimazole or miconazole topical cream	Apply in a thin layer in infant's mouth four times daily, after feedings	
Other Treatments for Candidiasis		
Gentian violet 0.5%–1% solution	To be swabbed into infant's mouth once daily for 5 days before a feeding	Can stain clothes and skin If nipples or mouth are not violet after application and the feeding, reapply the treatment

IM, intramuscular; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NTD, neural tube defect; po, orally; PR, per rectum; RDA, recommended daily allowance.

Clinical Confirmation and Associated Problems of Pregnancy and Lactation

Confirmation of Pregnancy

Positive urine or blood human chorionic gonadotropin followed by positive ultrasound, fetal heart sounds, and/or fetal movement.

Pregnancy Dating and Gestational Age

Calculated from the first day of the last menstrual period (LMP).

An ultrasound between 10 + 0 and 13 + 6 weeks determines gestational age based on crown-rump length and identifies multiple pregnancies.

Due dates typically are estimated at 40 weeks of gestation; however, infants delivered between 37 and 42 weeks are considered full term.

Pregnancy Symptoms

First trimester: Menstrual spotting, missed menses, fatigue, breast tenderness, increased urination, mood swings, nausea/vomiting, headache, heartburn, constipation

Second trimester: Frequent urination, heartburn, constipation, dry skin, edema, linea nigra, melasma

Third trimester: Backache, edema, shortness of breath, insomnia

Routine Pregnancy Visits

In an uncomplicated pregnancy, visits should occur monthly until 28 weeks of gestation, every 2 to 3 weeks from 28 to 36 weeks of gestation, and then weekly until delivery.

Assess for each of the following at each visit:

- Blood pressure
- Weight
- Urine protein (dipstick)
- Uterine size
- Fetal heart rate
- Fetal movement

Routine Lab Testing for Normal Pregnancies (First Trimester Unless Otherwise Indicated)

- Hemoglobin and hematocrit for anemia (repeated at 26–32 weeks)
- Blood type, Rh, red blood cell antibody screening
- Human immunodeficiency virus
- Venereal Disease Research Laboratory (VDRL) slide test for syphilis
- Rubella immunity
- Varicella immunity
- Hepatitis B surface antigen
- Urinalysis with culture for bacteriuria
- Gonorrhea and chlamydia
- Cervical cytology
- Screens for Down syndrome and NTDs (between 11 and 20 weeks)
- Gestational diabetes screening (at 24–28 weeks)
- Group B streptococcus (GBS) screening (at 35–37 weeks)
- Women at high risk for these conditions should be tested at the first visit:
  - Hypothyroidism
  - Type 2 diabetes
  - Sickle cell disease or thalassemia
  - Hepatitis C
  - Tuberculosis
  - Bacterial vaginosis

of early-onset neonatal GBS infection when administered to high-risk groups including women with GBS vaginal/rectal colonization, GBS bacteriuria in the current pregnancy, and those who previously delivered a neonate with GBS disease.[26]

All women should be screened for colonization using a vaginal-rectal swab between 35 and 37 weeks. If treatment is indicated, it should be started at the time of membrane rupture or onset of labor, whichever comes first and continued until delivery (Table 47–7). All women with unknown status should be treated if labor or PPROM occur before 37 weeks. IV penicillin G or ampicillin, or if penicillin-allergic, cefazolin (nonanaphylactic) or clindamycin (anaphylaxis), can be used (refer to Table 47–7 to know when clindamycin can be used). If sensitivity to clindamycin is unknown, vancomycin should be administered.[26]

Induction of Labor

Induction of labor aims to achieve a vaginal delivery by stimulating uterine contractions before spontaneous labor. Cervical ripening is the process of cervical softening, thinning, and dilating, when the cervix is not favorable to delivery.

Mechanical methods for ripening include cervical dilators (hygroscopic dilator, Foley catheter) and extraamniotic saline infusion.[28,29] Pharmacological methods include prostaglandin E1 (eg, vaginal misoprostol) and E2 (eg, vaginal or cervical dinoprostone). Prostaglandins are used both for cervical ripening and induction of labor. The controlled-release vaginal dinoprostone is easily removed in case of uterine tachysystole, which help to reverse it. Prostaglandins should not be used in women with a previous cesarean section due to the increased risk of uterine rupture.[29]

When the cervix is deemed favorable, nonpharmacological options for producing contractions are membranes sweeping, nipple stimulation, and amniotomy.[28]

Oxytocin is the most frequently used pharmacological method of labor induction.[28] If a prostaglandin has been used, oxytocin needs to be delayed 30 to 60 minutes after the removal of dinoprostone controlled-release insert, 4 hours after the last dose of misoprostol, and 6 to 12 hours after the administration of dinoprostone gel.[28] A rare but serious complication of high cumulative dose of oxytocin is water intoxication due to its antidiuretic action.[29]

Postpartum Hemorrhage

Postpartum hemorrhage is defined by the ACOG as blood loss greater than or equal to 1000 mL or blood loss with signs or symptoms of hypovolemia within 24 hours after birth, regardless

of route of delivery.[30] A blood loss greater than 500 mL after vaginal delivery is considered abnormal. Uterine atony accounts for up to 80% of primary postpartum hemorrhage, but other etiologies like genital or cervical trauma, retained placenta, and coagulopathies are also implicated.[30]

Oxytocin and carbetocin (long-acting analog of oxytocin) can prevent excessive blood loss associated with delivery and caesarian section. Of the treatment of postpartum hemorrhage, uterotonics (oxytocin, methylergonovine, carboprost tromethamine, and misoprostol) are effective in the presence of uterine atony. Methylergonovine should not be administered to women suffering from hypertension or coronary artery disease. Carboprost tromethamine should be used with caution in asthmatic women.[30] ACOG recommends that tranexamic acid, an antifibrinolytic agent, should be administered when uterotonics fail, and recent data indicate that it reduces mortality when given within 3 hours of birth.[30,31]

Nonpharmacologic approach, like uterine massage or compression (tamponade), is also used. More invasive procedures ranging from transfusion to hysterectomy are used in unresponsive postpartum hemorrhages.[30]

Thyroid Disorders

Thyroid hormones increase by 50% from 7 to 16–20 weeks' gestation, then plateau until delivery. Thyroxine-stimulating hormone (TSH) reference range shifts downward by 0.5 mIU/L (μIU/mL) because of the beta-human chorionic gonadotropin (β-hCG) effect. Universal screening of thyroid disorders in pregnancy is debated.[32] See Chapter 44 for further discussion on thyroid disorders.

Gestational (subclinical) hypothyroidism is defined by a TSH above normal pregnancy range, and is linked to adverse pregnancy outcomes. Replacement therapy is suggested for positive antithyroid peroxidase antibodies (anti-TPOAbs) and TSH above 2.5 mIU/L (strongly if above 4.0 mIU/L) or negative antibodies and TSH above 4.0 mIU/L (strongly if above 10.0 mIU/L).[32] For prepregnancy hypothyroidism, increase levothyroxine (LT_4) by 30%. Once treatment is initiated, monitor TSH every 4 to 6 weeks until 20 weeks and once in the early third trimester to aim TSH under 2.5 mIU/L. Resume prepregnancy dosage at delivery.

Gestational hyperthyroidism is self-remitting and not associated with adverse outcomes. In Graves' disease, propylthiouracil (PTU) is used until week 16 and methimazole thereafter (Tables 47–3 and 47–7).[32] Administer at the lowest effective dose to target FT_4 at or moderately above the reference range. Monitor fetus and neonate to detect signs of hypothyroidism (if antithyroid drugs) or hyperthyroidism (if mother is positive for thyroid-stimulating hormone receptors-stimulating antibodies [TSHR-Sabs]).

Monitor TSH levels 6 to 8 weeks after delivery in women with thyroid disorders. Both LT_4 and antithyroid drugs can be used during lactation.[16,32]

Hypertension

Preexisting and gestational hypertension increase the risk of maternal and perinatal morbidity and mortality. Preeclampsia, caused by impaired placentation, may present with hypertension and multiple maternal complications or fetal distress. Delivery leads to cure, although transient flare or de novo preeclampsia occur postpartum.[33,34] Timing of delivery depends on maternal and fetal status and gestational age, but is not deferred past 37 weeks.[34] IV magnesium sulfate is used in prevention of **eclampsia** (Table 47–7).[24,33,34]

Treat severe hypertension (systolic above 160 mm Hg or diastolic above 110 mm Hg) promptly to avoid target-organ damage (Table 47–7).[34,35] Threshold for treatment of nonsevere hypertension (130–155/85–105 mm Hg) is still debated. In nonpreeclamptic hypertension, tight control benefits mother without harming the fetus.[36] Methyldopa, labetalol, and extended release nifedipine are first-line treatments[33] (Table 47–7). Angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor antagonists, or renin inhibitors are contraindicated past the first trimester.[33]

To prevent preeclampsia and growth restriction in high-risk women, initiate low-dose aspirin (75–160 mg daily) early in pregnancy and calcium supplements (1.5–2.0 g elemental calcium/day) if low calcium intake in usual diet.[34]

Women with hypertension around pregnancy and delivery should be instructed to monitor blood pressure up to 10 days postpartum and on thresholds or symptoms requiring consultation.[33,34] Appointment 6 to 12 weeks postpartum is recommended to ensure correction of hypertension and proteinuria, and for counseling on future pregnancies and long-term care.

Preexisting Diabetes Mellitus

For gestational diabetes mellitus (GDM) discussion, see Chapter 43. Hyperglycemia is teratogenic. Women of childbearing age with preexistent diabetes should achieve a preconception hemoglobin A_{1c} less than 7% (ideally < 6.5%) to minimize risks of spontaneous abortions and malformations.[37] Refer to folic acid recommendations above.

Women with preexisting DM should be screened for diabetic nephropathy and retinopathy.[37] Type 1 diabetes mellitus (T1DM) are tested for gestational hypothyroidism and anti-TPOAbs. Low-dose aspirin is indicated to reduce preeclampsia risks.[34]

Optimal control of glycemia throughout pregnancy reduces risks of macrosomia, delivery complications, fetal demise, preeclampsia, and neonatal complications.[37] Self-monitoring of blood glucose (SMBG) goals during pregnancy are fasting less than 95 mg/dL (5.3 mmol/L), premeal less than 100 mg/dL (5.6 mmol/L), 1 hour postmeal less than 140 mg/dL (7.8 mmol/L), or 2 hour postmeal less than 120 mg/dL (6.7 mmol/L). Standard treatment is insulin. Oral hypoglycemics are not as efficacious, cross the placenta, and long-term safety data are missing.[5,37] Continue medication until the patient is safely switched to insulin.

Intrapartum glucose is maintained between 70 mg/dL (3.9 mmol/L) and 110 mg/dl (6.1 mmol/L) to avoid fetal acidosis and neonatal hypoglycemia. Postpartum, resume 2/3 of prepregnancy insulin dosage. Metformin and insulin are safe during breast-feeding.[5]

Anticoagulation

Thromboembolic risk increases during pregnancy and up to 12 weeks postpartum. Anticoagulation with low-molecular-weight heparins or unfractionated heparin may be required antepartum and/or postpartum for some women, even when not anticoagulated before pregnancy.[5,7] Dosage is specific to the underlying condition.

Warfarin is associated with a dose-dependent embryopathy when used between 6 and 12 weeks' gestation and with fetal and maternal bleeding when used near delivery (Table 47–3).[5,7] Its use is still recommended during pregnancy (except during those periods), in addition to low-dose aspirin, for prosthetic heart valves, which are highly thrombogenic.[7] Warfarin and heparins are safe to use during breast-feeding.[16]

Patient Encounter Part 2

The first trimester urine culture screening reports more than 10^8 cfu/L of sensitive *Escherichia coli*. The patient was successfully treated with oral amoxicillin for 3 days, and urine culture a week later was negative. At 18 weeks, she presents with pollakiuria and dysuria without fever or systemic symptoms. She tested negative for chlamydia and gonorrhea in the first trimester. Urinalysis shows leucocytes and glycosuria, and urine culture is positive for *Proteus mirabilis* at more than 10^5 cfu/L susceptible to amoxicillin. She denies past repeated urinary tract infections, symptoms after sexual intercourse, or new sexual partner. Home blood glucose monitoring is at target in the fasting state and 1-hour post meals, but is elevated around 108 mg/dL (6.0 mmol/L) before lunch and dinner.

Meds: Insulin glargine 20 units subcutaneously at bedtime, insulin aspart 10 units subcutaneously before every meal, aspirin 81 mg orally at bedtime, and multivitamin containing folic acid 1 mg.

What treatment do you recommend at this time?

Bacterial Vaginosis

Bacterial vaginosis is associated with spontaneous abortion, PPROM, chorioamnionitis, preterm birth, postcesarean wound infection, postpartum endometritis, and pelvic inflammatory disease.[38,39] Oral or topical treatment with metronidazole or clindamycin is recommended for symptomatic pregnant and lactating women.[38,39] Oral metronidazole or clindamycin is recommended to prevent preterm delivery in women at high risk (Table 47–7).[39] Culture should be performed 1 month after completion of therapy since the cure rate is approximately 70%.[39]

Vulvovaginal Candidiasis

Only symptomatic vulvovaginal candidiasis should be treated in pregnant or lactating women (Table 47–7).[38]

Patient Encounter Part 3

At 37 weeks' gestation, the patient presents with rapidly progressing edema, unusual headache, blurry vision, and blood pressure persistently slightly over 140/90 mm Hg. Her reflexes are brisk. Dipstick urinalysis shows 2+ protein. Serum uric acid is mildly elevated, but remaining preeclampsia workup (complete blood count [CBC], liver enzymes, lactate dehydrogenase, and creatinine) is normal. Nonstress test is reassuring. Cervix is closed. The fetus had an estimated fetal weight at 40th percentile and was in cephalic position. Vaginal-rectal swab was negative for group B *Streptococcus* (GBS).

Meds: Insulin glargine 10 units subcutaneously at awakening, 25 units subcutaneously at bedtime, insulin aspart 15 units subcutaneously before every meal, aspirin 81 mg orally at bedtime, and multivitamin containing folic acid 1 mg.

What is your diagnosis and what will you recommend now?

Sexually Transmitted Infections

Table 47–8 presents the management of sexually transmitted infections during pregnancy and lactation, associated risks, and recommended follow-up.[38] Treatment of all recent sexual partners is mandatory.

Enhancement of Lactation

Insufficient milk production is diagnosed when breast-feeding cannot meet neonate's requirements. Several factors affect milk production including fatigue, stress, smoking, premature delivery, cesarean section, pain, and some medications (Table 47–6). Optimization of breast-feeding techniques is the first-line strategy. Prolactin is the main hormone linked to milk production. No drug is currently approved by the FDA or recommended by the American Academy of Breastfeeding for lactation enhancement, but dopamine antagonists, metoclopramide, and domperidone (not available in the United States), which increase prolactin levels, are used for this purpose.[40] Metoclopramide's maternal adverse effects include fatigue, irritability, headache, and extrapyramidal symptoms. Domperidone has been associated with abnormal heart rhythm and sudden cardiac death in susceptible individuals; caution is advised when prescribing it with other drugs that prolong the QT interval or that inhibit its metabolism or for women with underlying cardiac conditions.[41] Very few adverse effects in the infant have been reported.

Mastitis

Bacterial mastitis, seen typically within the first 6 weeks of breast-feeding, is characterized by localized signs of inflammation and engorgement. Fever, shivering, and malaise can occur. Most commonly encountered bacteria are *Staphylococcus aureus* (including methicillin-resistant), followed by *Streptococcus*, *Staphylococcus epidermidis*, and *E. coli*.[42]

Cold or warm compresses and more frequent breast-feeding/breast pumping should be encouraged. Antibiotics (Table 47–7) and analgesics (eg, acetaminophen, NSAIDs) can be used to relieve pain.[16,42] Confirm abscess suspicion with ultrasound before surgical drainage.

Breast Candidiasis

Candidiasis (most commonly *Candida albicans*) presents with severe and persistent nipple pain, usually more intense during and immediately after breast-feeding. Breast-fed infant can be symptomatic or asymptomatic. It is recommended to breast-feed more frequently for a short period of time. Clothes and towels in contact with breasts and infant's mouth should be washed in hot water. Antifungal treatment must be given to mother and neonate simultaneously (Table 47–7). Analgesics (eg, acetaminophen, NSAIDs) can be used.[42]

Patient Encounter Part 4

After 10 hours of labor, the patient delivers vaginally a 6.6 lb (3.0 kg) baby. She plans to breast-feed.

What treatment plan do you recommend after delivery?

What surveillance do you suggest for the newborn/baby?

Can she breast-feed while taking her medications?

Table 47–8

Management of Sexually Transmitted Infections During Pregnancy and Lactation[38,39]

	Indications for Treatment	Associated Risks During Pregnancy	When to Repeat Testing During Pregnancy	Other
Chlamydia trachomatis	All women with a positive test, even if asymptomatic	Preterm labor; neonatal infection	Third trimester: < 25 years of age, those at increased risk of infection	Repeat testing 3–4 weeks and 3 months after therapy
Treatment	First choice: Azithromycin 1 g po once Alternative choices: Amoxicillin 500 mg po three times daily for 7 days Erythromycin base 500 mg po four times daily for 7 days or 250 mg po four times daily for 14 days Doxycycline 100 mg po twice daily for 7 days only during lactation (contraindicated during pregnancy)			
Gonorrhea	All women with a positive test, even if asymptomatic	Preterm labor, neonatal infection	Third trimester: if first screening positive or if at risk of reinfection	Repeat testing 2 weeks and 3 months after treatment
Treatment (uncomplicated infection of pharynx, cervix, urethra, rectum)	First choice: ceftriaxone 250 mg IM once + azithromycin 1 g po once Second choice during breast-feeding: ceftriaxone 250 mg intramuscularly once + doxycycline 100 mg po twice daily for 7 days (doxycycline contraindicated pregnancy)			
Genital Herpes Simplex	Active lesions, disseminated; Starting at 36 weeks: prevention of recurrence at term	Neonatal infection, especially if acquired near time of delivery (30%–50%)	No routine testing recommended	Cesarean section if active genital lesions at delivery; evaluate newborn for herpes infection
Treatment	**First episode:** Acyclovir: 400 mg po three times daily for 7–10 days, or 200 mg five times daily for 7–10 days Valacyclovir: 1000 mg po twice daily for 7–10 days **Recurrent episodes:** Acyclovir: 400 mg po three times daily for 5 days, or 800 mg twice daily for 5 days, or 800 mg three times daily for 2 days Valacyclovir: 500 mg po twice daily for 3 days **Suppressive therapy:** start at 36 weeks of gestation (or earlier if at risk of preterm delivery) until delivery Acyclovir: 400 mg po three times daily Valacyclovir: 500 mg po twice daily			
Syphilis	All women with confirmed positive serology	In utero fetal and neonatal infection; congenital malformations	At 28–32 weeks and at delivery if at risk of reinfection, if untested before, if positive serology in the first trimester, or if was previous stillborn at more than 20 weeks	Therapy is efficacious to treat the fetus and to prevent transmission; be aware of Jarisch-Herxheimer reaction; fetal evaluation should include ultrasounds
Treatment	Desensitize penicillin-allergic patients Primary, secondary, or early latent: Benzathine penicillin G 2.4 million units IM once Late latent or of unknown duration or tertiary: Benzathine penicillin G 2.4 million units IM three times at 1-week interval			
Trichomoniasis	Symptomatic women	PPROM, preterm birth, low birth weight; neonatal infection		Therapy does not decrease perinatal mortality
Treatment	Metronidazole 2 g po for one dose			

IM, intramuscular; IV, intravenous; po, orally; PPROM, preterm premature rupture of membranes.

Patient Care Process

Collect Information:

- Complete medical and obstetrical history.
- Inquire about disorders evolution and last follow-up with the treating physician.
- Conduct medication history (past/current treatments, compliance, efficacy, and safety).
- Verify immunization status.
- Assess for pregnancy signs and symptoms.
- Perform physical examination.
- Evaluate nutritional status and socioeconomic environment.
- Perform first trimester routine lab testing.
- Order serum drug levels.

(*Continued*)

Patient Care Process (*Continued*)

Assess the Information:

- Evaluate benefits and risks for mother and fetus of continuing medications.
- Assess efficacy, safety, and patient adherence, and screen for drug interactions.
- Evaluate whether safer and more effective alternative are available.

Develop a Care Plan:

- Choose treatments with evidence of benefit and safety data during pregnancy or that cannot be delayed until after delivery and or after breast-feeding is finished (Table 47–7).
- Address patient concerns (risks of medication or of relapse if condition is untreated, prescription coverage and access to care).
- Treat pregnancy symptoms (eg, nausea) if needed.
- When possible, use nonpharmacologic treatments.

Implement the Care Plan:

- Recommend appropriate folic acid and multivitamins.
- Counsel of lifestyle (healthy diet, exercise, avoidance of tobacco, alcohol, and illicit or unnecessary drugs).
- Encourage breast-feeding. If breast-feeding, choose drugs with the best safety profile.
- Communicate information to all other health care professionals to ensure continuing of care.

Follow-up: Monitor and Evaluate:

- Assess compliance, effectiveness, and safety of treatment at each prenatal visit.
- Review and repeat assessments as necessary.
- Monitor infants for birth defects, developmental delays, or unusual reactions, and report suspected drug-related reactions to the FDA or pharmaceutical companies.

Abbreviations Introduced in This Chapter

AAP	American Academy of Pediatrics
ACEi	Angiotensin-converting enzyme inhibitors
ACOG	American College of Obstetricians and Gynecologists
anti-TPOAbs	Antithyroid peroxidase antibodies
β-hCG	Beta-human chorionic gonadotropin
CNS	Central nervous system
DM	Diabetes mellitus
GA	Gestational age
GBS	Group B *streptococcus*
GDM	Gestational diabetes mellitus
LMP	Last menstrual period
LT_4	Levothyroxine
NSAID	Nonsteroidal anti-inflammatory drug
NTD	Neural tube defect
OTIS	Organization of Teratology Information Specialists
PCA	Postconceptional age
PPROM	Preterm Premature Rupture of Membranes
PTU	Propylthiouracil
SMBG	Self-monitoring of blood glucose
STEPS	System for Thalidomide Education and Prescribing Safety
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
T_4	Thyroxine
TSH	Thyroxine-stimulating hormone
TSHR-Sabs	Thyroid-stimulating hormone receptors-stimulating antibodies
VDRL	Venereal Disease Research Laboratory

REFERENCES

1. Miscarriage. March of Dimes. Available from: http://www.marchofdimes.com/loss/miscarriage.aspx. Accessed September 30, 2017.
2. Final Natality Data. March of Dimes. National Center for Health Statistics. Available from: www.marchofdimes.com/peristats. Accessed September 30, 2017.
3. Moore KL, Persaud TVN, Torchia MG. The Developing Human—Clinically Oriented Embryology. 9th ed. Philadelphia, PA: Elsevier Saunders; 2013:540.
4. Ferreira E, Martin E, Morin C, editors. Grossesse et allaitement: guide thérapeutique. 2nd ed. Montreal: Éditions du CHU Ste-Justine; 2013:1183.
5. Briggs GG, Freeman RK, editors. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 11th ed. Philadelphia, PA: Wolters Kluwer Health; 2017:1579.
6. Obican S, Scialli AR. Teratogenic exposures. Am J Med Genet C Semin Med Genet. 2011;157:150–169.
7. James A. Practice Bulletin No. 123. Thromboembolism in pregnancy. Obstet Gynecol. 2011 Sep;118:718–729.
8. Friedman JM. How do we know if an exposure is actually teratogenic in humans? Am J Med Genet C Semin Med Genet. 2011;157:170–174.
9. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling. Food and Drug Administration. Available from: https://www.federalregister.gov/d/2014-28241. Accessed September 29, 2017.
10. Conover EA, Polifka JE. The art and science of teratogen risk communication. Am J Med Genet C Semin Med Genet. 2011;157:227–233.
11. Meeting to Develop a Global Consensus on Preconception Care to Reduce Maternal and Childhood Mortality and Morbidity 2013. World Health Organization. Available from: www.who.int. Accessed July 19, 2017.
12. US Preventive Services Task Force. Folic acid for the prevention of neural tube defects: U.S. preventive services task force recommendation statement. JAMA. 2017;317:183–189.
13. Goh YI, Koren G. Folic acid in pregnancy and fetal outcomes. J Obstet Gynaecol. 2008;28:3–13.
14. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol. 2014;5:1–5.
15. Eidelman AI, Schanler RJ. Breastfeeding and the use of human milk. Pediatrics. 2012;129:e827–e841.
16. Hale TW, Rowe HE. Medications and Mother's Milk, 17th ed. New York: Springer Publishing Company, LLC; 2017:1095.
17. ACOG Practice Bulletin No. 95. Anemia in pregnancy. Obstet Gynecol. 2008;112:201–207.

18. ACOG Practice Bulletin. Nausea and vomiting of pregnancy. Obstet Gynecol. 2015;126:e12–e24.
19. Worthington I, Pringsheim T, Gawel MJ, et al. Pharmacological acute migraine treatment strategies: choosing the right drug for a specific patient. Can J Neurol Sci. 2013;40(5 suppl 3): S1–S80.
20. Glaser AP and Schaeffer AJ. Urinary tract infection and bacteriuria in pregnancy. Urol Clin North Am. 2015 Nov;42(4):547–560.
21. ACOG Committee Opinion No. 713. Antenatal corticosteroid therapy for fetal maturation. Obstet Gynecol. 2017;130(2): e102–e109.
22. ACOG Practice Bulletin. Management of preterm labor. Number 171. Obstet Gynecol. 2016;128(4):e155–e164.
23. Haas DM, Benjamin T, Sawyer R, Quinney SK. Short-term tocolytics for preterm delivery—current perspectives. Int J Womens Health. 2014;6:343–349.
24. ACOG Committee Opinion No. 652. Magnesium Sulfate Use in Obstetrics. Obstet Gynecol. 2016;127(1):e52–e53.
25. ACOG Practice Bulletin No. 172. Premature rupture of membranes. Obstet Gynecol. 2016;128(4):e165–e175.
26. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease—revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59:1–36.
27. ACOG Practice Bulletin No. 130. Prediction and prevention of preterm birth. Obstet Gynecol. 2012;120(4):964–973.
28. ACOG Practice Bulletin No. 107. Induction of labor. Obstet Gynecol. 2009;114(2 Pt 1):386–397.
29. Leduc D, Biringer A, Lee L, Dy J. Induction of labour. J Obstet Gynaecol Can. 2013;35(9):840–857.
30. ACOG Practice Bulletin No. 183. Postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168–e186.
31. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with postpartum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105–2016.
32. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27(3):315–389.
33. ACOG Executive Summary. Hypertension in pregnancy. Obstet Gynecol. 2013;122:1122–1131.
34. WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia, 2011. World Health Organization. Available from: www.who.int. Accessed July 16, 2017.
35. ACOG Committee Opinion No. 692. Emergent therapy for acute-onset, severe hypertension during pregnancy and the postpartum period. Obstet Gynecol. 2017:129:e90–95.
36. Magee LA, von Dadelszen P, Rey E, et al. Less-tight versus tight control of hypertension in pregnancy. N Engl J Med. 2015; 372:407–417.
37. American Diabetes Association. Management of diabetes in pregnancy. Section 13 in Standards of Medical Care in Diabetes 2017. Diabetes Care 2017;40(suppl 1):S114–S119.
38. Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015;64 (No RR-#3):1–135.
39. Yudin MH, Money D. No 211-Screening and management of bacterial vaginosis in pregnancy. J Obstet Gynaecol Can. 2017;39(8):e184–e191.
40. Bunik M, Chantry CJ, Howard CR, et al. ABM Clinical Protocol #9: use of galactogogues in initiating or augmenting the rate of maternal milk secretion (First Revision January 2011). Breastfeed Med. 2011;6:41–49.
41. Bozzo P, Koren G. Health Canada advisory on domperidone: should I avoid prescribing domperidone to women to increase milk production? Can Fam Physician. 2012;58:952–953.
42. Amir LH. Managing common breastfeeding problems in the community. BMJ. 2014;348:g2954.

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48 Contraception

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LEARNING OBJECTIVES

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

LO

1. Discuss the physiology of the female reproductive system.
2. Compare the efficacy of oral contraceptives with that of other methods of contraception.
3. State the mechanism of action of hormonal contraceptives.
4. Discuss adverse effects, risks, and contraindications associated with the use of contraceptives, and recommend strategies for minimizing or eliminating such risks.
5. Describe advantages and disadvantages of various contraceptives, including oral and nonoral formulations.
6. Cite important drug interactions that may occur with oral contraceptives.
7. Provide appropriate patient education regarding the use of oral and barrier methods of contraception.
8. Discuss how emergency contraception may be employed to prevent unintended pregnancy.

INTRODUCTION

Historically, the 1950s was an important time in the control of human fertility. It was during that decade that the first combination hormonal contraceptives (CHCs) were developed. Shortly after the discovery that the exogenous administration of hormones such as progesterone successfully blocked ovulation, the use of hormonal steroids quickly became the most popular method of contraception worldwide. CHCs are the most commonly used reversible form of contraception in the United States today, with an estimated 9.7 million women users.[1] Studies of women of childbearing age (15–44 years) in the United States estimate that 62% are currently using a contraceptive method.[1] Since the introduction of oral contraceptives, many additional contraceptive forms have been developed and are available for use in the United States, including transdermal systems, transvaginal systems, and intrauterine devices (IUDs). These additional forms of contraception offer women effective and potentially more convenient alternatives to oral contraceptives.

EPIDEMIOLOGY

According to the National Survey of Family Growth, approximately 6.37 million pregnancies occur annually in the United States.[2] It is estimated that nearly half of all pregnancies that occur each year in the United States are unintended.[2,3] A survey of women who had unintended births in the United States between 1998 and 2002 revealed that approximately 60% were not using any form of contraception.[1] In addition, many women who do use contraceptives use their chosen method of contraception imperfectly, and this also increases the risk of unintended pregnancy. For patients with certain medical conditions, such as epilepsy, hypertension, ischemic heart disease, sickle cell disease, lupus, or thromboembolic mutations, unintended pregnancy can further increase the risk for adverse health events.[4,5] The provision of appropriate and adequate instruction to patients regarding how to use contraceptive methods effectively is essential in order to reduce the risk of unintended pregnancy and, for some women, the associated increase in risk for adverse health-related events.

Exposure to sexually transmitted infections (STIs) is also a concern for women who are sexually active. It is estimated that 20 million people in the United States become newly infected annually with an STI.[6] Given that not all methods of contraception protect the user against STIs, the provision of proper patient education by health care professionals regarding this risk is absolutely essential.

PHYSIOLOGY

LO 1

The female menstrual cycle is divided into four functional phases: follicular, ovulatory, luteal, and menstrual.[4] The follicular phase begins the cycle, and ovulation generally occurs around day 14. The luteal phase then begins and continues until menstruation occurs.[4] The menstrual cycle is regulated by a negative-feedback hormone loop between the hypothalamus, anterior pituitary gland, and ovaries[4] (Figure 48–1).

Initially, the hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The levels of FSH and LH released vary depending on the phase of the menstrual cycle. Just prior to ovulation, FSH and LH both are at their peak levels. The FSH helps to promote growth of the follicle in preparation for ovulation by causing granulosa cells lining the follicle to grow and produce estrogen. LH promotes androgen production by theca cells in the follicle, promotes ovulation and oocyte maturation, and converts granulosa cells to cells that secrete progesterone after ovulation.

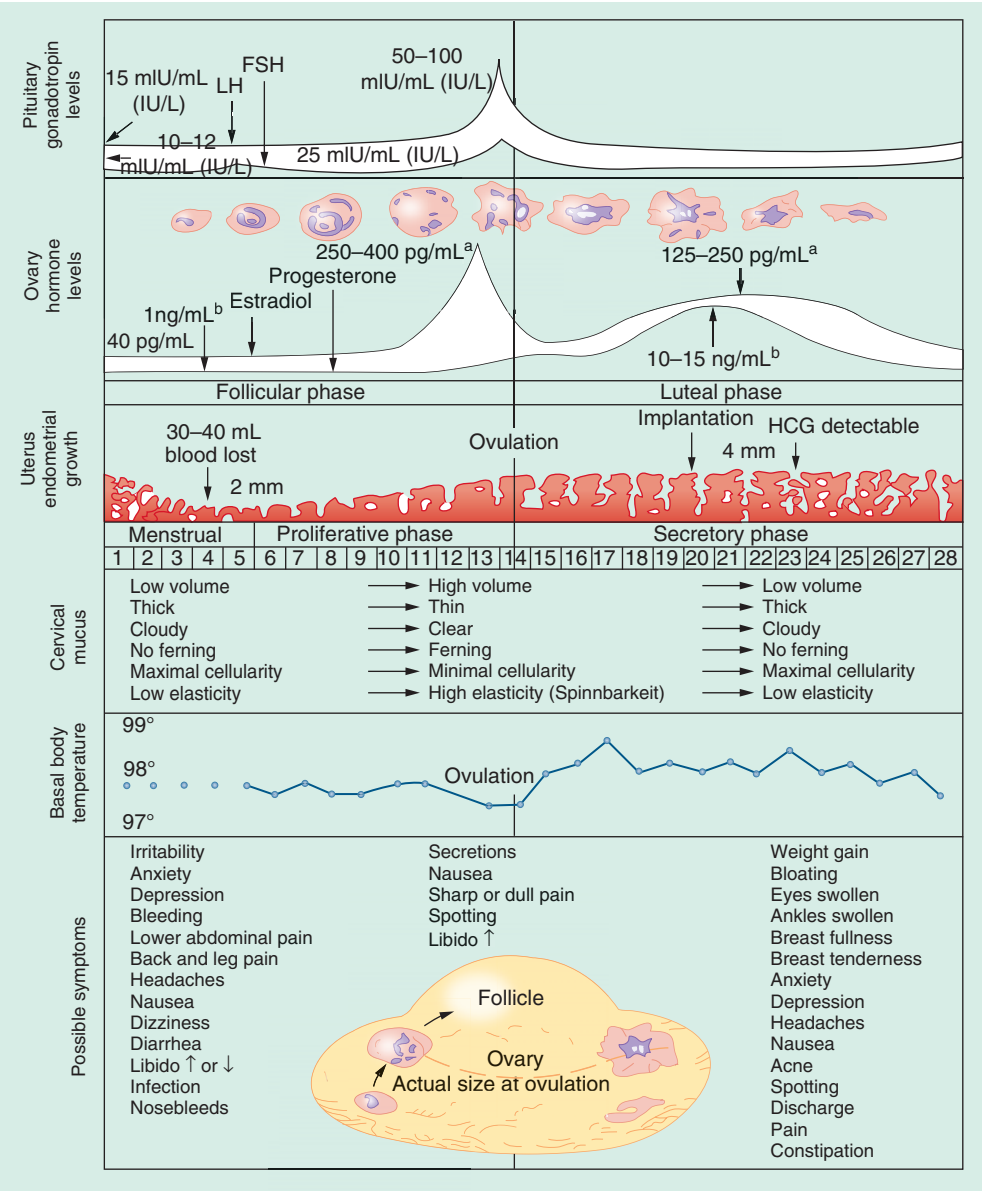

FIGURE 48–1. Menstrual cycle events. [a]Estradiol: 40 pg/mL = 147 pmol/L; 250 to 400 pg/mL = 918 to 1468 pmol/L; 125 to 250 pg/mL = 459 to 918 pmol/L. [b]Progesterone: 1 ng/mL = 3.18 nmol/L; 10 to 15 ng/mL = 32 to 48 nmol/L. (FSH, follice-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, leutinizing hormone.) (Adapted with permission from Shulman LP. The menstrual cycle. In: Hatcher RA, Trussel J, Nelson AL, Cates W Jr, Kowal D, Policar M. Contraceptive Technology, 20th rev. ed. New York: Ardent Media, 2011:29–44.)

Conception is most likely to occur when viable sperm are present in the upper region of the reproductive tract at the time of ovulation. Fertilization occurs when a spermatozoan penetrates an ovum. Approximately 6 to 8 days after ovulation, attachment of the early embryo to the lining of the uterine cavity—implantation—occurs.

PREVENTION OF PREGNANCY: CONTRACEPTIVES AND DEVICES

Goals of Contraception/Desired Outcome

The most common goal of contraception is the prevention of pregnancy. However, some patients use contraceptive methods for other benefits, such as menstrual cycle regulation, reduction of premenstrual symptoms, or treatment of acne.

Choice of Contraceptives: Important Considerations

When helping a patient with contraceptive selection, the most important goal is finding an option the patient is comfortable with and the clinician feels is beneficial for the patient. It is imperative to explain the side effects, safety concerns, and noncontraceptive benefits of each alternative to the patient so that she may make an informed decision. Fertility goals vary for each patient. It must be determined whether the goal is to postpone conception, space out the next pregnancy, or avoid further pregnancy altogether. Also, a clinician must understand the patient's desire to have or not have a regular bleeding pattern, because many contraceptives will affect menses.

As discussed later in this chapter, contraindications exist for various forms of contraception. Patients may be evaluated by a

health care professional to rule out medical contraindications to certain contraceptives, although a physical examination is not required and pharmacists can prescribe contraceptives in some states. Clinicians also should review family history for potential risks with certain forms of birth control.

Sexual behavior of the female must be determined to understand the risk for STIs. Women not in a monogamous relationship must consider their risk of STIs as a factor in their contraceptive decision. Some barrier methods protect against STIs, but hormonal contraceptives do not prevent STIs if used alone.

Personal preference plays a large role when determining the best contraceptive option. For instance, if a woman is not interested in using a method that interrupts sexual activity, then a diaphragm would be an inappropriate choice. Preference of the sexual partner may also be important. Certain agents such as male condoms require the male partner to play an active role in contraception. Patients must also consider their religious beliefs and cultural practices as some forms of birth control may violate certain religious rules or cultural beliefs.

Cost may also be an issue for patients. Insurance may not cover all forms of contraception, and patients may have to bear the entire cost for certain options.

Efficacy of Contraceptives

LO 2

The unintended pregnancy rate for women who do not use any form of contraception is unknown. Therefore, it is difficult to determine the true efficacy of contraceptives in preventing unwanted pregnancy. Table 48–1 shows the percentage of women who experience unintended pregnancy within 1 year of contraceptive use with ongoing sexual activity.[4]

Oral Contraceptives (Combination)

CHCs contain a synthetic estrogen and one of several steroids with progestational activity. Most oral contraceptives contain one of three types of estrogen: ethinyl estradiol (EE), which is pharmacologically active; mestranol, which is converted by the liver to EE; or estradiol valerate, which is metabolized to estradiol and valeric acid. Many different progestins are found in the various oral contraceptives. These include norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone, and dienogest.

LO 3

The primary mechanism by which CHCs prevent pregnancy is through inhibition of ovulation. FSH and LH regulate the production of estrogen and progesterone by the ovaries. Secretion of estrogen and progesterone by the ovaries occurs in a cyclic manner, which determines the regular hormonal changes that occur in the uterus, vagina, and cervix associated with the menstrual cycle. Cyclic changes in the levels of estrogen and progesterone in the blood, together with FSH and LH, modulate the development of ova and the occurrence of ovulation. The estrogen component of CHCs is most active in inhibiting FSH release.[4] However, at sufficiently high doses, estrogens also may cause inhibition of LH release. In low-dose CHCs (≤ 35 mcg EE), the progestin component causes suppression of LH.[4] Ovulation is prevented by this suppression of the midcycle surge of both FSH and LH and mimics the physiologic changes that occur during pregnancy.

LO 3

Although suppression of FSH and LH is the primary mechanism by which CHCs prevent ovulation, there are other mechanisms by which these hormones work to prevent pregnancy. Other mechanisms include reduced penetration of the egg by sperm, reduced implantation of fertilized eggs, thickening of cervical

Table 48–1

Unintended Pregnancy Rates

Method	Percentage of Women Experiencing Unintended Pregnancy Within First Year of Use: Typical Use[a]	Percentage of Women Experiencing Unintended Pregnancy Within First Year of Use: Perfect Use[b]	Percentage of Women Continuing Use at 1 Year[c]
No method	85	85	
Spermicides	28	18	42
Withdrawal	22	4	46
Fertility awareness–based methods	24		47
Standard days method		5	
Two-day method		4	
Ovulation method		3	
Symptothermal method		0.4	
Sponge			
Parous women	24	20	
Nulliparous women	12	9	
Diaphragm	12	6	57
Cervical cap	16–32	9–26	
Condom			
Female	21	5	41
Male	18	2	43
Combination pill and progestin-only pill	9	0.3	67
Transdermal patch	9	0.3	67
NuvaRing	9	0.3	67
Depo-Provera	6	0.2	56
IUD			
ParaGard (copper T)	0.8	0.6	78
Mirena (LNG-IUS)	0.2	0.2	80
Liletta	0.15		
Skyla	0.4		
Implanon	0.05	0.05	84
Nexplanon	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.1	100

[a]Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason. Estimates of the probability of pregnancy during the first year of typical use for spermicides, withdrawal, periodic abstinence, the diaphragm, the male condom, the pill, and Depo-Provera are taken from the 1995 National Survey of Family Growth corrected for underreporting of abortion.

[b]Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

[c]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

IUD, intrauterine device.

Adapted from Trussel J, Guthrie KA. Choosing a contraceptive: Efficacy, safety, and personal considerations. In: Hatcher RA, Trussel J, Nelson AL, Cates W Jr, Kowal D, Policar M. Contraceptive Technology, 20th rev. ed. New York: Ardent Media, 2011:45–74, with permission.

Additional Refs: Anonymous. Choice of contraceptives: Med Lett Drugs Ther. 2015; 57:127–134. Eisenberg DL, Schreiber CA, Turok DK, Teal SB, Westhoff CL, Creinin MD. Three-year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system. Contraception. 2015;92(1):10–16.

mucus to prevent sperm penetration into the upper genital tract, and slowed tubal motility, which may delay transport of sperm.[4] Thus, in addition to inhibiting ovulation, CHCs induce changes in the cervical mucus and endometrium that make sperm transport and implantation of the embryo unlikely.[4]

Table 48–2 contains a partial listing of the many oral contraceptives available in the United States.[7] Since the mid-1960s, EE has been the primary estrogen used in most CHCs. However, the amount of EE used in CHCs has decreased progressively since that time, and most now contain 35 mcg or less

Table 48–2

Some Available Oral Contraceptives

Estrogen (mcg/tablet)	Progestin (mg/tablet)	Examples of Brand Names
Monophasic Preparations		
EE (20)	Norethindrone acetate (1)	Junel 1/20, Junel Fe 1/20, Junel Fe 24, Larin 1/20, Larin Fe 1/20, Larin 24 Fe, Loestrin 21 1/20, Loestrin Fe 1/20, Lomenia 24 Fe, Mibelas 24 Fe, Microgestin 1/20, Microgestin Fe 1/20, Minastrin 24 Fe, Tarina Fe 1/20, Taytalla
EE (20)	Levonorgestrel (0.09)	Amethyst
EE (20)	Levonorgestrel (0.1)	Aviane, Falmina, Lessina, Lutera, Orsythia, Sronyx, Vienva
EE (20)	Drospirenone (3)	Beyaz,[a] Gianvi, Loryna, Nikki, Vestura, Yaz
EE (20)	Desogestrel (0.15)	Azurette
EE (25)	Norethindrone (0.8)	Generess Fe, Kaitlib Fe
EE (30)	Desogestrel (0.15)	Apri, Desogen, Emoquette, Enskyce, Reclipsen
EE (30)	Levonorgestrel (0.15)	Altavera, Kurvelo, Levora, Marlissa, Portia
EE (30)	Drospirenone (3)	Ocella, Safyral[a], Syeda, Yasmin, Zarah
EE (30)	Norgestrel (0.3)	Cryselle, Elinest, Lo/Ovral-28, Low-Ogestrel
EE (30)	Norethindrone acetate (1.5)	Blisovi 1.5/30, Junel 1.5/30, Junel Fe 1.5/30, Larin 1.5/30, Larin Fe 1.5/30, Loestrin 21 1.5/30, Loestrin Fe 1.5/30, Microgestin 1.5/30, Microgestin Fe 1.5/30
EE (35)	Norgestimate (0.25)	Estarylla, Mono-Linyah, MonoNessa, Ortho-Cyclen, Previfem, Sprintec
EE (35)	Norethindrone (0.4)	Balziva, Briellyn, Femcon Fe, Gildagia, Ovcon-35, Philith, Vyfemla, Wymza Fe, Zenchent, Zenchent Fe, Zeosa
EE (35)	Norethindrone (0.5)	Brevicon, Modicon, Necon 0.5/35, Nortrel 0.5/35, Wera
EE (35)	Norethindrone (1)	Alyacen 1/35, Cyclafem 1/35, Dasetta 1/35, Necon 1/35, Norinyl 1/35, Nortrel 1/35, Ortho-Novum 1/35, Pirmella 1/35
EE (35)	Ethynodiol diacetate (1)	Kelnor 1/35, Zovia 1/35
EE (50)	Norgestrel (0.5)	Ogestrel
EE (50)	Ethynodiol diacetate (1)	Zovia 1/50E
Mestranol (50)	Norethindrone (1)	Necon 1/50, Norinyl 1/50
Biphasic Preparations		
EE (10)	Norethindrone acetate (1,0)	Lo Loestrin Fe[b]
EE (20,0,10)	Desogestrel (0.15,0,0)	Bekyree[b], Kariva[b], Kimidess[b], Pimtrea[b], Viorele[b]
EE (35)	Norethindrone (0.5,1)	Necon 10/11
Triphasic Preparations		
EE (20,30,35)	Northindrone acetate (1)	Estrostep Fe, Tilia Fe, Tri-Legest Fe
EE (30,40,30)	Levonorgestrel (0.05,0.075,0.125)	Enpresse, Levonest, Myzilra, Trivora
EE (35)	Norgestimate (0.18,0.215,0.25)	Ortho Tri-Cyclen, Tri-Estarylla, Tri-Linyah, Tri-Nessa, Tri-Previfem, Tri-Sprintec
EE (35)	Norethindrone (0.5,1,0.5)	Aranelle, Leena, Tri-Norinyl
EE (35)	Norethindrone (0.5,0.75,1)	Alyacen 7/7/7, Cyclafem 7/7/7, Dasetta 7/7/7, Necon 7/7/7, Nortrel 7/7/7, Ortho-Novum 7/7/7, Pirmella 7/7/7
EE (25)	Norgestimate (0.18,0.215,0.25)	Ortho Tri-Cyclen Lo, Tri-Lo-Estarylla, Tri-Lo-Marzia, Tri-Lo-Sprintec
EE (25)	Desogestrel (0.1,0.125,0.15)	Caziant, Cyclessa, Velivet
Quadriphasic Preparations		
Estradiol valerate (3,2,2,1)	Dienogest (0,2,3,0)	Natazia
Extended Cycle Preparations		
EE (20)	Levonorgestrel (0.1)	Amethia Lo, Camrese Lo
EE (30)	Levonorgestrel (0.15)	Amethia, Ashylyna, Camrese, Daysee, Introvale, Jolessa, Quasense, Seasonale, Setlakin
EE (20,25,30,10)	Levonorgestrel (0.15,0)	Fayosim, Rivelsa, Quartette
EE (20,10)	Levonorgestrel (0.1)	LoSeasonique
EE (30,10)	Levonorgestrel (0.15)	Seasonique
Progestin-Only Preparations		
None	Norethindrone (0.35)	Camila, Errin, Heather, Jencycla, Jolivette, Nora-BE, Nor-QD, Ortho Micronor

[a]Each tablet also contains 451 mcg of levomefolate calcium.

[b]Some references may classify as monophasic since the variation in hormone content does not occur during the first 3 weeks of the pill pack.

EE, ethinyl estradiol

Data compiled in part from Anonymous. Choice of contraceptives: Med Lett Drugs Ther. 2015;57:127–134.

of EE. In addition, to reduce side effects and improve tolerability associated with oral contraceptive use, newer progestins and different routes of administration have been explored. In an attempt to minimize the undesirable androgenic side effects associated with the progestins of CHCs, the original synthetic progestins were modified to create "third generation" progestins (eg, desogestrel and norgestimate), and "fourth generation" progestins with antiandrogenic properties (eg, drospirenone). Overall, the synthetic progestins found in today's CHCs are extremely potent in their ability to inhibit ovulation and prevent pregnancy.

CHCs are available in monophasic, biphasic, triphasic, and quadriphasic preparations. Monophasic preparations contain fixed doses of estrogen and progestin in each active pill. Although all four preparations contain both estrogens and progestins, biphasic, triphasic, and quadriphasic preparations contain varying proportions of one or both hormones during the pill cycle. These preparations were introduced to reduce a patient's cumulative exposure to progestins, as well as to mimic more closely the hormonal changes of the menstrual cycle. However, there is no evidence to suggest that the multiphasic preparations offer any significant clinical advantage over monophasic pills.[7]

Most traditional CHCs are packaged as 21/7 cycles (ie, 21 days of active pills and 7 days of placebo). However, newer regimens offer either fewer hormone-free days per traditional, 28-day pill cycle or extended (or in some cases continuous) cycles (84- or 365-day pill cycle), which may allow for fewer withdrawal bleeds per year and fewer menstrual-related side effects (eg, menstrual pain, bloating, headaches) for some women.

▶ *Noncontraceptive Benefits of Combination Hormonal Contraceptives*

In addition to preventing pregnancy, there are several noncontraceptive benefits associated with the use of CHCs.

Reduction in the Risk of Endometrial Cancer The risk of endometrial cancer among women who have used oral contraceptives for at least 1 and 10 years is approximately 40% and 80% less than the risk in women who have never used oral contraceptives, respectively.[4,8] There is additional evidence to suggest that this reduced risk may persist for up to 20 years following discontinuation of oral contraceptives.[4,8]

Reduction in the Risk of Ovarian Cancer When compared with women who have never used oral contraceptives, women who have used oral contraceptives for at least 1 year are less likely to develop ovarian cancer than those who have never used oral contraceptives. While there is evidence to suggest the reduced risk of ovarian cancer may persist for years following discontinuation of oral contraceptives,[9-11] a recent study suggested possible attenuation of the protective effect of CHCs against ovarian cancer with use after 35 years of age.[12] Thus, further study may be needed to determine the influence of age of user on potential protection against this type of cancer.

Improved Regulation of Menstruation and Reduction in the Risk of Anemia Women who take oral contraceptives typically experience more regular menstrual cycles. In general, oral contraceptive use is associated with less cramping and dysmenorrhea.[4,7] Also, women who take oral contraceptives have a smaller volume of menstruum and experience fewer days of menstruation each month and consequently experience less blood loss with each menstrual period.[4,13] Some studies suggest that oral contraceptive use decreases overall monthly menstrual flow by 60% or more and conserves hemoglobin and ferritin levels, which may be particularly beneficial in women who are anemic or at risk for anemia.[4] In addition, some CHC formulations contain iron, which may also minimize the risk for anemia. (See **Unique Oral Contraceptives** section.)

Reduction in the Risk of Fetal Neural Tube Defects While CHCs are not 100% effective at preventing pregnancy, it is possible that a woman may conceive while taking a CHC. In addition, many women may become pregnant very soon after discontinuing a CHC. In order to decrease the risk of neural tube defects in the fetuses associated with such pregnancies, CHC formulations that contain a source of folate in every pill are also available.[4]

Relief from Symptoms Associated with Premenstrual Dysphoric Disorder CHCs have been widely used for the treatment of premenstrual dysphoric disorder (PMDD). Current evidence suggests that these agents are most effective at targeting the physical symptoms associated with the disorder and less effective in treating mood-related symptoms.[14] Although multiphasic CHCs have been used effectively in the treatment of PMDD, monophasic preparations may yield fewer mood swings and are generally easier to manage. Several drospirenone-containing CHCs now carry a US Food and Drug Administration (FDA)-approved indication for PMDD, including Yaz, Gianvi, Loryna, Nikki, and Vestura.[7]

Relief of Benign Breast Disease Women who use oral contraceptives are less likely to develop benign breast cysts or fibroadenomas and are less likely to experience progression of such conditions.[4,7]

Prevention of Ovarian Cysts Because oral contraceptives suppress ovarian stimulation, women who take them are less likely to develop ovarian cysts.[7]

Decrease in Symptoms Related to Endometriosis CHC use has been linked to a decreased incidence of symptomatic endometriosis. In women who suffer from endometriosis, the extended-cycle CHCs may provide the most effective relief from menstrual pain by reducing the total number of painful episodes per year.[4]

Improvement in Acne Control All CHCs can improve acne by increasing the quantity of sex hormone–binding globulin and thereby decreasing free testosterone concentrations.[7] Third-generation progestins, such as desogestrel and norgestimate, are believed to have less androgenic activity compared with older progestins, and drospirenone is considered to be antiandrogenic.[7] However, it is not clear that CHCs containing any of these progestins confer any advantage over other CHCs with respect to their ability to improve acne control. Ortho Tri-Cyclen, TriNessa, and Tri-Sprintec (EE and norgestimate); Estrostep Fe, Tilia Fe, and Tri-Legest Fe (EE and norethindrone acetate); Yaz, Beyaz, and Safyral (EE and drospirenone) each carry an FDA-approved indication for the treatment of acne.[4,7]

▶ *Potential Risks of Combination Hormonal Contraceptives*

LO 4

Although there are many noncontraceptive benefits associated with the use of CHCs, their use is not without risk or potential for adverse effects.

Sexually Transmitted Infections Because the use of CHCs may decrease the use of selected barrier contraceptive methods (eg, latex condoms) that do protect against STIs, one of the most common potential risks associated with the use of oral contraceptives is the increased risk of acquiring an STI.[5] However,

concerning risks for HIV acquisition studies have failed to show an increased risk and therefore the CDC considers HIV a condition for which there is no restriction for the use of the contraceptive method.

Cardiovascular Events and Hypertension A World Health Organization (WHO) collaborative study found that high-dose (50 mcg or more of EE) oral contraceptive users with uncontrolled hypertension have an increased risk of experiencing a myocardial infarction or stroke.[7,15] In this study, women who had the lowest risk for experiencing a myocardial infarction or stroke were those who did not smoke, took low-dose oral contraceptives, and had their blood pressure checked prior to beginning oral contraceptives.[16-18] Hypertension secondary to oral contraceptive use is thought to occur in up to 3% of women and is believed to be attributed to the effect of estrogens and progestins on aldosterone activity.[4] Given this and the risk for cardiovascular events, women should have their blood pressure checked prior to initiating oral contraceptives, as well as periodically throughout oral contraceptive use. If blood pressure is ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic, the risks outweigh advantages and there should be consideration to discontinue CHCs; if blood pressure is ≥ 160 mm Hg systolic or ≥ 100 mm Hg, then CHC use is not recommended.[5] Estrogen-containing contraceptives are not recommended for smokers who are 35 years of age or older or for women who experience migraine headaches with aura.[5,7]

Venous Thromboembolism It is believed that the estrogen component of CHCs stimulates enhanced hepatic production of clotting factors. CHCs have been associated with a two- to threefold increase in the risk of venous thromboembolism compared with women who do not use oral contraceptives.[7] Contraceptive users at greatest risk for the development of VTE include those who are obese, smoke, have hypertension, have diabetes complicated by end-organ damage, are immobile, have experienced recent trauma or surgery, or have a history of prior thromboembolism. It is important to note, however, that the increase in risk of VTE in oral contraceptive users is lower than that associated with pregnancy and the postpartum period.[7,19] Newer, less androgenic progestins, such as desogestrel and fourth generation drospirenone, have been reported to be associated with a higher risk of VTE.[20-23] Currently available studies validating this risk have produced conflicting results. Two studies published in 2011 reported a two- to threefold greater risk of venous thromboembolic events in women using oral contraceptives containing drospirenone when compared with women using levonorgestrel-containing contraceptives.[24,25] A more recent case-control study of > 10,000 women with VTE also found that exposure to drospirenone and desogestrel was associated with a higher risk of VTE compared to exposure to levonorgestrel.[26] Conversely, the results of the International Active Surveillance Study of Women Taking Oral Contraceptives, published in 2014, demonstrated similar rates of venous and arterial thromboembolism in women taking CHCs containing drosperinone, levonorgesterol, or other progestins.[27] In general, progestin-only contraceptives are preferred for women who are at increased risk of cardiovascular or thromboembolic complications, including women with a prior history of thromboembolic disease.[5,7]

Gallbladder Disease In women with preexisting gallstones, low-dose estrogen-containing oral contraceptives may enhance the potential for the development of symptomatic gallbladder disease and may worsen existing gallbladder disease.[4,5] Although this risk has not been demonstrated with the use of higher-dose oral contraceptives, CHCs containing estrogen should be used with caution in patients with a history of gallbladder disease or current gallbladder disease, especially if known cause is related to CHCs.

Hepatic Tumors Although the use of oral contraceptives is not associated with an increased risk for the development of hepatocellular carcinoma, long-term use of high-dose oral contraceptives has been associated with the development of benign liver tumors.[3] Because even benign liver tumors may pose significant risk to the patient, oral contraceptives should be discontinued if liver enlargement is noted on physical examination. In cases of benign hepatocellular adenoma and hepatoma (malignancy), the use of CHCs is contraindicated.[5]

Cervical Cancer There appears to be an increased risk for the development of cervical cancer among long-term users of oral contraceptives, particularly among women who test positive for human papilloma virus (HPV), a known risk factor for cervical cancer.[4] It is uncertain whether this increase in risk is directly attributed to the use of oral contraceptives. Data suggest that oral contraceptive users tend to have more sexual partners and use condoms less frequently, and as a result, this may increase their susceptibility to infection with HPV.

KEY CONCEPT Absolute and relative contraindications to the use of oral contraceptives are listed in Table 48–3.[4,5,28]

Adverse Effects of Oral Contraceptives and Their Management

LO 4

As with all medications, there are potential adverse effects with CHCs. KEY CONCEPT Many side effects can be minimized or avoided by adjusting the estrogen and/or progestin content of the oral contraceptive. It is also important to individualize the selection of oral contraceptives, because some women are at increased risk for potentially serious side effects.

Common complaints with CHCs include headaches, nausea, vomiting, **mastalgia**, and weight gain, although studies have shown a similar percentage of patients taking placebo experience

Patient Encounter Part 1

A 20-year-old nulliparous woman presents to your clinic requesting information on contraception. She specifically inquires about options that allow for fewer or no menstrual periods. You begin to take a history and determine that the patient is currently sexually active and is not using any method of birth control. She weighs 125 lb (56.8 kg), is 65 in (165 cm) tall, and has a blood pressure of 110/72 mm Hg. She has no history of smoking. She has migraines without aura and anxiety. Her only medication is propranolol. On further questioning, you discover that she has a positive family history of breast cancer (both her mother and maternal grandmother), but no personal history. As you discuss various contraceptive options with the patient, it is clear that she has a preference for an oral contraceptive agent.

What additional information do you need to know before recommending a contraceptive for this patient?

Based on the information provided by the patient, what oral contraceptive agent would you recommend for the patient and why?

What education would you provide to this patient regarding risks associated with oral contraceptive use?

Table 48–3

Conditions with Unacceptable Health Risk or with Theoretical or Proven Risks That Usually Outweigh the Advantages of CHC Use[3,4]

Conditions that represent an unacceptable health risk with CHC use

- History of thromboembolic disease
- History of stroke (or current cerebrovascular disease)
- History of (or current) coronary artery disease, ischemic heart disease, or peripheral vascular disease
- History of carcinoma of the breast (known or suspected)
- History of any estrogen-dependent neoplasm (known or suspected)
- Undiagnosed abnormal uterine or vaginal bleeding
- Pregnancy (known or suspected)
- Breastfeeding < 21 days postpartum
- Heavy smoking (defined as 15 cigarettes or more per day) by women who are 35 years of age or older
- History of hepatic tumors (benign or malignant)
- Active liver disease
- Migraine headaches with focal neurologic symptoms (aura)
- Postpartum (during the first 21 days in women with additional risk factors for thromboembolism, including age ≥ 35 years, history of previous venous thromboembolism, preeclampsia, recent cesarean delivery, obesity, and smoking)

Conditions for which the theoretical or proven risks usually outweigh the advantages of CHC use

- Smoking (< 15 cigarettes per day) at any age
- Migraine headache disorder without focal neurologic symptoms
- Hypertension (NOTE: WHO considers health risk posed by CHC use to be "unacceptable" when either systolic blood pressure is 160 mm Hg or more, or diastolic blood pressure is 90 mm Hg or more)
- Fibroid tumors of the uterus
- Breast-feeding > 21 days postpartum (with other risk factors for VTE such as > 35 years, previous VTE, transfusion at delivery, peripartum cardiomyopathy, obesity, postpartum hemorrhage, postcesarean delivery, preeclampsia or smoking)
- Superficial venous thrombosis (acute or history)
- Multiple sclerosis with prolonged immobility
- Diabetes mellitus
- Family history of dyslipidemia
- Sickle cell disease
- Active gallbladder disease
- Age > 50 years
- Elective major surgery requiring immobilization (planned in the next 4 weeks)
- Postpartum (during days 21 through 42 in women with additional risk factors for thromboembolism, including age ≥ 35 years, history of previous venous thromboembolism, preeclampsia, recent cesarean delivery, obesity, and smoking)

these side effects.[29] Given that oral contraceptives often are discontinued owing to side effects, proper counseling before initiation of CHCs is necessary.

Between 30% and 50% of women complain of breakthrough bleeding or spotting when oral contraceptives are initiated. All side effects tend to resolve by the third or fourth cycle.[4] Before changing formulations, other more serious causes of bleeding or spotting, such as pregnancy, infection, and poor absorption of the oral contraceptive owing to drug interaction or gastrointestinal problems, should be ruled out. Once these causes have been ruled out, the timing of the spotting must be determined in order to adjust the formulation appropriately.

LO 4 The most common side effects and ways to adjust therapy to minimize these side effects are listed in Table 48–4.[4,7,30]

As highlighted in Table 48–4, many of the side effects of CHCs may be minimized by adjusting the estrogen or progestin content of the preparation.

Progestin-Only Pills

LO 5 For women unable to take estrogen-containing oral contraceptives, there is an alternative: oral contraceptives containing only the progestin, norethindrone. These agents are slightly less effective than CHCs but have other advantages over CHCs. Progestin-only products have not shown the same thromboembolic risk as estrogen-containing products. Therefore, women at increased risk for or with a history of thromboembolism may be good candidates for progestin-only oral contraceptives. Also, these products can minimize menses, and many women have **amenorrhea** after six to nine cycles. These products have also been found safe to use in women who are nursing, so they are a viable option for women who breast-feed and desire hormonal contraception. In such patients, it should not be initiated until 42 days postpartum. Spotting may occur in some women, and this is a common cause for discontinuation. These products should be taken at the same time every day, and there is no pill-free or hormone-free period.

Unique Oral Contraceptives

LO 5 Along with varying doses of estrogen and different progestins, formulation modifications among select CHC products may yield certain benefits in some patient situations.

Lo-Loestrin Fe (norethindrone/EE) is a biphasic product that contains a low-dose estrogen, a high amount of progestin, and medium androgenic activity. Similar to other low-dose estrogen CHCs, Lo-Loestrin Fe may offer a smaller margin of error when pills are missed but provide the potential advantage of fewer estrogen-related side effects (eg, nausea and breast tenderness). Unlike the typical 28-pill packs that contain 21 active tablets and seven placebo tablets, Lo-Loestrin Fe contains 24 combination hormone tablets, two estrogen-only tablets, and two placebo (iron-only) tablets. This product provides a shorter hormone-free interval and may allow for shorter menstrual periods and fewer menstrual-related symptoms, such as menstrual-related headaches, menorrhagia, and anemia.

There are several monophasic combinations that are packaged as a 91-day treatment cycles with 84 active tablets that are taken consecutively followed by seven placebo tablets. These include Amethia, Ashlynn, Camrese, Daysee, Introvale, Jolessa, Seasonale, and Setlakin (levonorgestrel/EE). The extended cycle length of these products allows for one menstrual cycle per "season," or four per year. This type of formulation may be appealing to women with perimenstrual side effects or those at higher risk for anemia with menstrual bleeding. These products may improve anxiety, headache, fluid retention, dysmenorrhea, breast tenderness, bloating, and menstrual migraines. However, in the SEA 301 clinical trial comparing the efficacy of Seasonale with that of an equivalent-dosage 28-day cycle regimen, 7.7% versus 1.8% of women discontinued prematurely for unacceptable bleeding.[31] The risk of intermenstrual bleeding and/or spotting may be higher for patients taking these extended-cycle combinations than for patients taking typical 28-day-regimen CHCs.[32]

Seasonique and LoSeasonique (levonorgestrel/EE) are also extended cycle preparations that are similar to those mentioned earlier, but instead these preparations contain seven tablets with low-dose estrogen rather than placebo. Menstruation-related

Table 48–4

Management of Adverse Effects of Oral Contraceptives[4,7,30]

Adverse Effect	Cause	Adjustment	Notes
Spotting/bleeding before finishing active pills	Insufficient progestin	Monophasic with increased progestin or triphasic with increasing progestin	
Continued bleeding after menses	Insufficient estrogen	Increase estrogen or triphasic with lower early progestin	
Midcycle bleeding	Difficult to determine	Increase estrogen and progestin	
Increased breakthrough bleeding in general	Insufficient estrogen	Increase estrogen or triphasic formulation	Will increase amount of withdrawal bleeding during menses
Acne, PMDD, hirsutism	Progestin with higher androgenicity (eg, norgestrel, levonorgestrel)	Switch to progestin with lower androgenicity such as norgestimate, norethindrone or drospirenone	
Nausea, vomiting	Related to estrogen	Take at bedtime or with food; decrease estrogen or switch to a progestin-only product	Symptoms often resolve in 1–3 months
Constipation, bloating, distention	Related to progestin	Decrease progestin	Symptoms often resolve in 1–3 months
Headache	Must be evaluated because of warning sign for stroke – monitor blood pressure	If determined to not be serious, but still troublesome consider: a. Discontinue oral contraceptive b. Decrease estrogen c. Decrease progestin d. Eliminate pill-free interval for 2–3 cycles (when headaches occur during pill-free interval)	Discontinue oral contraceptive immediately if any neurologic symptoms or blurred vision
Decrease in libido, decreased vaginal lubrication	Insufficient estrogen	Increase estrogen or consider vaginal hormonal ring (NuvaRing)	Feelings of depression may coincide
Dyslipidemia in general	Progestin with higher androgenicity (eg, norgestrel, levonorgestrel)	Switch to progestin with lower androgenicity such as norgestimate, norethindrone or drospirenone	Obtain a baseline lipid panel in women with risk factors for dyslipidemia—smoking, hypertension, family history of heart disease
Triglycerides > 350 mg/dL (3.96 mmol/L)	Related to estrogen	Decrease estrogen to 20–25 mcg or a progestin-only formulation[3]	
Mastalgia	Related to estrogen	Decrease estrogen or switch to an extended cycle formulation (see Unique Oral Contraceptives, later) if it occurs prior to menses	
Weight gain, fluid retention	Excess estrogen and progestin with higher androgenicity (eg, norgestrel, levonorgestrel)	Decrease estrogen and switch to progestin with lower androgenicity such as norgestimate, norethindrone or drospirenone	
Visual changes or disturbances with contact lenses	Related to estrogen	Use saline eye drops	Referral to ophthalmology if eye drops do not help
Melasma, chloasma	Related to estrogen stimulation of melanocyte production	Consider progestin-only product and use of sunscreen	Women with darker pigmentation are more susceptible; melasma may not be completely reversible on discontinuation

problems that may improve with Seasonique or LoSeasonique include menstrual-related headaches, menorrhagia, and anemia. In addition, endometriosis-related menstrual pain may be relieved by providing a continuous regimen without a pill-free interval.[33]

Yasmin and Yaz (drospirenone/EE) are examples of unique oral contraceptives that contain the progestin drospirenone, that has antiandrogenic properties, but also showed antimineralocorticoid activity such as diuresis and hyperkalemia. Drospirenone has a unique application in young women who experience problems associated with producing too much androgen. Drospirenone is a spironolactone analog, and the 3-mg dose available in CHC preparations has antimineralocorticoid activity equal to 25 mg of spironolactone. It can affect the sodium and water balance in the body, although it has not shown superior efficacy for side effects such as bloating compared with other oral contraceptives. Caution should be used in women with chronic conditions or in women taking other medications that may affect serum potassium.

Yaz (drospirenone/EE) is an extended-cycle preparation that contains a low-dose estrogen and antimineralocorticoid and antiandrogenic activity. Yaz also contains 24 active tablets and four placebo tablets, allowing for shorter menstrual periods and fewer menstrual-related symptoms, such as menstrual-related headaches, menorrhagia, and anemia.

In 2003, the FDA Advisory Committee for Reproductive Health Drugs recommended the development of a CHC tablet containing folic acid in order to minimize the risk of neural tube defects in cases of contraceptive failure. Beyaz and Safyral, which were FDA approved in 2010, are combination tablets containing drospirenone and EE and 451 mcg of levomefolate calcium, the primary metabolite of folic acid. Beyaz is an extended-cycle preparation, which may allow for shorter menstrual periods and fewer menstrual-related symptoms.

In addition to the prevention of pregnancy, Yaz, Beyaz, Safyral; Ortho Tri-Cyclen, TriNessa, and Tri-Sprintec (norgestimate/EE); and Estrostep Fe, Tilia Fe, and Tri-Legest Fe (norethindrone acetate/EE) each carry an approved indication for treatment of moderate acne vulgaris in females 15 years of age or older desiring contraception who have not responded adequately to conventional antiacne medication. This can help clinicians to streamline medications by serving dual purposes.

Bekyree, Kariva, Kimidess, Pimtrea, and Viorele (desogestrel/EE) have a unique dosing schedule. After the usual 21 active tablets, there are only two tablets with inert ingredients. The last five tablets in the package have 10 mcg of EE. In theory, this may minimize bleeding during the menstrual cycle, although the clinical significance of this dosing schedule has not been established. With each of these products, it is important to counsel patients to complete the entire pack and not to discard the last 7 days of medication.

Another unique formulation is a chewable tablet available to women who have difficulty swallowing medications. Ovcon 35 (norethindrone/EE) has all 28 tablets in chewable form and has added spearmint flavoring.

Natazia was approved by the FDA in 2010 and is a quadriphasic CHC containing estradiol valerate and the progestin, dienogest. Estradiol valerate is metabolized endogenously to estradiol, and dienogest is a strong progestin with antiandrogenic activity. Natazia provides a unique estrogen step-down (estradiol valerate dose gradually decreases from 3 mg to 1 mg)/progestin step-up regimen (dienogest dose gradually increases from 0 mg to 3 mg), and this CHC offers the advantage of a shorter hormone-free interval. This results in fewer days of withdrawal bleeding and may help with menstrual-related headaches.

Patient Encounter Part 2: Adverse Effects

After 3 months of taking LoSeasonique, she returns to your clinic complaining of breakthrough bleeding during her sixth week of active pills. She reports no change or increase in frequency of her migraine headaches, and her blood pressure is 108/70 mm Hg. She is frustrated with the breakthrough bleeding and wants to explore other contraceptive options.

What are some potential causes of the breakthrough bleeding that the patient has been experiencing?

What strategy would you recommend to eliminate or minimize the potential adverse effects experienced by the patient?

Finally, Quartette, Fayosim, and Rivelsa (levonorgestrel/EE) are extended-cycle, quadriphasic preparations that contain increasing doses of EE throughout the 91-day pill period. The increasing dose of EE is intended to reduce the rate of breakthrough bleeding or spotting.

Drug Interactions with Oral Contraceptives

LO 6

EE is metabolized in the liver primarily via cytochrome P-450 (CYP450) 3A4. KEY CONCEPT When reviewing drug interactions of oral contraceptives, clinicians should be aware of the many drugs that may potentially interact with contraceptives—especially those that may reduce the effectiveness of contraceptives. Refer to Table 48–5 for a list of some of the most common drug interactions seen with oral contraceptives.[4,34]

Nonoral Hormonal Contraceptives

LO 5

KEY CONCEPT As an alternative to oral contraceptive pills, which must be taken daily in order to reliably prevent pregnancy, nonoral contraceptives in the form of transdermal, transvaginal, and injectable preparations are available and offer patients safe and effective alternatives to the pills for prevention of pregnancy. These formulations also do not require daily administration, making them more convenient than the pill formulations.

Xulane is a transdermal patch that contains both an estrogen (35 mcg of EE) and a progestin (150 mcg of norelgestromin). A new patch is applied to the abdomen, buttocks, back, or upper (outer) arm once weekly for 3 weeks, followed by 7 patch-free days.[7] Although some women have noted irregular bleeding during the first two cycles of patch use, the patch has been demonstrated to provide similar menstrual cycle control and contraceptive efficacy to that of CHCs. It is important to note, however, that higher contraceptive failure rates are seen when the patch is used in women weighing more than 90 kg (about 198 lb).[7] Further, manufacturer prescriber information indicates that women who take transdermal contraception are exposed to approximately 60% more estrogen than women who take CHCs with 35 mcg of estrogen.[35] Although the clinical significance of this is not well defined, studies have suggested a link between the use of the patch and an increased risk for VTE. A slightly higher reported incidence of breast discomfort and local skin irritation has also been reported with the patch.[7,36]

NuvaRing is a unique transvaginal delivery system that provides 15 mcg of EE and 120 mcg of etonogestrel for the prevention of ovulation. NuvaRing is inserted into the vagina on or before day 5 of the menstrual cycle and is removed from the vagina 3 weeks later.[7] Seven days after the ring is removed, a new ring should be inserted. In clinical trials, NuvaRing demonstrated comparable efficacy and cycle control to CHCs as well as a similar side-effect profile.[7,37] NuvaRing should not be removed during intercourse.

Depo-Provera is a progestin-only, injectable contraceptive that contains depot medroxyprogesterone acetate. Depo-Provera is administered intramuscularly as a 150-mg injection once every 3 months. An advantage of Depo-Provera is that it provides an estrogen-free method of contraception either for women in whom estrogens are contraindicated or for women who cannot tolerate estrogen-containing preparations. Depo-Provera is extremely effective in preventing pregnancy. However, the incidence of menstrual irregularities (including amenorrhea) and weight gain appears to be much greater than that seen with CHCs. The use of Depo-Provera also has been demonstrated to result in significant loss of bone mineral density (BMD).[38] Although the effect is known to be reversible following product discontinuation, a black-box warning within the product labeling

Table 48–5

Commonly Seen Drug Interactions with CHCs[4,34]

Medication	Mechanism	Clinical Effect
Anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate, and felbamate)	Increase metabolism of CHCs via induction of various cytochrome P-450 enzymes	Decrease efficacy of CHCs (EE doses < 35 mcg are not recommended in women on these medications)
Bosentan	Increase metabolism of CHCs via induction of cytochrome P-450 3A4 enzyme	Decrease efficacy of CHCs
Griseofulvin	Increase metabolism of CHCs	Decrease efficacy of CHCs; backup method of contraception is recommended
Lamotrigine	CHCs increase metabolism of lamotrigine via induction of glucuronidation	Decrease efficacy of lamotrigine; dose adjustment may be necessary
Nonnucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine, rilpivirine)	Increase metabolism of CHCs	Decrease efficacy of CHCs; alternative method of contraception may be considered with efavirenz
Protease inhibitors (atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir)	Increase or decrease in metabolism of CHCs	Decrease efficacy of CHCs or increase side effects of CHCs; alternative method of contraception is recommended with fosamprenavir and may be considered with ritonavir-boosted protease inhibitors, atazanavir and nelfinavir
Rifampin, rifabutin	Increase metabolism of CHCs	Decrease efficacy of CHCs; backup method of contraception is recommended
St. John's wort	Increase metabolism of CHCs via induction of various cytochrome P-450 enzymes	Decrease efficacy of CHCs; avoid use with CHCs
Theophylline	CHCs decrease theophylline clearance by 34% and increase half-life by 33%	Increase side effects of theophylline

CHC, combined hormonal contraception; EE, ethinyl estradiol.

cautions against the risk of potentially irreversible BMD loss associated with long-term use (eg, > 2 years) of the injectable product. Although injectable contraceptives offer no protection against STIs, it is important to note the CDC finds that the risk of HIV acquisition does not outweigh the benefit of contraceptive use in a patient at high risk of HIV infection. Although the extended duration of activity of this product may offer women the advantage of less frequent administration, it is important to note that on discontinuation of Depo-Provera, the return of fertility can be delayed by approximately 10 to 12 months (range 4–31 months).[7]

Depo-SubQ Provera 104 is also an injectable contraceptive product that contains only progestin (depot medroxyprogesterone acetate). This product differs from Depo-Provera in that it is given subcutaneously rather than intramuscularly, and it contains only 104 mg of medroxyprogesterone acetate (~30% less hormone) administered every 3 months for the prevention of pregnancy. Clinical trials have demonstrated that the subcutaneous formulation of depot medroxyprogesterone acetate is as effective as the intramuscular formulation in the prevention of pregnancy.[39] This product carries the same warning in its package labeling regarding possible effects on BMD as Depo-Provera. It is also used for the management of endometriosis-associated pain along with its use for contraception.

Long-Acting Reversible Contraception

The currently available products for long-term reversible contraception (LARC) are listed in Table 48–6. Surveys have shown that LARC has the highest satisfaction rate among patients using reversible contraceptives, and use within the United States is on the rise.[1]

Although the mechanism of action for IUDs is not completely understood, several theories have been suggested. The original theory is that the presence of a foreign body in the uterus causes an inflammatory response that interferes with implantation. It is believed that copper-containing IUDs may interfere with sperm transport and fertilization and prevent implantation. Progestin-containing implantable contraceptives can have direct effects on the uterus, such as thickening of cervical mucus and alterations

Table 48–6

Long-Acting Reversible Contraception

Product	Ingredient	Dosage Form	Duration
Mirena	Levonorgestrel	Intrauterine device	Up to 5 years
Skyla	Levonorgestrel	Intrauterine device	Up to 3 years
Kyleena	Levonorgestrel	Intrauterine device	Up to 5 years
Liletta	Levonorgestrel	Intrauterine device	Up to 4 years
ParaGard T 380A	Copper	Intrauterine device	Up to 10 years
Implanon	Etonorgestrel	Implantable device	Up to 3 years
Nexplanon	Etonorgestrel	Implantable device	Up to 3 years

to the endometrial lining. Paragard T 380A does not prevent ovulation, although the other LARCs can because they are progestin-containing products.

It is important to evaluate a patient to determine whether she is an appropriate candidate for an implantable contraceptive. IUDs are recommended for women who are in a monogamous relationship, are at low risk for acquiring STIs, and have no current **pelvic inflammatory disease** (PID). Contraindications to the use of progestin-containing LARC products include (a) known or suspected pregnancy, (b) hepatic tumors or active liver disease, (c) undiagnosed abnormal genital bleeding, (d) known or suspected carcinoma of the breast or personal history of breast cancer, (e) history of thrombosis or thromboembolic disorders, and (f) hypersensitivity to any components of the products. There are also multiple additional contraindications to IUD use. Evaluation of the patient is essential because IUDs cannot be used in the following situations: (a) anatomically abnormal or distorted uterine cavity, (b) acute PID, (c) postpartum **endometritis** or infected abortion in the past 3 months, (d) known or suspected uterine or cervical malignancy, (e) untreated acute **cervicitis**, (f) previously inserted IUD still in place, (g) increased susceptibility to pelvic infections, and (h) **Wilson disease** (Paragard T 380A only).

The most common adverse effects are abdominal/pelvic cramping, abnormal uterine bleeding, and expulsion of the device. Other side effects seen are **ectopic pregnancy**, sepsis, PID, embedment of the device, uterine or cervical perforation, and ovarian cysts.

Nonpharmacologic Contraceptive Methods

▶ *Barrier Contraceptives*

LO 5

As an alternative to hormonal contraceptives, several barrier contraceptive options are available for the prevention of pregnancy. Although barrier contraceptives are associated with far fewer adverse effects compared with hormonal contraceptives, their efficacy is highly user-dependent. Overall, compared with both hormonal contraceptives and IUDs, barrier contraceptives are associated with much higher unintended pregnancy rates[7] (see Table 48–1).

Diaphragms and Cervical Caps Diaphragms and cervical caps are dome-shaped rubber caps that are placed over the cervix to provide barrier protection during intercourse. Both diaphragms and cervical caps require fitting by a health care professional, and they must be refitted in the event of weight gain or weight loss. Diaphragms or cervical caps typically can be placed over the cervix as much as 6 hours prior to intercourse. They must be left in place for at least 6 hours after intercourse before they can be removed. Diaphragms should not be left in place longer than 24 hours, and smaller cervical caps should not be left in place longer than 48 hours owing to the risk of toxic shock syndrome (TSS). Diaphragms and cervical caps are used along with spermicides to prevent pregnancy. When sexual intercourse is repeated with the diaphragm, reapplication of the spermicide is necessary. However, when sexual intercourse is repeated with a cervical cap, reapplication of the spermicide typically is not necessary.[7] Whether or not diaphragms or cervical caps provide adequate protection against STIs remains unclear.[40]

Spermicides Nonoxynol-9, a surfactant that destroys the cell membranes of sperm, is the most commonly used spermicide in the United States.[4,7] Nonoxynol-9 is available in a variety of forms, including a cream, foam, film, gel, and suppository. Spermicides may be used alone, with a barrier method, or adjunctively with other forms of contraceptives to provide additional protection against unwanted pregnancy.[4] To be used most effectively, spermicides must be placed in the vagina not more than 1 hour prior to sexual intercourse, and they must come in contact with the cervix.[7] Additionally, film and suppositories must dissolve to be effective. Although the efficacy of spermicides depends largely on how consistently and correctly they are used, their efficacy is enhanced when they are used in combination with a barrier contraceptive device.[40] Clinical trials assessing the ability of spermicides to protect against STIs have failed to produce positive results.[4] Further, there exists some evidence to suggest that frequent use of spermicides actually may increase risk for acquisition of human immunodeficiency virus (HIV) secondary to vaginal mucosal tissue breakdown, which may allow a portal of entry for the virus.[7] In December 2007, the FDA issued a statement requiring manufacturers of nonoxynol-9 products to include a warning on the product label indicating that the spermicide does not provide protection against infection from HIV or other STIs. Patients should be encouraged not to use spermicides alone, but it is recommended with a barrier method.

Condoms Condoms, which are available for both male and female use, act as physical barriers to prevent sperm from coming into contact with ova.[4] Condoms are easy to use, available without a prescription, and inexpensive. Most condoms are made of latex. When used correctly, condoms can be very effective in prevention of unwanted pregnancy.[41] Condoms should be stored in a cool, dry place, away from exposure to direct sunlight. When stored improperly or when used with oil-based lubricants, however, latex condoms can break during intercourse, increasing the risk of pregnancy.[7] For latex-sensitive individuals, condoms made from lamb intestine ("natural membrane" condoms) and synthetic polyurethane condoms are available. Unlike latex condoms, condoms made from lamb intestine contain small pores that may permit the passage of viruses and therefore do not provide adequate protection against STIs.[4] As well, synthetic polyurethane condoms may be more likely to break than latex condoms. KEY CONCEPT Both latex and synthetic condoms can provide some protection against many STIs. Data from one meta-analysis suggested that HIV transmission can be reduced by as much as 90% when condoms are consistently used.[42] This is in contrast to hormonal contraceptives (oral, transdermal, or vaginal), IUDs, and most other barrier contraceptives, which do not protect against STIs. Relative to male condoms, female condoms may offer even better protection against STIs because they provide more extensive barrier coverage of external genitalia, including the labia and the base of the penis.[4] It is important to note that the male and female condoms are not recommended to be used together because they may adhere to one another, causing displacement of one or both condoms.[4]

Sponge The Today Sponge is a small, pillow-shaped polyurethane sponge impregnated with nonoxynol-9.[40] It is an over-the-counter barrier contraceptive that has been shown to be generally less effective at preventing pregnancy than diaphragms.[42] The sponge is moistened with water and then is inserted and placed over the cervix for up to 6 hours prior to sexual intercourse. The sponge then is left in place for at least 6 hours following intercourse.[4] Although the sponge maintains efficacy for 24 hours (even if intercourse is repeated), as with diaphragms, the sponge should be removed after 24 hours owing to the risk of TSS.[7]

▶ *Fertility Awareness–Based Methods*

Fertility awareness–based methods (natural methods) represent another nonpharmacologic means of pregnancy prevention.

Patient Encounter Part 3: Missed Doses

The patient calls your clinic in a panic today because she forgot to take her oral contraceptive for the past 2 days, beginning the third week of active pills. Two days have elapsed since she took her last active pill, and she reports having had unprotected sexual intercourse last night. The patient is very concerned about her risk of pregnancy and is interested to learn more about emergency contraception and what her options are.

Given this patient's reported imperfect use of her oral contraceptive, what information can you provide to the patient regarding her risk of pregnancy?

What additional education should be provided to the patient regarding her risk of STIs related to unprotected intercourse?

Provide appropriate patient education regarding the use of various forms of emergency contraception, in the event she decides to use EC.

Although failure rates of such methods can be high, some couples still prefer these types of approaches. Fertility awareness–based methods depend on the ability of the couple to identify the woman's "fertile window," or the period of time in which pregnancy is most likely to occur as a result of sexual intercourse.[4] During the fertile window, the couple practices abstinence, or avoidance of intercourse, in order to prevent pregnancy. In general, fertility awareness–based methods are not recommended for women who have irregular menstrual cycles or who have difficulty interpreting their fertility signs correctly.[4]

Emergency Contraception

Emergency contraception (EC) is used to prevent pregnancy after known or suspected unprotected sexual intercourse. Ideally it should be used as soon as possible after unprotected sexual intercourse and within 72 hours (120 hours with ella), but it can still remain effective beyond this time frame. If a woman is already pregnant, EC cannot stop the pregnancy or harm the fetus. It is unknown how EC works although it is theorized it may prevent or delay ovulation or possibly prevent fertilization if ovulation has occurred. It is not recommended that EC be used as a regular form of birth control.

There are six FDA-approved oral agents available for use as EC, with availability from over the counter to prescription-only access. The product known as ella (ulipristal acetate), a progesterone-receptor agonist/antagonist, can delay follicular rupture if taken just before ovulation and may cause endometrial changes to interfere with implantation. The available products are LO 7 listed in Table 48–7 along with information on availability and correct dosage. It is important to note that EC is more effective the earlier it is used after unprotected intercourse. Common side effects include headache, nausea, abdominal pain, dysmenorrhea, fatigue, and dizziness. If severe abdominal pain occurs, patients should be referred to their health care provider for evaluation of risk of an ectopic pregnancy. Patients should also contact their health care provider if their menstrual cycle is more than 1 week late after taking EC.

OUTCOME EVALUATION

Side effects of contraceptives tend to occur in the first few months of therapy. Schedule follow-up visits as needed and at the discretion of the provider. At each follow-up visit, assess blood pressure, headache frequency, and menstrual bleeding patterns, as well as compliance with the prescribed regimen. Strict adherence to the prescribed hormonal contraceptive regimen is essential for effective prevention of unintended pregnancy. KEY CONCEPT When a contraceptive dose is missed, the risk of accidental pregnancy may be increased. Depending on how many doses were missed, the contraceptive formulation being used, and the phase of the cycle during which doses were missed, counseling regarding the use of additional methods of contraception may be warranted. For further information, patients can be referred to https://www.cdc.gov/reproductivehealth/contraception/pdf/Recommended-Actions-Late-Missed_508Tagged.pdf.

Table 48–7

Emergency Contraception

Product	Where Stocked	Availability	Ingredient	Dose	When Recommended[a]
Plan B One-Step	Over the counter	All ages with no identification required	Levonorgestrel	1.5 mg	Within 72 hours of unprotected sex
Take Action	Over the counter	All ages with no identification required	Levonorgestrel	1.5 mg	Within 72 hours of unprotected sex
Next Choice One Dose	Behind the counter	Over the counter for 17 years and older; prescription required for 16 years and younger	Levonorgestrel	1.5 mg	Within 72 hours of unprotected sex
My Way	Behind the counter	Over the counter for 17 years and older; prescription required for 16 years and younger	Levonorgestrel	1.5 mg	Within 72 hours of unprotected sex
Levonorgestrel	Behind the counter	Over the counter for 17 years and older; prescription required for 16 years and younger	Levonorgestrel	0.75 mg (two tablets for a total of 1.5 mg)	Both tablets within 72 hours of unprotected sex
ella	Behind the counter	Only as a prescription	Ulipristal acetate	30 mg	Within 120 hours of unprotected sex

[a]Although these are the preferred time frames for optimal efficacy, these products can be taken after 72 hours.

Patient Care Process

Collect Information:

- Determine goals related to contraceptive use (pregnancy prevention, menstrual regulation, control of acne).
- Based on medical, social (ie, smoking), and family history, determine if patient qualifies for hormonal contraceptives. Rule out pregnancy, and evaluate patient's risk for STIs.
- Conduct thorough medication history to identify potential for drug interactions.

Assess the Information:

- At follow-up visits, assess blood pressure, weight, and menstrual patterns for changes from baseline.
- Assess tolerability of and adherence to the prescribed contraceptive method.
- Assess safety by using the mnemonics, "ACHES"[4] for hormonal contraceptives, and "PAINS" for IUDs:

  ACHES[4]

  A = Abdominal pain

  C = Chest pain

  H = Headaches (especially if associated with focal neurologic symptoms)

  E = Eye problems (blurred vision, ocular pain, visual changes)

  S = Severe leg pain

- Also monitor for missed periods, signs of pregnancy, appearance of jaundice, and/or severe mood changes.

  PAINS

  P = Period late

  A = Abdominal pain, pain with intercourse

  I = Infection, abnormal/odorous vaginal discharge

  N = Not feeling well, fever, chills

  S = String (missing, shorter, longer)

Develop a Care Plan:

- Select a contraceptive option that the patient is comfortable with, that is likely to achieve the patient's desired goal(s), and is not contraindicated.
- Educate regarding the potential for side effects, safety risks, drug interactions, and any noncontraceptive benefits that may result for the chosen method.
- Determine the patient's sexual behavior and evaluate whether the contraceptive method will impact the risk for STIs.
- Evaluate insurance coverage/cost factors.

Implement the Care Plan:

- Instruct the patient to consult a health care professional upon noticing or experiencing any warning signs.
- Stress the importance of adherence (especially if prevention of pregnancy is desired).
- Educate on what to do in the event of missed doses.

Follow-up: Monitor and Evaluate:

- Schedule a follow-up visit 3 to 6 months after initiating a new contraceptive.
- Assess blood pressure, headache frequency, and menstrual bleeding patterns.
- Assess patient tolerance and evaluate for the occurrence of side effects specific to the regimen prescribed.
- Assess adherence to the prescribed regimen.

Abbreviations Introduced in This Chapter

BMD	Bone mineral density
CHC	Combination hormonal contraceptive
CYP450	Cytochrome P-450
EC	Emergency contraception
EE	Ethinyl estradiol
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
IUD	Intrauterine device
LARC	Long-acting reversible contraception
LH	Luteinizing hormone
PID	Pelvic inflammatory disease
PMDD	Premenstrual dysphoric disorder
STI	Sexually transmitted infection
TSS	Toxic shock syndrome
WHO	World Health Organization

REFERENCES

1. Daniels K, Daugherty J, Jones J. Current contraceptive status among women aged 15–44: United States, 2011–2013. Hyattsville, MD: NCHS data brief, no 173.
2. Cutrin SC, Abma JC, Ventura SJ, Henshaw SK. Pregnancy rates for U.S. women continue to drop. NCHS data brief, no 136. Hyattsville, MD: National Center for Health Statistics 2013.
3. Mosher WD, Jones J, Abma JC. Intended and unintended births in the United States: 1982–2010. National health statistics reports; no 55. Hyattsville, MD: National Center for Health Statistics. 2012.
4. Hatcher RA, Trussel J, Nelson AL, et al. Contraceptive Technology, 20th rev. ed. New York: Ardent Media, 2011.
5. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep 2016;65:1–104.
6. 2015 Sexually Transmitted Disease Surveillance. Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/std/stats15/default.htm. Accessed July 19, 2018.
7. Anonymous. Choice of contraceptives. Med Lett Drugs Ther. 2015;57:127–134.
8. Maxwell GL, Schildkraut JM, Calingaert B, et al. Progestin and estrogen: potency of combination oral contraceptives and endometrial cancer risk. Gynecol Oncol. 2006;103:535–540.
9. Lurie G, Thompson P, McDuffie KE, et al. Association of estrogen and progestin potency of oral contraceptives with ovarian carcinoma risk. Obstet Gynecol. 2007;109:597–607.
10. Tworoger S, Fairfield K, Colditz G, et al. Association of oral contraceptive use, other contraceptive methods, and infertility with ovarian cancer risk. Am J Epidemiol. 2007; 166:894–901.

11. Schildkraut JM, Calingaert B, Marchbanks PA, et al. Impact of progestin and estrogen potency in oral contraceptives on ovarian cancer risk. J Natl Cancer Inst. 2002;94:32–38.
12. Wu AH, Pearce CL, Lee AW, et al. Timing of births and oral contraceptive use influencing ovarian cancer risk. Int J Cancer. 2017;141(12):2392–2399.
13. Hillard P. Menstrual suppression: current perspectives. Int J Womens Health. 2014;6:631–637.
14. Kroll R, Rapkin AJ. Treatment of premenstrual disorders. J Reprod Med. 2006;51:359–370.
15. Tanis BC, van den Bosch MA, Kemmeren JM, et al. Oral contraceptives and the risk of myocardial infarction. Arch Intern Med. 2001;161:1065–1070.
16. Schwingl PJ, Ory HW, Visness CM. Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States. Am J Obstet Gynecol. 1999;180:241–249.
17. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. BMJ. 1999;318:13–18.
18. Curtis KM, Chrisman CE, Peterson HB, WHO Programme for Mapping Best Practices in Reproductive Health. Contraception for women in selected circumstances. Obstet Gynecol. 2002; 99:1100–1112.
19. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30 year population-based study. Ann Intern Med. 2005;143:697–706.
20. Hennessy S, Berlin JA, Kinman JL, et al. Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis. Contraception. 2001; 64:125–133.
21. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ. 2001;323:131–134.
22. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestin type: results of the MEGA case-control study. BMJ. 2009;339:b2921.
23. Lidegaard Ø, Løkkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ. 2009;339:b2890.
24. Parkin L, Sharples K, Hernandez RK, et al. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ. 2011;340:d2139.
25. Jick SS, Hernandez RK. Risk of non-fatal venous thrombo-embolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ. 2011;340:d2151.
26. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2015;350:h2135.
27. Dinger J, Bardenheuer K, Heinemann K. Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the International Active Surveillance Study of Women Taking Oral Contraceptives. Contraception. 2014;89:253.
28. Centers for Disease Control and Prevention (CDC). Update to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2010: revised recommendations for the use of contraceptive methods during the postpartum period. MMWR Morb Mortal Wkly Rep. 2011;60:878.
29. Grimes DA, Schulz KF. Nonspecific side effects of oral contraceptives: nocebo or noise? Contraception. 2011:83:5–9.
30. Burkman RT, Fisher AC, LaGuardia KD. Effects of low-dose oral contraceptives on body weight: results of a randomized study of up to 13 cycles of use. J Rep Med. 2007:52:1030–1034.
31. Duramed Pharmaceuticals. Product information for Seasonale. Pomona, NY: Duramed Pharmaceuticals, 2003.
32. Wright K, Johnson J. Evaluation of extended and continuous use oral contraceptives. Ther Clin Risk Manag. 20008;4(5): 905–911.
33. Vercellini P, Frontino G, De Giorgi O, et al. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril. 2003;80:560–563.
34. Tom W. Oral contraceptive drug interactions. Pharmacist's Letter/Prescriber's Letter 2005;21:210903.
35. Anonymous. An update on Ortho Evra and the risk of thromboembolism. Pharmacist's Letter/Prescribers Letter. 2005;21:211202.
36. Smallwood GH, Meador ML, Lenihan JP, et al. for the Ortho Evra/Evra 002 Study Group. Efficacy and safety of a transdermal contraceptive system. Obstet Gynecol. 2001;98:799–805.
37. Merck & Co., Inc. Product information for NuvaRing. Whitehouse Station, NJ. 2017;1–21.
38. Westhoff C. Bone mineral density and DMPA. J Reprod Med. 2002;47:795–799.
39. Toh YC, Jain J, Rahnny MH, et al. Suppression of ovulation by a new subcutaneous depot medroxyprogesterone acetate (104 mg/0.65 mL) contraceptive formulation in Asian women. Clin Ther. 2004;26:1845–1854.
40. Moench TR, Chipato T, Padian NS. Preventing disease by protecting the cervix: the unexplored promise of internal vaginal barrier devices. AIDS. 2001;15:1595–1602.
41. Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. Fam Plann Perspect. 1999;31:272–279.
42. Kuyoh MA, Toroitich-Ruto C Grimes DA, et al. Sponge versus diaphragm for contraception: A CHChrane review. Contraception. 2003;67:15–18.

49 Menstruation-Related Disorders

Kylie N. Barnes, Jacqueline M. Klootwyk and Elena M. Umland

LEARNING OBJECTIVES

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

1. Describe the underlying etiology and pathophysiology of dysmenorrhea, amenorrhea, anovulatory bleeding, and abnormal uterine bleeding and how they relate to selecting effective treatment modalities.
2. Describe the clinical presentation of dysmenorrhea, amenorrhea, anovulatory bleeding, and abnormal uterine bleeding.
3. Recommend appropriate nonpharmacologic and pharmacologic interventions for patients with dysmenorrhea, amenorrhea, anovulatory bleeding, and abnormal uterine bleeding.
4. Identify the desired therapeutic outcomes for patients with dysmenorrhea, amenorrhea, anovulatory bleeding, and abnormal uterine bleeding.
5. Design a monitoring plan to assess the safety and effectiveness of pharmacotherapy for dysmenorrhea, amenorrhea, anovulatory bleeding, and abnormal uterine bleeding.

INTRODUCTION

Problems related to the menstrual cycle are common among women of reproductive age. The most common menstruation-related disorders include dysmenorrhea, amenorrhea, anovulatory bleeding, and abnormal uterine bleeding. These disorders can negatively affect quality of life, reproductive health, and productivity; they may also lead to adverse long-term health consequences, such as increased risk for osteoporosis with amenorrhea.

DYSMENORRHEA

Dysmenorrhea is pelvic pain, generally described as painful cramping, occurring during or just prior to menstruation. Primary dysmenorrhea occurs with normal pelvic anatomy and physiology, whereas secondary dysmenorrhea is associated with underlying pelvic pathology.[1]

Epidemiology and Etiology

Dysmenorrhea is the most commonly reported menstrual complaint, with more than one-half of menstruating women reporting pain for at least 1 or 2 days each month.[2] Of women with dysmenorrhea, around 51% report limited daily activities or missing work or school.[3] Risk factors include irregular or heavy menses, age less than 30, menarche prior to age 12, body mass index (BMI) less than 20 kg/m^2, history of sterilization or sexual abuse, and smoking.[1,4] Causes of secondary dysmenorrhea may include endometriosis, pelvic inflammatory disease (PID), uterine or cervical polyps, and uterine fibroids.[4-5]

LO 1

Pathophysiology

LO 1

KEY CONCEPT In primary dysmenorrhea, elevated arachidonic acid levels in the menstrual fluid lead to increased concentrations of prostaglandins and leukotrienes in the uterus. This induces uterine contractions, stimulates pain fibers, reduces uterine blood flow, and causes uterine hypoxia.[3]

Treatment

▶ *Desired Outcomes*

LO 4

Desired treatment outcomes (Figure 49–1) are reduction of pelvic pain, improved quality of life, and fewer missed days from school and work.

▶ *Nonpharmacologic Therapy*

LO 3

Exercise may reduce dysmenorrhea by increasing pelvic blood flow and stimulating the release of beta-endorphins which act as analgesics.[1,3,6] In addition, a low-fat vegetarian diet has been shown to lessen the intensity and duration of dysmenorrhea. Evidence supporting acupuncture, heat therapy, transcutaneous nerve stimulation, yoga, and massage therapy is insufficient to recommend as standards of care.

▶ *Pharmacologic Therapy*

LO 3

Medication management options are summarized in Table 49–1.

Nonsteroidal Anti-inflammatory Drugs

KEY CONCEPT Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for dysmenorrhea, and up to 80% of patients will respond to them.[7] By inhibiting prostaglandin production, they exert analgesic properties, decrease uterine contractions, and reduce menstrual blood flow. Choice of one agent over another is based on effectiveness, tolerability, and patient preference, as no NSAID has been proven more effective than others.[1,3,4] The most commonly used nonprescription NSAIDs utilized in the United States are naproxen and ibuprofen. Of note, aspirin is not used for the treatment of dysmenorrhea as it is not potent enough in usual dosages.

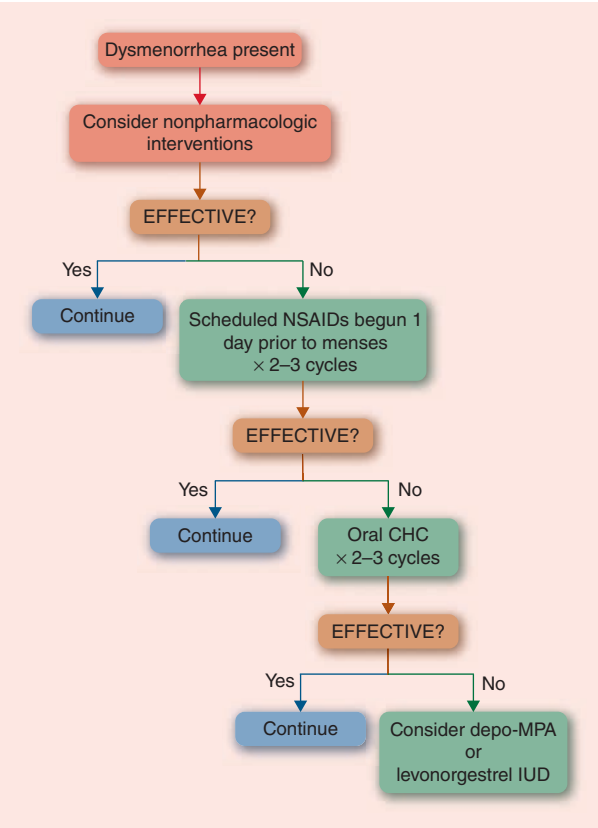

FIGURE 49–1. Treatment algorithm for dysmenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; MPA, medroxyprogesterone acetate; NSAID, nonsteroidal anti-inflammatory drug.) (Data from Umland EM, Klootwyk J. Menstruation-related disorders. In: Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014, with permission.)

Clinical Presentation and Diagnosis of Dysmenorrhea

LO 2

General

- May be in acute distress depending on the severity of pain.

Symptoms

- Recurrent, crampy pelvic pain (lasting 2–3 days) beginning shortly before or during menses. Pain may radiate into lower back or thighs. Associated symptoms may include nausea, vomiting, diarrhea, headache, dizziness, bloating, and fatigue. Symptoms generally begin in adolescence.

Laboratory Tests

- Gonorrhea, chlamydia cultures or polymerase chain reactions test, wet mount

Other Diagnostic Tests

- Pelvic examination for sexually active females, females reporting severe pain or limitation of activity, or who have not responded to first- and second-line treatments
- Pelvic ultrasound may identify anatomic abnormalities (eg, masses/lesions), ovarian cysts, or endometriomas.

Patient Encounter 1, Part 1

A 17-year-old white woman presents reporting severe, crampy pelvic pain that radiates to her lower back during menses, causing her to miss 1–2 school days each menstrual cycle. Her last menses was 20 days ago, and her first menstrual cycle occurred at age 11. She has never been sexually active. She has been taking acetaminophen as needed for pain. She is a runner, 5'8" (173 cm) tall, and weighs 126 pounds (57.2 kg).

What risk factors does the patient have for primary dysmenorrhea?

What risk factors does the patient have for secondary dysmenorrhea?

NSAID treatment should begin 1 to 2 days prior to the start of menses, or at dysmenorrhea onset, and continued for 2 to 3 days or until pain resolves.[1,4] A loading dose (twice the usual single dose) is recommended, followed by the usual recommended dose.[1,5] For patients which contraindications to NSAID therapy, or with dysmenorrhea unresponsive to initial NSAID treatment, combination hormonal contraceptives (CHCs) should be considered.[4]

Combination Hormonal Contraceptives

CHCs improve mild to severe dysmenorrhea by decreasing endometrial lining and inhibiting ovulation, which decreases the formation of prostaglandins and leukotrienes contributing to menstrual pain.[3-5] Data supporting CHC efficacy, including oral, intravaginal, transdermal patch, and vaginal ring, for treatment of primary dysmenorrhea are limited, although their use is common in clinical practice.[1,4] Two to three months of therapy are often required to achieve full effects, and can take up to 6 months.[4] Both standard (28-day) and extended cycle (91-day) therapies are effective for primary dysmenorrhea.[1,4] Continuous CHC may show more immediate pain relief when compared to cyclic therapy; however, both effects are similar when evaluated at 6 months.[1,4] For dysmenorrhea secondary to endometriosis, CHCs, specifically extended cycle regimens, are considered first-line.[1,4] Additionally, the patch and vaginal ring have both shown comparable efficacy to oral agents.[8] If no response with any agent occurs after 3 months, the patient should be reevaluated.[5]

Progestin-Only Hormonal Contraceptives

Progestin-only agents diminish dysmenorrhea by reducing or eliminating menses over time, thus eliminating prostaglandin release.[5] Three long-acting reversible contraceptive agents are available: depot medroxyprogesterone acetate, etonogestrel implant, and levonorgestrel-releasing IUD. Observational data show women with dysmenorrhea reduced from 60% to 29% after 3 years of levonorgestrel-releasing IUD therapy.[6]

Dysmenorrhea in Adolescents

Dysmenorrhea is the most common gynecologic complaint amongst female adolescents, reported in 60% to 90%, and the most common reason for missed school or work.[6] At diagnosis, a pelvic examination should be performed in adolescents who

Table 49–1

Therapeutic Agents for Selected Menstrual Disorders

Specific Menstrual Disorders(s)	Agent(s)	Dose Recommended	Common Adverse Effects
Amenorrhea (primary or secondary)	CEE[a]	0.625–1.25 mg by mouth daily on cycle days 1–26[9]	Thromboembolism, breast enlargement, breast tenderness, bloating, nausea, GI upset, headache, peripheral edema
	Ethinyl estradiol patch[a]	50–100 mcg/24 hours[9]	
	Oral CHC[a]	30–40 mcg formulations	
Amenorrhea (secondary)	Oral medroxyprogesterone acetate[a]	10 mg by mouth on cycle days 14–26[9]	Edema, anorexia, depression, insomnia, weight gain or loss, elevated total and LDL cholesterol, may reduce HDL cholesterol
Amenorrhea (hyperprolactinemia)	Bromocriptine	2.5 mg by mouth two to three times daily[15]	Hypotension, nausea, constipation, anorexia, Raynaud phenomenon
	Cabergoline	0.25 mg by mouth twice weekly[15]	
Anovulatory bleeding	Oral CHC[a]	Optimal dose unknown[19] For acute or severe bleeding, product containing 35 mcg ethinyl estradiol; take one tablet by mouth three times daily × 1 week; then one tablet by mouth daily × 3 weeks.[19] Therapy continuation may be necessary to prevent future occurrences	As noted above for CEE, ethinyl estradiol, and oral CHC (progesterone side effects with the CHC depend on agent chosen)
	Oral medroxyprogesterone acetate[a]	For acute bleeding, 20 mg by mouth three times daily × 1 week; then 20 mg by mouth once daily × 3 weeks[19]	As noted above for oral medroxyprogesterone acetate
Dysmenorrhea	Oral CHC[38,a]	< 35 mcg formulations + norgestrel or levonorgestrel[39]; use of extended-cycle formulations is beneficial for this indication	As noted above for CEE, ethinyl estradiol, and oral CHC (progesterone side effects with the CHC depend on agent chosen)
	Depot medroxyprogesterone acetate[a]	150 mg intramuscularly every 12 weeks	Irregular menses, amenorrhea
	Levonorgestrel IUD[10,a]	20 mcg released daily	Irregular menses, amenorrhea
	NSAIDs—any are acceptable except aspirin or salicylates; the most commonly studied/ cited are included in this table[1,3–5,38]	Ibuprofen 800 mg by mouth three times daily[a] Naproxen 550-mg loading dose by mouth started 1–2 days prior to menses, followed by 275 mg by mouth every 6–12 hours as needed[c] Mefenamic acid 500 mg by mouth as a loading dose, then 250 mg by mouth up to four times daily as needed[b] Diclofenac 50 mg by mouth three times daily[b] Treatment should begin 1–2 days prior to the expected onset of menses	GI upset, stomach ulcer, nausea, vomiting, heartburn, indigestion, rash, dizziness
Abnormal uterine bleeding	Oral CHC[a]	Optimal dose unknown	As noted above
	Levonorgestrel IUD[a]	20 mcg released daily	As noted above
	Medroxyprogesterone acetate (oral)[a]	5–10 mg by mouth on days 5–26 of the cycle *or* during the luteal phase[32]	As noted above
	NSAIDs	Doses as recommended for above; therapy should be initiated with the onset of menses[32]	As noted above
	Tranexamic acid	1300 mg (650 mg × 2) by mouth three times days × 5 days[35–37]	Fatigue, abdominal, back, or muscle pain

(*Continued*)

Table 49–1

Therapeutic Agents for Selected Menstrual Disorders (*Continued*)

Specific Menstrual Disorders(s)	Agent(s)	Dose Recommended	Common Adverse Effects
PCOS-related amenorrhea and/or anovulatory bleeding	If pregnancy is an immediate goal: Clomiphene[6] plus insulin-sensitizing agent Or Letrozole plus insulin-sensitizing agent	Clomiphene: 50 mg by mouth daily × 5 days starting 3–5 days after the start of menses; doses up to 100 mg by mouth daily have been used in significantly obese patients Letrozole: 2.5–7.5 mg by mouth cycle days 3–7[23] Metformin[a,c]: 1500–2000 mg by mouth daily in 2–3 divided doses	Clomiphene: Hot flashes, ovarian enlargement, thromboembolism, blurred vision, breast discomfort Letrozole: Hot flashes, fatigue, dizziness, edema Metformin: Anorexia, nausea, vomiting, diarrhea, flatulence, lactic acidosis
	If pregnancy is not an immediate goal: Insulin sensitizing agent +/- use of CHC containing an anti-androgenic progesterone or levonorgestrel IUD	Metformin[a,c]: 1500–2000 mg by mouth daily in 2–3 divided doses Oral CHC: 35 mcg or less ethinyl estradiol and progesterone with antiandrogenic effects (eg, drospiernone) Levonorgestrel IUD: 20 mcg released daily	As noted above
	Women with side effects or contraindications to estrogen: Medroxyprogesterone acetate (oral)[a]	10 mg by mouth × 10 days[17]	As noted above
	Depot medroxyprogesterone acetate[a]	150 mg intramuscularly every 12 weeks	

[a]Use is contraindicated in patients with severe hepatic impairment.

[b]Not recommended in patients with severe renal impairment.

[c]Use is contraindicated with creatinine clearance < 30 mL/min (0.5 mL/s).

CEE, conjugated equine estrogen; CHC, combination hormonal contraceptive; GI, gastrointestinal; HDL, high-density lipoprotein; IUD, intrauterine device; LDL, low-density lipoprotein; NSAIDs, nonsteroidal anti-inflammatory drugs; PCOS, polycystic ovary syndrome.

have had vaginal intercourse due to high risk of PID. Adolescents who have never had vaginal intercourse do not require a pelvic examination.[4] NSAIDs are the preferred initial treatment in adolescents, followed by hormonal treatment. KEY CONCEPT Adolescents with symptoms unresponsive to NSAID therapy for three menstrual periods should be offered hormonal therapy.[5] If symptoms do not improve within 6 months of NSAIDs and CHC, further evaluation through laparoscopy is indicated. CHC also provides effective contraception, which may be desired for sexually active adolescents.

Patient Encounter 1, Part 2

Additional workup reveals:

PMH: Seasonal allergic rhinitis

PSH: Appendectomy at age 15

FH: Mother and father alive and well; two younger siblings (ages 8 and 13), both alive and well

SH: (–) tobacco use; (–) illicit drug use; (–) alcohol use

Medications: Cetirizine 10 mg once daily as needed for allergies

Past Gynecologic History: Menarche at age 11; never pregnant; (–) sexual activity; (+) history of painful menses beginning at age 12; (+) heavy menstrual flow; menstrual cycle 27–30 days

ROS: (+) fatigue with menses; (–) headaches; (+) mild acne on face, chest, and upper back; (+) moderate to severe pelvic pain radiating to lower back with menses

PE:

General: Thin, white woman, in no acute distress

VS: BP 112/72, P 68, RR 14, Wt 126 lbs (57.2 kg), Ht 5′8″ (173 cm), BMI: 19.2 kg/m^2

HEENT: (–) hirsutism

Breasts: (–) galactorrhea

Pelvic examination: Normal appearance of external genitalia and vagina, cervix without lesions, uterus midposition without masses

Labs: (–) hCG

Given this information, what is your assessment of this patient's condition?

Identify the treatment goals for this patient.

What nonpharmacologic therapies are recommended for this patient?

Is the patient's self-treatment with acetaminophen appropriate? Why or why not?

What pharmacologic therapies are recommended for this patient?

AMENORRHEA

Amenorrhea is the absence of menses. **Primary amenorrhea** is failure to reach menarche. Evaluation for amenorrhea should occur if there is no pubertal development by age 13, menarche has not occurred within 5 years after initial breast development, or the patient is 15 years or older.[9-11] **Secondary amenorrhea** is the cessation of menses for 3 months in a previously regular menstruating woman, or 6 months in a previously irregular menstruating woman.[9]

Epidemiology and Etiology

KEY CONCEPT Unrecognized pregnancy is the most common cause of amenorrhea; therefore, a urine pregnancy test should be one of the first steps in evaluating amenorrhea. Amenorrhea not related to pregnancy, lactation, or menopause occurs in 3% to 4% of women.[11] Primary amenorrhea is often caused by chromosomal irregularities resulting in primary ovarian insufficiency or anatomic abnormalities.[9] Causes of secondary amenorrhea include **polycystic ovary syndrome** (PCOS), hypothalamic suppression, hyperprolactinemia, or primary ovarian insufficiency.[9] Additional causes include undernutrition or anorexia and excessive exercise.

LO 1

Pathophysiology

Normal menstrual cycle physiology depends on hormonal interactions involving the hypothalamus, anterior pituitary gland, ovary, and endometrium (Figure 49–2).[5,9] Table 49–2 shows causative condition(s) and the organ system(s) involved in the pathophysiology of amenorrhea. Amenorrhea is a potential side effect from using low-dose or extended oral CHCs, depot medroxyprogesterone acetate, or levonorgestrel-releasing IUD.[9,12] Many women experience delayed return of menses after discontinuing hormonal contraception. If resolution of amenorrhea does not occur within 3 to 6 months after discontinuing contraception, evaluation for other conditions should be considered (eg, PCOS).

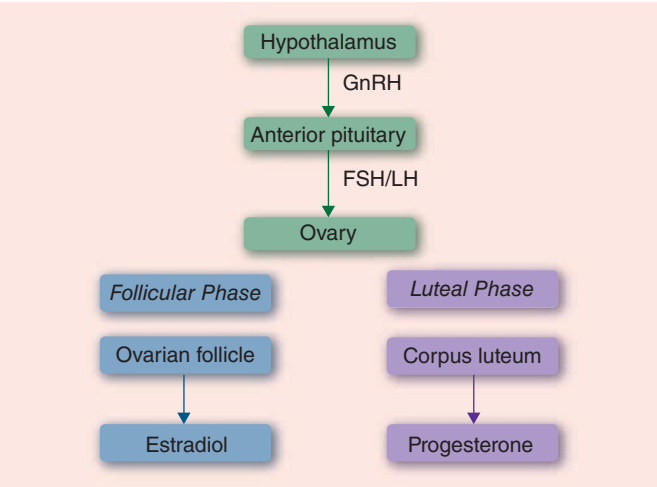

FIGURE 49–2. Hormonal fluctuations with the normal menstrual cycle. (FSH, follicle-stimulating hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone.) (Data from Umland EM, Klootwyk J. Menstruation-related disorders. In: Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014, with permission.)

Treatment

▶ *Desired Outcomes*

LO 4

Treatment goals include ensuring normal puberty is occurring, restoring the normal menstrual cycle, preserving bone density, preventing bone loss, improving quality of life, and restoring ovulation, thus improving fertility.[9,13] Amenorrhea attributable to hypoestrogenism (eg, premature ovarian insufficiency) can cause hot flashes and dyspareunia, thus reduction of those symptoms becomes an additional goal.

▶ *Nonpharmacologic Therapy*

LO 3

Nonpharmacologic therapy depends on the underlying cause. Amenorrhea secondary to undernutrition or anorexia may respond to weight gain and psychotherapy.[11] If excessive exercise is the cause, exercise reduction is recommended.[9]

▶ *Pharmacologic Therapy*

LO 3

Estrogen/Progestin Replacement Therapy KEY CONCEPT For most conditions associated with primary or secondary amenorrhea, estrogen treatment is recommended. To minimize risk of endometrial hyperplasia and cancer, progestin should also be given to women with an intact uterus. Estrogen's role is to reduce osteoporosis risk, stimulate and maintain secondary sexual characteristics, and improve quality of life.[11] Table 49–1 lists the types and doses of estrogen and progestin therapy for amenorrhea.

Dopamine Agonists In women with hyperprolactinemia with or without a pituitary tumor, dopamine agonists are the preferred treatment.[11] Dopamine agonists restore normal prolactin levels and resolve amenorrhea. Additionally, they restore ovulation in 80% to 90% of women.[14] Bromocriptine and cabergoline are the most commonly studied agents, with cabergoline being more effective in resolving amenorrhea.[14,15]

Progestins Progestins are commonly used to induce withdrawal bleeding in women with secondary amenorrhea. Efficacy varies depending on the formulation used. Withdrawal bleeding occurs with intramuscularly injected progesterone and oral medroxyprogesterone acetate in 70% and 95% of patients, respectively.[16] The usual dose of medroxyprogesterone acetate is 10 mg orally once daily for 7 to 10 days.[9]

Insulin-Sensitizing Agents PCOS-induced amenorrhea may respond well to insulin sensitizing agents.[17] Using metformin for this purpose is discussed in the anovulatory bleeding section.

All patients experiencing amenorrhea should follow a diet rich in calcium and vitamin D to support bone health. Supplemental calcium and vitamin D (1200 mg/800 International Units per day) should be recommended for patients with inadequate dietary consumption.[9] Figure 49–3 illustrates treatment recommendations for amenorrhea.[9]

Amenorrhea in Adolescents

Adolescence is when peak bone mass is achieved. The cause of amenorrhea and appropriate treatment must be identified promptly because hypoestrogenism negatively impacts bone development.[11] Estrogen replacement, typically through a CHC, is recommended. Although recent data suggest that CHCs and depot medroxyprogesterone acetate may reduce bone mineral density (BMD) for short term, their long-term effects on

Table 49–2

Pathophysiology of Selected Menstrual Bleeding Disorders[9,17,19,25,40]

Organ System	Condition	Pathophysiology/Laboratory Findings
Amenorrhea[9,40]		
Uterus	Asherman syndrome	Postcurettage/postsurgical uterine adhesions
	Congenital uterine abnormalities	Abnormal uterine development
Ovaries	Turner syndrome	Lack of ovarian follicles
	Gonadal dysgenesis	Other genetic anomalies
	Premature ovarian failure	Early loss of follicles
	Chemotherapy/radiation	Gonadal toxins
Anterior pituitary	Pituitary prolactin-secreting adenoma	↑ Prolactin suppresses HPO axis
	Hypothyroidism	TRH causing ↑ prolactin, other abnormalities
	Medications—antipsychotics, verapamil	↑ Prolactin suppresses HPO axis
Hypothalamus	"Functional" hypothalamic amenorrhea	↓ Pulsatile GnRH secretion in the absence of other abnormalities
	Disordered eating	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to weight loss
	Excessive exercise	↓ Pulsatile GnRH secretion, ↓ FSH and LH secondary to low body fat
	Anovulation/PCOS	Asynchronous gonadotropin and estrogen production, abnormal endometrial growth
Anovulatory Bleeding[17,19]		
Physiologic causes	Adolescence	Immature HPO axis: no LH surge
	Perimenopause	Declining ovarian function
Pathologic causes	Hyperandrogenic anovulation (PCOS, congenital adrenal hyperplasia, androgen-producing tumors)	Hyperandrogenism: high testosterone, high LH, hyperinsulinemia, and insulin resistance
	Hypothalamic dysfunction (physical or emotional stress, exercise, weight loss, anorexia nervosa)	Suppression of pulsatile GnRH secretion and estrogen deficiency: low LH, low FSH
	Hyperprolactinemia (pituitary gland tumor, psychiatric medications)	High prolactin
	Hypothyroidism	High TSH
	Premature ovarian failure	High FSH
Abnormal Uterine Bleeding[25]		
Hematologic	von Willebrand disease	Factor VII defect causing impaired platelet adhesion and increased bleeding time
	Idiopathic thrombocytopenic purpura	Decrease in circulating platelets—can be acute or chronic
Hepatic	Cirrhosis	Decreased estrogen metabolism, underlying coagulopathy
Endocrine	Hypothyroidism	Alterations in HPO axis
Uterine	Fibroids	Alteration of endometrium, changes in uterine contractility
	Adenomyosis	Alteration of endometrium, changes in uterine contractility
	Endometrial polyps	Alteration of endometrium
	Gynecologic cancers	Various dysplastic alterations of endometrium, uterus, cervix

↑, high; ↓, low; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPO, hypothalamic-pituitary-ovarian axis; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

fractures are unknown. The effects on BMD appear to be reversible; therefore, CHCs are recommended in the adolescent population.[18] Ensuring adequate dietary or supplemental calcium and vitamin D intake in this population is imperative.

ANOVULATORY BLEEDING

Anovulatory uterine bleeding (AUB) is irregular menstrual bleeding from the endometrium ranging from light spotting to heavy blood flow.[19] KEY CONCEPT It includes noncyclic menstrual bleeding due to ovulatory dysfunction (AUB-O), including anovulation or oligo-ovulation.[19] AUB-O is secondary to the effects of unopposed estrogen and does not include bleeding due to an uterine anatomic lesion. Many women pursue medical care to regulate menstrual cycles or improve fertility.

Epidemiology and Etiology

LO 1

AUB is the most common form of noncyclic uterine bleeding. PCOS is the most common cause, occurring in 5% to 10% of women, and is responsible for 55% to 91% of ovulatory dysfunction cases.[17,19] It typically presents with irregular menstrual bleeding, hirsutism, obesity, and/or infertility. Anovulation results from dysfunction at any level of the hypothalamic-pituitary-ovarian (HPO) axis which can be due to physiologic life stages such as adolescence, perimenopause, pregnancy, and lactation or pathologic causes (see Table 49–2).[10,19] Anovulation may also occur at any time during the reproductive years due to a pathologic cause. The most common causes of nonphysiologic ovulatory dysfunction are PCOS, hypothalamic amenorrhea, hyperprolactinemia, and premature ovarian failure.

Clinical Presentation and Diagnosis of Amenorrhea

LO 2

General

- Concerns about cessation of menses and fertility implications
- Generally no acute distress

Symptoms

- Cessation of menses
- Possible reports of infertility, vaginal dryness, decreased libido

Signs

- Absence of menses by age 15 in the presence of normal secondary sexual development or within 5 years of thelarche (if occurs before age 10)
- Recent significant weight loss or gain
- Presence of acne, hirsutism, hair loss, or acanthosis nigricans suggest androgen excess

Laboratory Tests

- Pregnancy test
- Thyroid Stimulating Hormone (TSH)
- Prolactin
- If PCOS is suspected, consider free or total testosterone, 17-hydroxyprogesterone, fasting glucose, and fasting lipid panel
- If premature ovarian failure is suspected, consider follicle-stimulating hormone (FSH) and luteinizing hormone (LH) measurements

Other Diagnostic Tests

- Pelvic ultrasound to evaluate for polycystic ovaries
- May consider progesterone challenge, by administering either progesterone 100–200 mg intramuscular injection or oral medroxyprogesterone acetate 10 mg daily for 5–10 days to see if it induces a menstrual period. If bleeding occurs beyond spotting within 2 weeks after progesterone is given, the amenorrhea is due to anovulation. If no withdrawal bleeding occurs, amenorrhea is due to other causes.

Pathophysiology

LO 1

During a normal ovulatory cycle, the ovary produces a mature, estrogen-secreting follicle in response to FSH release from the pituitary gland. The endometrium proliferates and undergoes secretory changes throughout the cycle, first due to ovarian production of estrogen alone, followed by a combination of estrogen and progesterone. The presence of progesterone halts endometrial growth and stimulates endometrial differentiation. At cycle end, if conception and implantation do not occur, estrogen and progesterone withdrawal begins, leading to menstrual flow as the endometrium sloughs. In anovulation, a corpus luteum does not develop, and the ovary fails to secrete progesterone. This causes the endometrium to continue proliferation under the influence of unopposed estrogen, and eventually it becomes thick, vascular, and fragile. The clinical result is unpredictable, heavy, noncyclic bleeding, as sporadic sloughing of the endometrium begins to occur.[19] Chronic anovulatory cycles and unopposed estrogen secretion lead to increased risk of polyps, endometrial hyperplasia, and endometrial carcinoma (see Table 49–2).

Treatment

▶ *Desired Outcomes*

LO 4

The desired outcomes are to stop acute bleeding, restore natural cycle of endometrial growth and shedding, decrease long-term complications of anovulation (eg, osteopenia and infertility), and improve quality of life.[19]

▶ *Nonpharmacologic Therapy*

LO 3

Nonpharmacologic treatment options depend on the underlying cause. For women with PCOS, weight loss may be beneficial. In overweight or obese women, a 5% weight reduction is associated with resumption of menses, improved pregnancy rates, and decreased hirsutism, glucose, and lipid levels.[17] In women who have completed childbearing or who have failed medical management,

Patient Encounter 2

A 38-year-old woman presents for a routine gynecologic examination. She started menarche at age 11; her last period was 4 months ago. Her periods are irregular, and occur every 2 to 4 months. All previous Pap smears have been normal, and she denies a history of sexually transmitted infections. She reports history of one sexual partner, her husband, of 20 years. Currently sexually active, she is not on any form of contraception, and does not desire any more children. Reports history of one pregnancy, after three courses of clomiphene due to "follicles" on her ovaries, after several years of infertility. PMH significant for diabetes and hypertension. Current medications include metformin 1000 mg twice daily and lisinopril 20 mg once daily. On examination, patient is overweight with mild hirsutism.

Labs: (–) hCG; free testosterone 105 ng/dL (3.6 nmol/L; elevated); TSH 2.4 µIU/mL (mIU/L; WNL); prolactin 8 ng/mL (mcg/L; WNL); fasting glucose 122 mg/dL (6.8 mmol/L); total cholesterol 192 mg/dL (4.97 mmol/L); LDL cholesterol 115 mg/dL (2.97 mmol/L), HDL cholesterol 60 mg/dL (1.55 mmol/L); triglycerides 68 mg/dL (0.77 mmol/L)

Pelvic ultrasound: 15 follicles in right ovary, 11 follicles in left ovary; increased ovarian volume of 13 mL

What anovulatory disorder is this patient most likely experiencing?

What signs/symptoms support your conclusion?

What pharmacologic therapies are recommended for this patient?

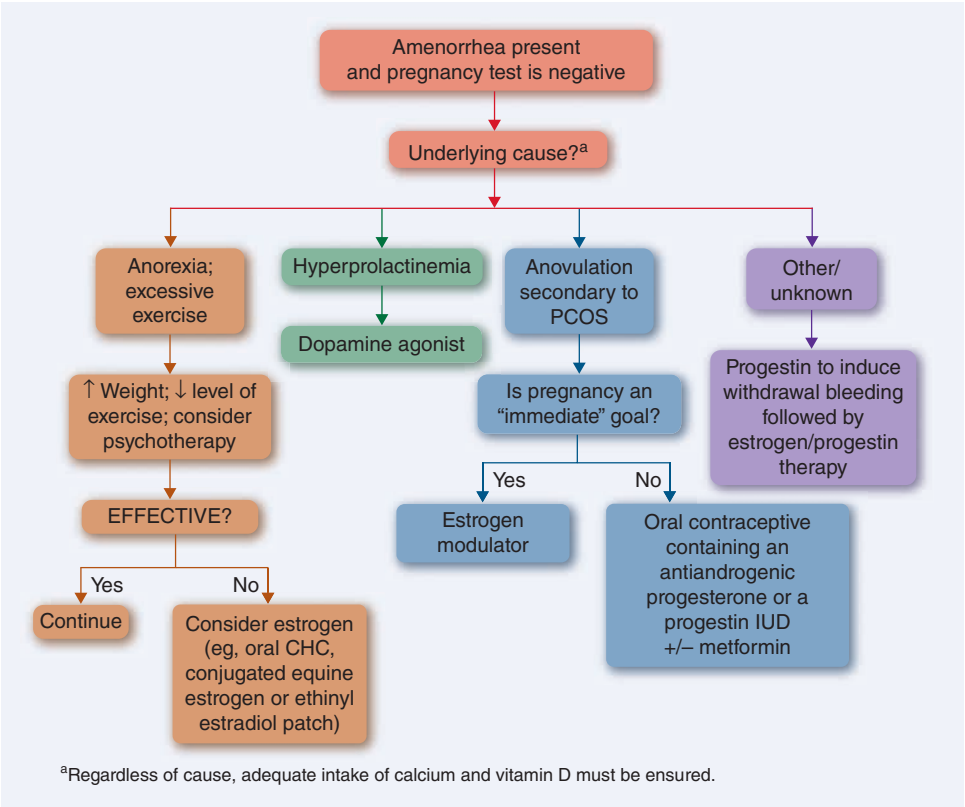

FIGURE 49–3. Treatment algorithm for amenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; PCOS, polycystic ovary syndrome.) (Data from Umland EM, Klootwyk J. Menstruation-related disorders. In: Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014, with permission.)

endometrial ablation or resection, and hysterectomy are surgical options. The preferred procedure is unclear. For short term, it appears ablation or resection results in less morbidity and shorter recovery periods.[20] However, a significant number of these women undergo hysterectomy within 5 years.[19]

▶ *Pharmacologic Therapy*

LO 3

Estrogen Table 49–1 summarizes therapeutic agents and doses. Estrogen is the recommended treatment for managing acute bleeding episodes because it promotes endometrial growth and stabilization.[19] Long-term therapy with a CHC reduces the risk of endometrial cancer compared to unopposed estrogen therapy.[9] CHCs suppress ovarian hormones and adrenal androgen production and indirectly increase sex hormone–binding globulin (SHBG). This, in turn, binds and reduces circulating androgen.[17,19,21] Women with high androgen levels or signs of hyperandrogenism (eg, hirsutism, acne) are recommended to start low-dose CHCs (35 mcg or less ethinyl estradiol).[19] CHCs with low-dose estrogen and a progesterone that exhibits minimal androgenic side effects (eg, norgestimate or desogestrel) or with antiandrogenic effects (eg, drospirenone) may be considered.[22] However, to date, there is no consensus regarding the best CHC choice for treating PCOS.[17]

Medroxyprogesterone Acetate Women who experience side effects or have contraindication(s) to estrogen, or who have abnormal uterine bleeding due to anovulatory bleeding, should consider progesterone-only products. For women with PCOS, depot and intermittent oral medroxyprogesterone acetate suppress pituitary gonadotropins and circulating androgens, leading to endometrial shedding.[17] If contraception is desired, placement of a levonorgestrel-releasing IUD is an option.

Estrogen Modulators If pregnancy is an immediate goal, clomiphene may be used to induce ovulation. Oral medroxyprogesterone acetate 10 mg/day for 10 days is initiated to induce withdrawal bleeding, followed by clomiphene citrate 50 mg/day for 5 days, cycle days 3 through 5. If ovulation does not

LO 2

Clinical Presentation and Diagnosis of Anovulatory Bleeding

General

- Acute distress may or may not be present.

Symptoms

- Irregular, heavy, or prolonged vaginal bleeding, perimenopausal symptoms (hot flashes, night sweats, vaginal dryness, dyspareunia)

Signs

- Acne, hirsutism, obesity

Laboratory Tests

- If suspect PCOS: free or total testosterone, fasting glucose, fasting lipid panel
- If suspect perimenopause: TSH and FSH

Other Diagnostic Tests

- Pelvic ultrasound to evaluate for polycystic ovaries

occur, the dose may be increased to 100 mg/day. Approximately 50% of women who are going to conceive using clomiphene do so at the 50 mg/day dose, and another 20% conceive at the 100 mg/day dose.[17]

Recent data have shown beneficial effects with the use of letrozole to improve fertility. In a large trial, when compared to clomiphene citrate, letrozole had a statistically higher live birth rate with a similar adverse effect profile. Additional trials are needed to support this finding.[22,23]

Insulin-Sensitizing Agents Metformin improves insulin sensitivity and is recommended in women who cannot tolerate CHC and have impaired glucose tolerance (IGT) or type-2 diabetes mellitus.[22] KEY CONCEPT In patients with PCOS, metformin reduces circulating androgen concentrations, increases ovulation rates, and improves glucose tolerance, due to the SHBG increase that occurs via increased insulin sensitivity. Additionally, metformin may decrease cardiovascular risk and promote weight loss.[17] Notably, metformin is not recommended as monotherapy to improve ovulation and fertility. Limited data have shown adding metformin to clomiphene may increase pregnancy rates, especially in obese women with PCOS who are resistant to clomiphene monotherapy.[17,22,24] Thiazolidinediones are no longer recommended due to a poor risk-benefit ratio.[22]

Anovulatory Bleeding in Adolescents

Anovulation is the most common cause of AUB in adolescents. Anovulatory bleeding in teenagers can become excessive, persistent, and require medications to treat. The differential diagnosis is similar to adults, and should include evaluation for blood dyscrasias.[19,25] Patients should also be evaluated for PCOS by assessing for signs of hyperandrogenism, including acne and hirsutism.[19]

Blood dyscrasias are treated based on guideline recommendations. Adolescents with chronic anovulation are treated with low-dose CHCs (20–35 mcg of ethinyl estradiol).[19] Extended cycle therapies can be utilized to extend the interval of menstruation, which allows for resolution of anemia, mental recovery from prolonged acute bleeding, and time for additional imaging or consultations as needed. Patients with acute, severe bleeding may require brief hospitalization and treatment with high-dose estrogen. If the patient is overweight or obese, lifestyle changes are also recommended first-line, and if IGT or metabolic syndrome is present, metformin is often recommended.[22]

ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding describes prolonged menstrual bleeding (lasting > 7 days) or cyclic, heavy menstrual bleeding (> 80 mL per cycle).[26-28] It can be difficult to quantify menstrual blood loss in clinical practice. Many women with less than 80 mL of blood loss seek medical attention with concerns of containment flow problems, unpredictable heavy flow, reduced quality of life, anemia, and other dysmenorrhea symptoms.[27]

Epidemiology and Etiology

Abnormal uterine bleeding occurs in an estimated 10% of women, although as high as 30% will seek treatment for the condition.[8]

LO 1 KEY CONCEPT Causes of abnormal uterine bleeding is divided into systemic disorders and reproductive tract abnormalities. KEY CONCEPT Women presenting with heavy menses should be examined to rule out intrauterine pregnancy, ectopic pregnancy, and miscarriage. Additionally, genital tract malignancies and infections may present with abnormal bleeding.[19] Systemic disorders include coagulation dysfunction such as von Willebrand disease, hemophilia, and platelet function disorders, in addition to hypothyroidism.[19,25,26] Specific reproductive tract causes of abnormal uterine bleeding are more common in older childbearing women, and include fibroids, adenomyosis, endometrial polyps, PID, and gynecologic malignancies.[29,30]

LO 2

Clinical Presentation and Diagnosis of Abnormal Uterine Bleeding

General

- Acute distress may or may not be present.

Symptoms

- Reports of heavy/prolonged menstrual flow. Associated symptoms may include dysmenorrhea, fatigue, or lightheadedness in the case of severe blood loss.

Signs

- Orthostasis, tachycardia, and pallor may be noted, especially with significant acute blood loss.

Laboratory Tests

- Complete blood count (CBC) and ferritin levels; hemoglobin and hematocrit results may be low.
- TSH to rule out thyroid deficiencies
- If the history dictates, testing may be done to identify coagulation disorder(s) as a cause.

Other Diagnostic Tests

- Pelvic ultrasound
- Pelvic magnetic resonance imaging (MRI)
- Papanicolaou smear
- Endometrial biopsy
- Hysteroscopy
- Sonohysterogram

Pathophysiology

Table 49–2 describes the pathophysiology of abnormal uterine bleeding and specific conditions resulting in abnormal uterine bleeding.

Treatment

▶ *Desired Outcomes*

LO 4 Goals of therapy include reducing menstrual blood flow, preventing or correcting iron-deficiency anemia, improving quality of life, and deferring the need for surgical intervention. Treatment recommendations are outlined in Table 49–1 and Figure 49–4.

▶ *Nonpharmacologic Therapy*

LO 3 Surgical interventions may be considered, and are based on the clinical stability of the patient, severity of bleeding, contraindications to medical management, and patient response to medical management. Options include dilation and curettage, endometrial ablation, uterine artery embolization, and hysterectomy and choice is often guided based on the patient's desire to maintain fertility.[19]

▶ *Pharmacologic Therapy*

LO 3 NSAIDs are first-line treatment for abnormal uterine bleeding associated with ovulatory cycles in women who do not desire

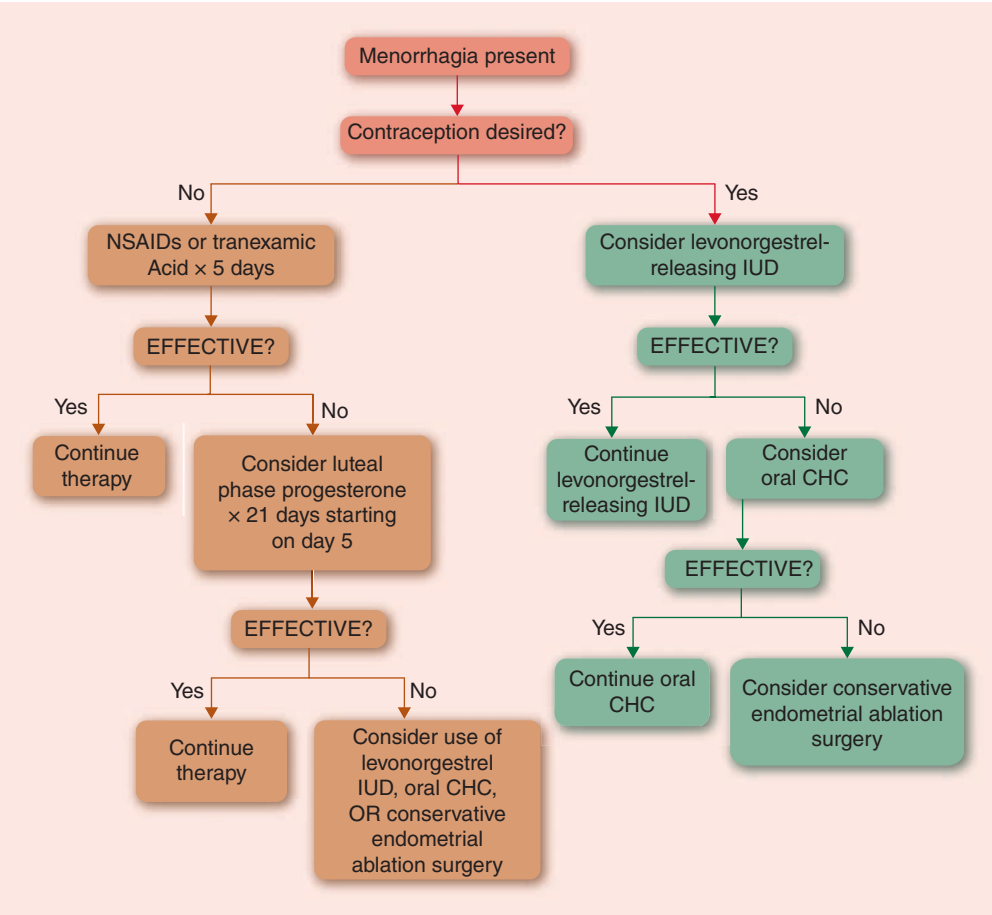

FIGURE 49–4. Treatment algorithm for abnormal uterine bleeding. (CHC, combination hormonal contraceptive; IUD, intrauterine device; NSAID, nonsteroidal anti-inflammatory drug.) (Data from Umland EM, Klootwyk J. Menstruation-related disorders. In: Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014, with permission.)

contraception or hormonal therapy.[21] They can be taken only during menses, and result in up to a 40% reduction in blood loss.[31] KEY CONCEPT This reduction is directly proportional to the amount of pretreatment blood loss.[32] NSAIDs are also beneficial if the patient is experiencing dysmenorrhea with the abnormal uterine bleeding.

Patient Encounter 3

A 15-year-old adolescent girl presents reporting moderate pelvic pain and cramping during menses. She notes her periods are "heavy" and require a change in super-size tampon every 2–3 hours. She reports issues with flow containment, and associated embarrassment. She has noticed over the last few months, she feels tired and her hair has thinned. Her last menstrual cycle was 10 days ago, and she entered menarche at age 10. She is not sexually active and she does not take any medications. She plays basketball for the high school team, and runs during the off season.

What diagnostic tests should be considered for the patient?

What nonpharmacologic and pharmacologic therapies are recommended for this patient?

What monitoring parameters are recommended to assess efficacy and safety of the therapeutic options?

Combination Hormonal Contraceptives CHCs are beneficial to women with abnormal uterine bleeding who do not desire pregnancy, and considered first-line for patients with known or suspected bleeding disorders.[19] Blood loss can be reduced by up to 40% to 50% with use of cyclic CHCs.[8] Continuous and extended cycle options may also reduce the number of menstrual cycles, and may achieve amenorrhea in some women.[8] KEY CONCEPT As with NSAIDs, the reduction in blood loss is proportional to pretreatment blood loss.

Progestins Abnormal uterine bleeding may also be treated with progestin-only contraceptives. The levonorgestrel IUD reduces menstrual flow by up to 86% after 3 months, and up to 97% after 12 months of use. Additionally, 20% to 80% of women experience amenorrhea by month 12.[8,21,32,33] In a small open-label study, the levonorgestrel IUD resulted in a greater blood loss reduction and number of days missed at work or school when compared to oral CHCs.[34] When compared to endometrial ablation, the levonorgestrel IUD causes similar reductions in menstrual blood loss and improved quality of life after 6, 12, and 24 months.[8] Its use may also help postpone or cancel the need for endometrial ablation or hysterectomy.

Cyclic progestin therapy, either during the luteal phase or for 21 days of the menstrual cycle, leads to regulation of the menstrual cycle in 50% of women.[31] A comparison of oral norethindrone and the levonorgestrel IUD concluded that IUD therapy is more effective, and had higher patient satisfaction rates.[8] Oral progestin use has also not been shown to be superior to NSAIDs.

Table 49–3

Expected Outcome Measures for Selected Menstrual Bleeding Disorders[10,12,19,25,28]

Menstrual Disorder	Expected Outcome Measures
Dysmenorrhea	*Efficacy:* Reduction in menses-related pelvic pain; reduction in time lost from work/school; improved quality of life. *Time to relief/effect:* Improvement in pain may be observed within hours of NSAID therapy; improvement with other options such as oral CHCs may be observed after a full 1–3 cycles of use.
Amenorrhea	*Efficacy:* Normal breast development (especially primary amenorrhea in adolescents); BMD preservation/improvement; return of menses. *Time to relief/effect:* Menses should occur within 1–2 months of therapy.
Anovulatory bleeding	*Efficacy:* Alleviation of acute bleeding when present; ovulation and subsequent pregnancy in women desiring this; reduced risk of developing the long-term complications of PCOS (eg, diabetes and cardiovascular disease); improved quality of life. *Time to relief/effect:* The acute treatment of heavy bleeding should reduce bleeding within 10 days of therapy onset; return of ovulation may require several months of therapy; when oral CHCs are used, abnormal bleeding control can be expected within 1–2 treatment cycles.
Abnormal uterine bleeding	*Efficacy:* Decline in amount of blood loss with menses (monitor a decline in the number of times feminine hygiene products such as pads and tampons require changing during menses); increase in hemoglobin/hematocrit if anemia was present as because of abnormal uterine bleeding. *Time to relief/effect:* A decline in menstrual blood loss should be realized within 1–2 cycles of therapy initiation.

BMD, bone mineral density; CHCs, combination hormonal contraceptives; NSAID, nonsteroidal anti-inflammatory drug; PCOS, polycystic ovary syndrome.

Progestin-related side effects are typically greater in women using the levonorgestrel-releasing IUD when compared with oral progestin, and often include intermenstrual bleeding and breast tenderness.[8]

Tranexamic Acid Tranexamic acid works by preventing fibrin degradation, and is effective for patients with chronic abnormal uterine bleeding.[19] Evidence has shown that its use reduces bleeding in patients with chronic issues by 30% to 55%.[19] While an immediate-release product has been available for a long time, a modified-release product has recently become available. It has better gastrointestinal tolerability and gives women another nonhormonal option to manage abnormal uterine bleeding.[35,36] Additionally, it can be recommended for women with von Willebrand disease.

Abnormal Uterine Bleeding in Adolescents

An estimated 50% of adolescents with abnormal uterine bleeding have a bleeding disorder, most commonly von Willebrand disease or platelet dysfunction.[25] The incidence of von Willebrand disease is 1% to 2% in the general population; however, an estimated 5% to 36% of adolescents presenting with heavy menses have von Willebrand disease.[12,25] In addition, 74% to 92% of women with von Willebrand disease have abnormal uterine bleeding.[37] Platelet function disorders exist in 2% to 44% of adolescents with abnormal uterine bleeding.[25]

OUTCOME EVALUATION

Treatment success for menstruation-related disorders is measured by how well the treatment (a) relieves or reverses symptoms, (b) prevents or alleviates complications (eg, osteoporosis, anemia, and infertility), and (c) causes minimal adverse effects. A regular menstrual cycle should resume, with minimal premenstrual or dysmenorrhea symptoms. Depending on the desire for conception and related therapy, these cycles may be ovulatory or anovulatory.

LO 5

Assess treatment effectiveness in restoring normal menstrual cycles with minimal adverse effects after an appropriate treatment interval (1–2 months). Assess improvement in well-being and quality-of-life (eg, physical, psychological, and social functioning). Evaluate the patient for adverse drug reactions (see Table 49–1), drug allergies, and drug interactions. Table 49–3 lists the expected outcome measures for each discussed menstruation-related disorder.

Patient Care Process

Collect Information:

- Review medical history and physical assessment findings, and complete physical examination and review of systems, including gynecological history (eg, start of menarche, presence of galactorrhea, symptoms of androgen excess, review of typical menstrual cycle including frequency, duration, and associated symptoms, sexual history, and history of gynecological infections). Additional workup may be necessary depending on patient's presenting problem(s) (eg, amenorrhea, abnormal uterine bleeding, AUB, or PCOS), including a pregnancy test or pelvic examination.
- Perform medication history for use of prescription, nonprescription, and dietary supplements. Determine if any treatments have previously helped with chief complaint(s). Identify allergies to medications or other substances.
- Review current and future desire for children and contraception beliefs and preferences with the patient.

(*Continued*)

Patient Care Process *(Continued)*

Assess the Information:

- Based on medical history and presenting symptoms, determine which menstruation-related disorder the patient currently has.
- Review available diagnostic data to determine hormonal, reproductive, and pregnancy status.
- Document presenting symptoms and medical history, including pertinent family medical history.
- Based on physical examination, review of symptoms, and patient history, determine if patient is experiencing signs or symptoms of complications from menstruation-related disorder, such as symptoms of anemia in women presenting with abnormal uterine bleeding, or difficulty conceiving in women with amenorrhea or anovulatory bleeding.
- Assess the appropriateness, efficacy, safety, and adherence of current therapy.

Develop a Care Plan:

- Educate patient on lifestyle modifications and nonpharmacological therapy that will improve symptoms and prevent complications.
- Select pharmacotherapy, if indicated, that is safe and effective.
- Determine whether long-term maintenance treatment is necessary.
- Discuss the importance of adherence to medication management and lifestyle modifications.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about their menstruation-related disorder and its management.
- Address any secondary concerns the patient may be experiencing (eg, infertility, anemia, decline in quality of life).
- Determine whether the patient has insurance coverage or whether recommended agents are included on the patient's insurance formulary.

Follow-up: Monitor and Evaluate:

LOS

- Follow up in 3–6 month intervals, or more frequently if needed, to assess efficacy and safety of therapy until goals are met, or symptoms resolve.
- Assess improvement in quality of life.
- Review medical history, physical examination findings, and laboratory and diagnostic tests to assess changes in clinical status and continued need for pharmacological therapy.
- Evaluate for adverse drug reactions, drug allergies, and drug interactions.

ACKNOWLEDGMENT

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Abbreviations Introduced in This Chapter

ACOG	American College of Obstetricians and Gynecologists
AUB	Anovulatory uterine bleeding
BMD	Bone mineral density
BMI	Body mass index
CBC	Complete blood count
CHC	Combination hormonal contraceptive
FSH	Follicle-stimulating hormone
HCG	Human chorionic gonadotropin
HPO	Hypothalamic-pituitary-ovarian
IGT	Impaired glucose tolerance
IUD	Intrauterine device
LH	Luteinizing hormone
MRI	Magnetic resonance imaging
NSAID	Nonsteroidal anti-inflammatory drug
PCOS	Polycystic ovary syndrome
PID	Pelvic inflammatory disease
SHBG	Sex hormone–binding globulin
TSH	Thyroid stimulating hormone

REFERENCES

1. Osayande AS, Mehulic S. Diagnosis and initial management of dysmenorrhea. Am Fam Physician. 2014;89(5):341–346.
2. Dysmenorrhea: Painful Periods. American College of Obstetricians and Gynecologists. Available from: https://www.acog.org/Patients/FAQs/Dysmenorrhea-Painful-Periods. Accessed July 9, 2018.
3. Morrow C, Naumburg EH. Dysmenorrhea. Prim Care Clin Office Pract. 2009;36:19–32.
4. Ryan SA. The treatment of dysmenorrhea. Pediatr Clin North Am. 2017;64:331–342.
5. Harel Z. Dysmenorrhea in adolescents. Ann NY Acad Sci. 2008;1135:185–195.
6. Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. Expert Opin Pharmacother. 2012; 13:2157–70.
7. Marjoribanks J, Ayeleke RO, Farquhar C, Proctor M. Nonsteroidal anti-inflammatory drugs for dysmenorrhea. Cochrane Database Syst Rev. 2015;CD001751.
8. Noncontraceptive uses of hormonal contraceptives. ACOG Practice Bulletin No. 110. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2010 (reaffirmed 2014);115:206–218.
9. Klein DA, Poth MA. Amenorrhea: an approach to diagnosis and management. Am Fam Physician. 2013;87:781–788.
10. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. ACOG Committee Opinion No. 349. American Academy of Pediatrics; American College of Obstetricians and Gynecologists. Obstet Gynecol. 2006 (Reaffirmed 2009);108:1323–1328.

11. Current evaluation of amenorrhea. The Practice Committee of the American Society for Reproductive Medicine. Fertil Steril. 2008;90:S219–S225.
12. Adams Hillard PJ. Menstruation in adolescents what's normal, what's not. Ann NY Acad Sci. 2008;1135:29–35.
13. Heiman DL. Amenorrhea. Prim Care. 2009;36:1–17,vii.
14. Majumdar A, Mangal NS. Hyperprolactinemia. J Hum Reprod Sci. 2013 Jul-Sep;6(3):168–175.
15. Wang AT, Mullan RJ, Lane MA, Hazem A, Prasad C, Gathaiya NW, Fernandez-Balsells MM Bagatto A, Coto-Yglesias F Carey J, Elraiyah TA, Erwin PJ, Gandhi GY, Montori VM, Murad MH. Treatment of hyperprolactinemia: a systematic review and meta-analysis. Systematic Reviews. 2012;1:33.
16. Simon JA. Progestogens in the treatment of secondary amenorrhea. J Reprod Med. 1999;44:185–189.
17. Polycystic ovary syndrome. ACOG'; Practice Bulletin No. 108. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2009 (Reaffirmed 2013); 114:936–949.
18. Tolaymat LL, Kaunitz AM. Use of hormonal contraception in adolescents: skeletal health issues. Curr Opin Obstet Gynecol. 2009;21(5):396–401.
19. Management of Abnormal Uterine Bleeding Associated with Ovulatory Dysfunction. ACOG Practice Bulletin No. 136 (2013). American College of Obstetricians and Gynecologists. Obstet Gynecol. 2013;122:176–185.
20. Munro MG, Dickersin K, Clark MA, Langenberg P, Scherer RW, Frick KD. The Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding: summary of an Agency for Health Research and Quality-sponsored randomized trial of endometrial ablation versus hysterectomy for women with heavy menstrual bleeding. Menopause. 2011;18(4):445–452.
21. Casablanca Y. Management of dysfunctional uterine bleeding. Obstet Gynecol Clin N Am. 2008;35:219–234.
22. Legro RS, Arslanian SA, Ehrmann DA. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2013;98: 4565–4592.
23. Legro RS, Brzyski RG, Diamond MP, et al.; NICDH Reproductive Medicine Network. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med. 2014;371: 119–129.
24. Khorram O, Helliwell JP, Katz S, Bonpane CM, Jaramillo L. Two weeks of metformin improves clomiphene citrate-induced ovulation and metabolic profiles in women with polycystic ovary syndrome. Fertil Steril. 2006;85(5):1448–1451.
25. Boswell HB. The adolescent with menorrhagia: why, who, and how to evaluate for a bleeding disorder. J Pediatr Adolesc Gynecol. 2011;24(4):228–230.
26. Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility, 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010:591–619.
27. Duckitt K. Menorrhagia. BMJ Clin Evid. 2015;09:805.
28. Matteson KA, Boardman LA, Munro MG, Clark MA. Abnormal uterine bleeding: a review of patient-based outcome measures. Fertil Steril. 2009;92(1):205–216.
29. Rao S. Menorrhagia. Obstet Gynaecol Reprod Med. 2011;21: 254–256.
30. Davies J, Kadir RA. Heavy menstrual bleeding: an update on management. Thromb Res. 2017;151(suppl 1):S70–S77.
31. Bradley LD, Gueye NA. The medical management of abnormal uterine bleeding in reproductive-aged women. Am J Obstet Gynecol. 2016;214(1):31–44.
32. Fraser IS, Porte RJ, Kouides PA, Lukes AS. A benefit-risk review of systemic haemostatic agents: part 2: in excessive or heavy menstrual bleeding. Drug Saf. 2008;31(4):275–282.
33. Long-Acting Reversible Contraception: implants and Intrauterine Devices. ACOG Practice Bulletin No. 121. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2011(Reaffirmed 2013);118:184–195.
34. Shaaban MM, Zekherah MS, El-Nashar SA Sayed GH. Levonorgestrel-releasing intrauterine system compared to low dose combined oral contraceptive pills for idiopathic menorrhagia: a randomized clinical trial. Contraception. 2011;83:48–54.
35. Kost A, Pitney C. Tranexamic acid (lysteda) for cyclic heavy menstrual bleeding. Am Fam Physician. 2011;84(8):883–886.
36. Hrometz SL. Oral modified-release tranexamic acid for heavy menstrual bleeding. Ann Pharmacotherapy. 2012;46(7–8): 1047–1053.
37. James AH, Kouides PA, Abdul-Kadir R et al. Von Willebrand disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel. Am J Obstet Gynecol. 2009;201:12e1–12e8.
38. Long-acting reversible contraception: implants and intrauterine devices. ACOG Practice Bulletin No. 121. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2011(Reaffirmed 2013);118:184–195.
39. Sweet MG, Schmidt-Dalton TA Weiss PM. Evaluation and management of abnormal uterine bleeding in premenopausal women. Am Fam Physician. 2012;85(1):35–43.
40. Deligeoroglou E, Athanasopoulos N, Tsimaris P, Dimopoulos KD, Vrachnis N, Creatsas G. Evaluation and management of adolescent amenorrhea. Ann NY Acad Sci. 2010;1205:23–32.

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50 Hormone Therapy in Menopause

Nicole S. Culhane and Regine Beliard

LEARNING OBJECTIVES

LO

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

1. Explain the physiologic changes associated with menopause.
2. Identify the signs and symptoms associated with menopause.
3. Determine the desired therapeutic outcomes for a patient taking hormone therapy (HT).
4. Explain how to evaluate a patient for the appropriate use of HT.
5. Recommend nonpharmacologic therapy for menopausal symptoms.
6. Explain the risks, benefits, and contraindications associated with HT.
7. Describe the circumstances by which nonhormonal therapies should be recommended.
8. Describe the monitoring parameters for a patient taking HT.

INTRODUCTION

Menopause is the permanent cessation of menses following the loss of ovarian follicular activity. The clinical diagnosis of menopause is made after a woman experiences amenorrhea for 12 consecutive months. The loss of ovarian follicular activity leads to an increase in follicle-stimulating hormone (FSH), which on laboratory examination may confirm the diagnosis.

The role of hormone therapy (HT) has changed dramatically. HT has long been prescribed for relief of menopausal symptoms and, until recently, has been purported to protect women from coronary heart disease (CHD). Recommending HT in postmenopausal women revolved around a simple theory: hormones lost during menopause could be replaced through drug therapy and protect women from both menopausal symptoms and sequelae of menopause. Recent studies have disproved this theory.

In 1996, the United States Preventive Services Task Force published its recommendations that not all postmenopausal women should be prescribed HT, but that therapy should be individualized based on risk factors. This recommendation was supported with publication of the Heart and Estrogen/Progestin Replacement Study (HERS) in 1998, which demonstrated that women with established CHD were at an increased risk of experiencing a myocardial infarction within the first year of HT use compared with similar women without CHD risk factors. As a result, the authors concluded that HT should not be recommended for secondary prevention of CHD.[1] In 2002, the Women's Health Initiative (WHI) study was published. This trial demonstrated that HT was not protective against CHD but rather could increase the risk in women with underlying CHD risk factors. The risk of breast cancer was also increased after a woman was on combination estrogen and progestogen for approximately 3 years. Notably, this was not the case with estrogen alone. As a result of this study, the US Food and Drug Administration (FDA) issued a statement that HT, in general, should not be initiated or continued for primary prevention of CHD.[2,3]

This trial led to changes in how HT is prescribed and greater understanding of the associated risks. Systemic HT should be used primarily to reduce the frequency and severity of moderate to severe **vasomotor symptoms** (VMS) associated with menopause in women without risk factors for CHD or breast cancer.

EPIDEMIOLOGY AND ETIOLOGY

Menopause is a period of time marked by loss of ovarian follicular activity, inadequate estradiol production, and the subsequent cessation of menses. The median age for women to experience menopause is 52 years. However, women who have undergone a **total abdominal hysterectomy with bilateral salpingo-oophorectomy** experience menopause earlier compared with women who experience natural menopause. Other factors associated with early menopause include low body weight, increased menstrual cycle length, **nulliparity**, and smoking. Smokers generally experience menopause approximately 2 years earlier than nonsmokers.[4]

Perimenopause, known as the climacteric, is the transitional period prior to menopause when hormonal and biologic changes begin. These changes may begin 2 to 8 years prior to menopause and eventually lead to irregular menstrual cycles, an increase in cycle interval, and a decrease in cycle length. During this time, women also may experience physical symptoms similar to menopausal symptoms, which may require treatment depending on symptom severity.[4]

Because the perimenopausal and postmenopausal periods are marked by many biologic changes, women should inform their health care provider when they experience any signs and symptoms in order to discuss the most appropriate therapy.

PHYSIOLOGY

Reproductive physiology is regulated primarily by the hypothalamic–pituitary–ovarian axis. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the

Clinical Presentation and Diagnosis of Menopause

Menopausal Symptoms

- Vasomotor symptoms
- Sleep disturbances
- Mood swings
- Vaginal dryness, dyspareunia
- Depression

Less Common Symptoms

- Fatigue
- Irritability
- Migraine
- Arthralgia
- Myalgia
- Decreased libido

Diagnosis

- Amenorrhea for 1 year
- FSH greater than 40 mIU/mL (IU/L)
- Fivefold increase in LH

anterior pituitary to secrete FSH and luteinizing hormone (LH). FSH and LH regulate ovarian function and stimulate the ovary to produce sex steroids. These hormones are influenced by a negative-feedback system and increase or decrease based on the levels of estradiol and progesterone.

LO 1 The physiologic changes that occur during the perimenopausal and menopausal periods are caused by the decrease and eventual loss of ovarian follicular activity. As women age, the number of ovarian follicles decreases. The remaining follicles require higher levels of FSH for maturation and ovulation. During perimenopause, **anovulatory cycles** are more likely. The lack of progesterone production leads to irregular and unpredictable menses. During menopause, FSH concentrations increase 10- to 15-fold, LH concentrations increase fivefold, and levels of circulating estradiol decrease more than 90%.[5]

Patient Encounter Part 1

A 53-year-old woman with a history of hypertension and hypothyroidism presents to the clinic complaining of hot flashes, vaginal dryness, dyspareunia, and insomnia. She states that she experiences approximately three hot flashes per day and is awakened from sleep at least two times a week requiring her to change her bed clothes. Her symptoms began about 3 months ago, and over that time, they have worsened to the point where they have become very bothersome. Upon questioning, she states she had a hysterectomy 1 year ago.

Which of the patient's symptoms and past medical history are consistent with menopause?

What additional information do you need to know in order to make an appropriate therapeutic plan for this patient?

LO 2 KEY CONCEPT Common symptoms of menopause include VMS and genitourinary syndrome of menopause (GSM), which includes **vulvovaginal atrophy**, vaginal dryness, and **dyspareunia**. Women less commonly may experience mood swings, depression, insomnia, arthralgia, myalgia, urinary frequency, and decreased **libido**. Menopausal symptoms tend to be more severe in women who undergo surgical menopause compared with natural menopause because of the more rapid decline in estrogen concentrations.[3] Women who seek medical treatment should undergo laboratory evaluation to rule out other conditions that may present with similar symptoms, such as abnormal thyroid function or pituitary adenoma, before HT may be considered.

TREATMENT

Desired Outcomes

KEY CONCEPT HT remains the most effective treatment for VMS and vulvovaginal atrophy and should be considered, especially for women experiencing moderate to severe symptoms. The goals of LO 3 treatment are to alleviate or reduce menopausal symptoms and to improve the patient's quality of life (QOL) while minimizing adverse effects of therapy. Appropriate dose, duration, regimen, and route of administration should be patient specific, and aim to utilize the lowest effective dose of HT.

General Approach to Treatment

There are a number of national and international guidelines and consensus statements available on the management of menopause.[5-10] The most current guidelines should be consulted before making pharmacotherapeutic recommendations for women. Women with VMS should attempt lifestyle or behavioral modifications before seeking medical treatment. Women who seek medical treatment usually have symptoms that diminish their QOL, such as multiple **hot flashes** per day or week, sleep disturbances, vaginal dryness, or mood swings. HT should be considered for these women but is not the most appropriate choice for all women. LO 4 KEY CONCEPT Women should receive a thorough history and physical examination, including assessing for CHD and breast cancer risk factors and contraindications, before HT is considered. They should be informed of the risks and benefits of HT and encouraged to be involved in the decision-making process. If a woman does not have any contraindications to HT, HT could be an appropriate therapy option (**Figure 50–1**). Nonhormonal and alternative treatment options are available for women who are not candidates for HT or are unwilling to take HT, but they have limited effectiveness and may also have adverse effects.

Nonpharmacologic Therapy

Nonpharmacologic therapies for menopause-related symptoms have not been studied in large randomized controlled trials (RCTs), and evidence of benefit is limited. Nonpharmacologic interventions with the most evidence for improving VMS include cognitive-behavioral therapy and clinical hypnosis.[5,13] Group- and individual-based cognitive behavioral therapies are effective in reducing VMS symptoms. Evidence supporting clinical hypnosis is limited; however, two RCTs demonstrated significantly reduced hot flashes. Mindfulness-based stress reduction and weight loss may also be recommended. Due to the minimal adverse effects LO 5 of these interventions, patients should try lifestyle or behavioral modifications before and in addition to pharmacologic therapy. The following nonpharmacologic interventions are not routinely

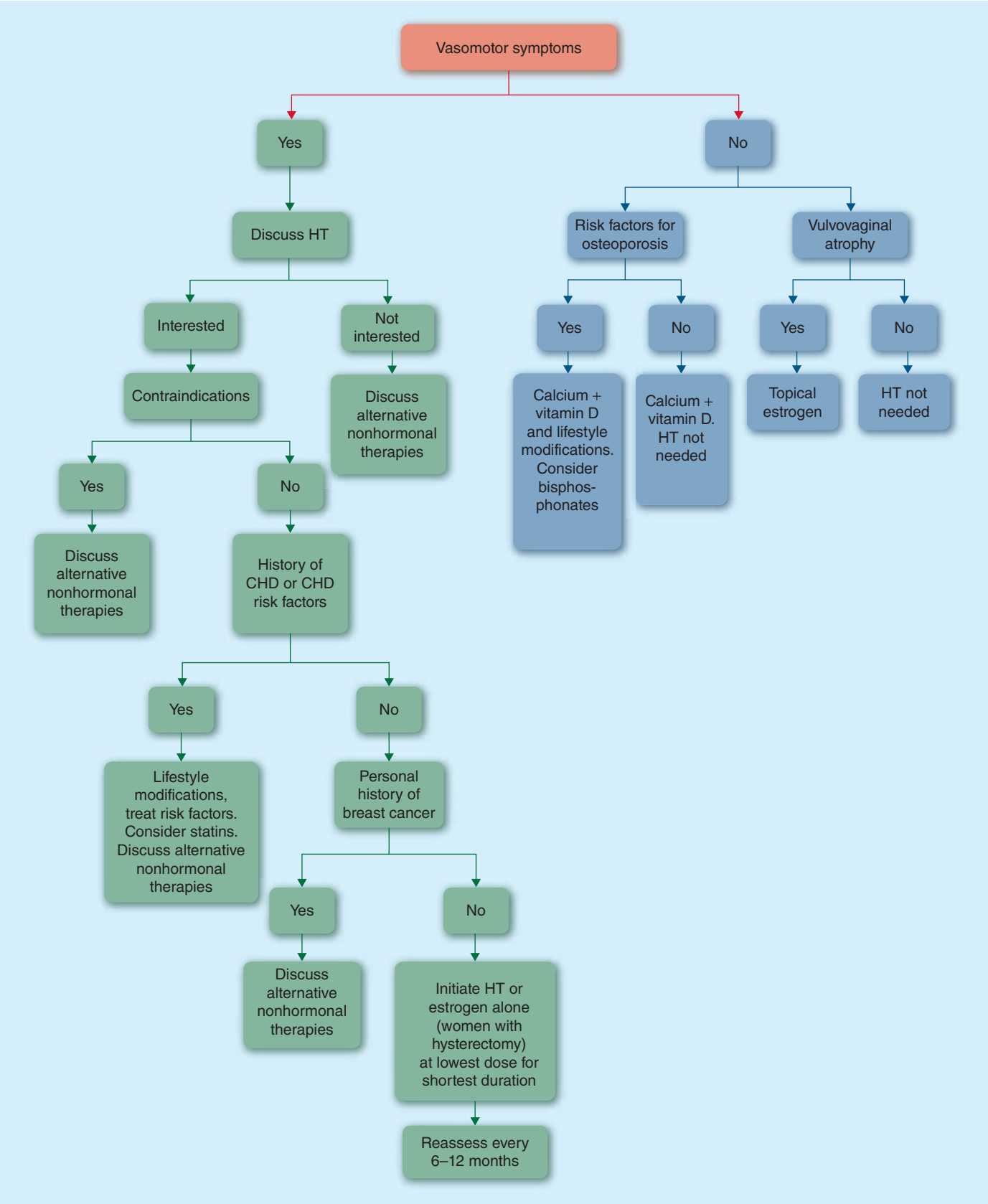

FIGURE 50–1. Treatment algorithm for postmenopausal women.[2,5,12,13] (CHD, coronary heart disease; HT, hormone therapy.)

recommended for relief of VMS, as there are negative, insufficient or inconclusive data supporting their use:

- Cooling techniques
- Avoidance of triggers
- Exercise
- Yoga
- Paced respiration
- Relaxation

Dyspareunia may result from vaginal dryness. Water-based lubricants may provide relief for several hours after application. Vaginal moisturizers may provide relief for a longer period of time and potentially can prevent infections by maintaining the acidic environment in the vagina. Both these treatments require frequent application.

A decline in estrogen concentrations may be associated with urinary stress incontinence. Kegel exercises are a first-line intervention for stress incontinence, followed by pharmacotherapy if needed. Kegel exercises strengthen the pelvic floor muscles and help to keep the urethral sphincter from relaxing at inappropriate times, such as when lifting heavy objects, coughing, or sneezing. These exercises have no adverse effects, take little time, and may be done inconspicuously.

Pharmacotherapy: Hormonal Therapy

▶ *Estrogens*

Estrogen is indicated for the treatment of moderate to severe VMS and vulvovaginal atrophy associated with menopause. It is also indicated for the prevention of postmenopausal osteoporosis in women with significant risk; however, it is recommended that nonestrogen medications be used long-term. KEY CONCEPT Appropriate dose, duration, regimen and route of administration should be patient specific, and aim to utilize the lowest effective dose of HT to provide relief of VMS. Topical vaginal products in the form of creams, tablets, or rings should be prescribed for women experiencing GSM without VMS.

Many systemically administered estrogen products are available in the United States. Transdermal estrogen preparations are also available and usually are prescribed for patients who experience adverse effects, elevated triglycerides (TG), or liver function abnormalities while taking an oral product. Multiple observational studies suggest that transdermal preparations have a lower incidence of venous thromboembolism (VTE) than oral preparations.[5,10,14]

▶ *Progestogens*

KEY CONCEPT Women who have an intact uterus should be prescribed a progestogen in addition to estrogen in order to decrease the risk of endometrial hyperplasia and endometrial cancer.[4] Progestogens should be prescribed for at least 12 to 14 days of the month and often are prescribed continuously. Even low doses of oral estrogen therapy, as well as high dose vaginal preparations, require daily or intermittent administration of a progestogen in order to provide endometrial protection. Table 50–1 lists estrogen and progestogen preparations and dosages.

▶ *Adverse Effects*

Therapy with estrogen with or without a progestogen should be initiated at the lowest dose in order to minimize adverse effects. Because the adverse effects of these preparations can be similar, it may be difficult to assess whether the estrogen or the progestogen is the cause. Changing preparations, particularly the progestogen,

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

The workup reveals the following additional information:

PMH: Hypertension since age 45, currently controlled; hypothyroidism since age 25; hysterectomy 1 year ago.

FH: Father: Alive with HTN and CHD (MI at age 60). Mother: Alive with hypothyroidism, HTN, and GERD. Siblings: Two sisters alive and well, menopausal with hx of hot flashes.

SH: Occupation: physician assistant; nonsmoker; drinks one glass of red wine with dinner on the weekends; denies illicit drug use.

Meds: Lisinopril 20 mg once daily; levothyroxine 0.1 mg by mouth once daily; multivitamin with iron by mouth once daily (discontinued 2 months ago)—takes all medications 30 minutes before breakfast.

ROS: (+) hot flashes, night sweats, (+) dyspareunia; vaginal dryness and itching; (+) insomnia, (–) bowel changes, 5-lb (2.3 kg) weight loss since last visit 6 months ago.

PE:

VS: BP 120/70, P 72, RR 16, T 37.0°C (98.6°F), Wt 74.4 kg (164 lbs)

HEENT: WNL

Neck: Supple; no bruits, no adenopathy, no thyromegaly

Breasts: Supple; no masses

CV: RRR, normal S_1 and S_2; no murmurs, rubs, or gallops

Abd: Soft, nontender, nondistended; (+) BS, no masses

Genitourinary: Pelvic examination normal except (+) mucosal atrophy; (+) hysterectomy

Labs:

FSH: 125 mIU/mL (IU/L)

TSH: 0.27 μIU/mL (mIU/L)

Chem-7: Na 135 mEq/L (mmol/L), K 4.5 mEq/L (mmol/L), Cl 109 mEq/L (mmol/L), CO_2 25 mEq/L (mmol/L), BUN 9 mg/dL (3.2 mmol/L), SCr 0.9 mg/dL (80 μmol/L), Glucose 98 mg/dL (5.4 mmol/L)

CBC: Hgb 13 g/dL (130 g/L or 8.07 mmol/L), Hct 39% (0.39 volume fraction), WBC 5.5 × 10^3/mm^3 (5.5 × 10^9/L), platelets 234 × 10^3/mm^3(234 × 10^9/L)

Fasting lipid levels: Total cholesterol (TC) 180 mg/dL (4.65 mmol/L), low-density lipoprotein (LDL) 110 mg/dL (2.84 mmol/L), high-density lipoprotein (HDL) 50 mg/dL (1.29 mmol/L), triglycerides (TG) 115 mg/dL (1.30 mmol/L)

Assess the patient's condition based on this additional information.

What are the goals of treatment for this patient?

Assess the patient's risk factors for heart disease and breast cancer.

Recommend nonpharmacologic and pharmacologic treatment for this patient. Justify your recommendations.

Table 50–1

Hormone Formulations and Dosages[11,15,16]

Product	Available Strengths	Common Dosages
Oral estrogens		
Conjugated estrogens (Premarin)	0.3–1.25 mg	0.3–0.625 mg/day
Esterified estrogens (Menest)	0.3–1.25 mg	0.3–1.25 mg/day
Estradiol (Estrace[a])	0.5–2 mg	1–2 mg/day
Estropipate[a]	0.75–3 mg	0.75–6 mg/day
Transdermal estrogens		
Estradiol patch (Alora, Minivelle, Vivelle Dot)	0.025–0.1 mg/24 hour	0.025–0.1 mg, changed twice weekly
(Climara, Menostar[b])	0.025–0.1mg/24 hour	0.025–0.1 mg, changed weekly
Topical estrogens		
Vaginal creams		
Conjugated estrogens (Premarin)	0.625 mg/g	0.5–2 g/day
Estradiol (Estrace)	0.01%	1 g one to three times/week
Gel		
Estradiol gel		
(Elestrin)	0.06%	1–2 actuations of pump once daily
(EstroGel)	0.06%	1 actuation of pump once daily
(Divigel)	0.1%	0.25 gram/day packet once daily
Spray		
Estradiol spray (Evamist)	1.53 mg/actuation	1–3 sprays daily
Vaginal inserts		
Vaginal ring		
Estradiol (Estring)	2 mg	1 ring every 3 months
Estradiol acetate (Femring)	0.05–0.1mg/24 hour	1 ring every 3 months
Vaginal tablet		
Estradiol (Vagifem)	10 mcg estradiol	One tablet twice weekly
Progestogens[c,d]		
Medroxyprogesterone acetate (Provera)	2.5–10 mg	
Micronized progesterone (Prometrium®)	100–200 mg	
Norethindrone acetate (Aygestin®)	5 mg	
Combination products		
Oral		
Conjugated estrogens + medroxyprogesterone (Prempro; Premphase)	0.3/1.5 mg–0.625/5 mg	One tablet daily
Conjugated estrogens + bazedoxifene (Duavee)	0.45 mg/20 mg	One tablet daily
Estradiol + norethindrone (Activella; Amabelz)	0.5/0.1 mg–1/0.5 mg	One tablet daily
Estradiol + drospirenone (Angeliq)	0.25/0.5 mg–0.5/1 mg	One tablet daily
Ethinyl estradiol + norethindrone acetate (Femhrt low dose, others)	2.5 mcg/0.5 mg–5 mcg/1 mg	One tablet daily
Estradiol + norgestimate (Prefest)	1/0.09 mg	One tablet daily
(Covaryx)	1.25/2.5 mg	One tablet daily
(Covaryx HS)	0.625/1.25 mg	One to two tablets daily
Transdermal		
Estradiol + norethindrone acetate (Combipatch)	0.05/0.14–0.05/0.25 mg/24 hour	Apply one patch twice weekly
Estradiol + levonorgestrel (Climara Pro)	0.045/0.015 mg/24 hour	Apply one patch once weekly

[a]FDA-approved commercially available bioidentical product.

[b]Indicated for the prevention of postmenopausal osteoporosis only; available in 14 mcg patch.

[c]May be administered cyclically or continuously.

[d]Dose varies based on daily or cyclic administration.

CEE, conjugated equine estrogens; MPA, medroxyprogesterone acetate.

LO 6 or changing the method of administration may help to alleviate adverse effects. Table 50–2 lists the adverse effects that may be associated with estrogen and progestogen preparations.

► *Contraindications*

LO 6 HT should not be prescribed to women with a history of or active thromboembolic disease, CHD, breast cancer, or estrogen-dependent neoplasm, pregnancy, liver disease, or undiagnosed vaginal bleeding. It also should not be used for the prevention or treatment of cardiovascular disease, cerebrovascular disease, or dementia.[5]

► *Methods of Administration*

Continuous Estrogen and Cyclic Progestogen Estrogen is administered daily, and progestogen is administered for 12 to 14 days of the month. The disadvantage of this method of administration is the return of monthly menses in approximately 90% of women 1 to 2 days following the last progestogen dose.

Table 50–2

Adverse Effects of Estrogens and Progestogens[5,11,15,16]

Estrogens
Common adverse effects
- Nausea
- Headache
- Bloating
- Breast tenderness
- Breakthrough uterine bleeding

Serious adverse effects
- Coronary heart disease
- Stroke
- Venous thromboembolism
- Breast cancer
- Gallbladder disease

Progestogens
Common adverse effects
- Nausea
- Headache
- Weight gain
- Bleeding
- Irritability
- Depression

Serious adverse effects
- Venous thromboembolism
- Breast cancer (in combination with estrogen)
- Decreased bone mineral density (effect of injectable medroxyprogesterone acetate)

Women may view this scheduled bleeding as an advantage to this method of administration as it limits spotting or soiling of undergarments.

Continuous Combined Estrogen and Progestogen Estrogen and progestogen are administered daily and result in endometrial atrophy. Therefore, women do not experience a withdrawal bleed but may experience unanticipated breakthrough bleeding or spotting during the month. Although this may sound more appealing than a withdrawal bleed, women may view the unpredictable bleeding or spotting as a disadvantage to this type of administration. If bleeding persists beyond 6 to 12 months, women should seek medical attention to rule out endometrial hyperplasia or carcinoma.

▶ *Low-Dose HT*

There is an increasing body of evidence proving the effectiveness of low-dose HT regimens in the management of menopausal symptoms. Several trials demonstrated that lower doses of conjugated equine estrogens (CEE) ± medroxyprogesterone acetate (MPA) (CEE 0.45 mg or 0.3 mg ± MPA 2.5 mg or 1.5 mg) decreased hot flashes comparable with standard HT, improved vulvovaginal atrophy, increased bone mineral density (BMD) at the spine and hip, and provided sufficient endometrial protection.[17-20] Currently, no data are available on the effects of low-dose HT on the incidence of VTE, breast cancer, or CHD. Although many women have switched to low-dose HT, time will tell if lower doses translate into lower risks.

▶ *Bioidentical HT*

Bioidentical hormones are exogenous hormones that are identical to those produced in a woman's body (eg, estradiol, estrone, estriol, and progesterone). They are either commercially manufactured or custom-compounded in pharmacies into formulations such as topical creams, gels, and suppositories. The commercially manufactured prescription products are subject to regulation by the FDA and have been tested for potency, purity, efficacy, and safety (see Table 50–1). Conversely, custom-compounded formulations are not subject to the same regulations and therefore, the efficacy and safety may be questionable. Often women view bioidentical hormones, particularly the custom-compounded formulations, as "natural" and assume these formulations are safer than currently marketed prescription hormone products. Women may feel more comfortable using custom-compounded products that are formulated based on individual hormone levels; however, due to a lack of regulation, these products may potentially cause more harm than benefit. In addition, custom-compounded formulations can result in higher costs, because they are generally not covered by third-party payers. There is little evidence comparing the safety and efficacy of conventional HT to prescription bioidentical HT, and thus the same risks and benefits should be assumed.[5,21]

▶ *Benefits of HT*

LO 6

Vasomotor Symptoms HT remains the most effective treatment for VMS, and systemic HT should be considered only in women experiencing these symptoms. Benefits must outweigh risks, and decisions should be made only after careful consideration by the woman and her health care provider. If it is decided to use HT, pharmacotherapy should be individualized for route, dose, and duration. Women should be reassessed every 6–12 months, and discontinuation of therapy should be considered. Extended treatment duration may be warranted for relief of persistent VMS and GSM and prevention of bone loss and fracture when unable to tolerate therapy primarily indicated for osteoporosis.[5]

LO 6

Vulvovaginal Atrophy Vulvovaginal atrophy is associated with vaginal dryness and dyspareunia and also may be associated with recurrent urinary tract infections, urethritis, and urinary urgency and frequency. Topical vaginal preparations should be prescribed as first-line therapy unless the patient is also experiencing VMS. Local vaginal estrogen has demonstrated increased efficacy over systemic estrogen and generally does not require supplementation with a progestogen in women with an intact uterus using low or ultralow doses.[4] Women using high doses of topical estrogen products may require intermittent treatment with a progestogen. Estradiol in the form of a vaginal tablet or ring is not significantly absorbed systemically, with the exception of Femring which is the only vaginal ring indicated for VMS. Other vaginal rings may be used safely in women with contraindications to estrogen therapy and symptoms of vulvovaginal atrophy.[5]

LO 6

Osteoporosis Prevention Postmenopausal osteoporosis is a condition that affects millions of women. Fractures, particularly hip fractures, are associated with a high incidence of morbidity and mortality and decreased QOL. Before the WHI study, only observational data were available regarding the association of HT and the reduction of fractures. The WHI was the first RCT that demonstrated a reduction in total fractures, including the hip, spine, and wrist.[2,22]

KEY CONCEPT Extended treatment duration with HT may be warranted in women with VMS for prevention of bone loss and fracture when unable to tolerate therapy primarily indicated for osteoporosis. Because of the associated risks, HT should not be prescribed solely for the prevention of osteoporosis.

▶ *Risks of HT*

Cardiovascular Disease CHD is the leading cause of death among women in the United States. The WHI was the first RCT conducted

in women without established CHD. Women with an intact uterus received HT daily. The WHI demonstrated an increased risk of CHD and stroke with HT compared with placebo.[23,24]

The estrogen-alone arm of the WHI did not demonstrate an increased risk of CHD compared with placebo. However, there was an increased risk of stroke with estrogen-alone compared with placebo.[3] Women who initiate HT 10 or more years after menopause have an increased cardiovascular risk.[5,25,26] A recent long-term analysis of the WHI study demonstrates that among postmenopausal women, use of oral estrogen plus progesterone for 5.5 years or oral estrogen alone for 7 years did not increase the risk of all-cause mortality.[27]

LO 6 HT should not be prescribed for the prevention of CHD or in patients with preexisting CHD.

Breast Cancer Breast cancer is the most common cancer in women in the United States. Observational data indicated an association between HT and breast cancer risk. The WHI was the first RCT to demonstrate an increased risk of invasive breast cancer among women taking HT.[2,28] The increase in risk did correlate with increased age of the women, and the risk appears to be greater in those who initiate therapy within 5 years of menopause. There were also more deaths from breast cancer and deaths overall with combination therapy than with placebo.[29] It should be noted that any increase in risk for breast cancer appears to dissipate over 2 to 3 years after HT is discontinued.[5,30] Whether HT is associated with an increased risk for breast cancer recurrence is still questionable.

Breast cancer was not increased in the estrogen-alone arm of the WHI.[3] These data point to a possible link of progestogen with breast cancer risk. Whether or not the risk differs between type of progestogen or continuous and sequential use of progestogens is controversial. Some evidence suggests that sequential use may be safer than taking progestogen each day.[5,31]

LO 6 Women with a personal history of breast cancer and possibly even a strong family history of breast cancer should avoid the use of HT and should consider nonhormonal therapies for the treatment of VMS.

Venous Thromboembolism The WHI demonstrated an increased risk for VTE with HT compared with placebo.[2] The risk for deep vein thrombosis was also increased in the estrogen-alone arm of the WHI, but pulmonary embolism was not increased significantly.[3] The risk of thromboembolism may be dose-related, and the oral route of administration is associated with a higher risk compared with the transdermal route.[14]

LO 6 KEY CONCEPT In summary, combined estrogen plus progestogen or estrogen alone should not be used for the prevention of chronic diseases.

▶ *Other Effects of HT*

QOL and Cognition Women consider QOL measures when deciding whether to use HT; however, the effects of HT on overall QOL have been inconsistent. HT did not demonstrate a clinically meaningful effect on QOL but women taking HT did have a small improvement in sleep disturbances, physical functioning, and bodily pain after 1 year of therapy.[32] Results from the HERS demonstrated that HT did improve emotional measures such as depressive symptoms, but only if women suffered from flushing at trial entry.[33]

Observational studies suggested a potential benefit of HT on cognitive functioning and dementia. However, the Women's Health Initiative Memory Study (WHIMS), conducted in postmenopausal women aged 65 years or older, failed to demonstrate an improvement in cognitive function and demonstrated a small increase in dementia rate, including Alzheimer disease.[34,35] The estrogen-alone arm of the WHIMS also demonstrated similar results.[36,37]

LO 6 KEY CONCEPT HT improves overall well-being and mood in women with VMS, but it has not demonstrated an improvement in QOL in women without VMS.

▶ *Discontinuation of HT*

KEY CONCEPT When treating moderate to severe postmenopausal symptoms, the benefit-to-risk ratio appears to be best when HT is started close to the time of menopause. Consider tapering therapy before discontinuation to limit the potential recurrence of hot flashes. Although VMS in most women will subside within 4 years, approximately 10% of women continue to experience symptoms that interfere with their QOL. Literature suggests that one of every four women needs to be reinitiated on HT due to persistent and bothersome symptoms. There is no evidence to suggest that tapering is beneficial; however, it may be prudent to avoid bothersome recurrent symptoms.[5,38]

Limited evidence is available to guide health care providers regarding the least disruptive way to taper HT. Slowly discontinuing HT over 3 to 6 months may be associated with less risk of symptom return. Tapering HT may be done by a dose taper or day taper. The dose taper involves decreasing the dose of estrogen over several weeks to months and monitoring closely for symptom return. The day taper involves decreasing the number of days of the week that a woman takes the HT dose. If symptoms recur, the next reduction in dose or days should not occur until symptoms resolve or stabilize. These tapering regimens have not been studied in clinical trials and may not prove to be beneficial in individual women.[38]

Hormone Modulating Therapy

▶ *Selective Estrogen Receptor Modulators (SERMs)*

Although estrogen +/– progestogen remains first-line therapy for the relief of moderate to severe VMS and vulvovaginal atrophy, additional hormone options utilizing SERMs are available.

Ospemifene (Osphena) is approved for the treatment of moderate to severe dyspareunia associated with vulvovaginal atrophy. This drug acts as an estrogen agonist in some tissues (vaginal and endometrial) and antagonist in other tissues. Data suggests there is an increase in hot flashes and that there may be an increased risk of endometrial cancer in women with an intact uterus. This drug may be considered in women with symptoms of vulvovaginal atrophy. However, the risks and benefits should be discussed with women also presenting with VMS and an intact uterus.[5]

CEE 0.45 mg/bazedoxifene (BZA) 20 mg (Duavee), the first tissue selective estrogen complex, is approved for the treatment of postmenopausal osteoporosis and moderate to severe VMS in women with an intact uterus. This drug acts as an agonist in bone tissue and an antagonist in breast and uterine tissue. Clinical trials have demonstrated efficacy with no stimulation of breast or uterine tissue. Thus, progestogens are not needed. Adverse effects with CEE/BZA are minimal with musculoskeletal symptoms reported most commonly. When considering the place in therapy for CEE/BZA, efficacy appears to be similar to CEE/MPA with potentially less occurrence of estrogen-like adverse effects with CEE/BZA. In addition, an advantage of the formulation may be for women intolerant to progestogen adverse effects or when progestogen is contraindicated. However, because no long-term

Table 50–3

Nonhormonal Therapies for Menopause[13,39,40,42]

Drug	Brand Name	Initial Dose	Usual Dose Range	Potential Adverse Effects
Venlafaxine[a,b]	Effexor, Effexor XR	37.5 mg	37.5–150 mg/day	Nausea, HA, somnolence, dizziness, insomnia, hypertension, xerostomia constipation, diaphoresis, weakness
Desvenlafaxine[a,b]	Pristiq	25–50 mg/day	100–150 mg/day	Nausea, xerostomia, constipation, vomiting, anorexia, dizziness, drowsiness, and insomnia
Paroxetine mesylate[c]	Brisdelle	7.5	7.5 mg/day	Nausea, somnolence, insomnia, HA, dizziness, xerostomia, constipation, diarrhea, weakness, diaphoresis
Paroxetine CR	Paxil CR	12.5 mg CR	12.5 mg–25 mg CR/day	
Paroxetine HCl	Paxil	10–20 mg	10–20 mg/day	
Citalopram	Celexa	10 mg/day	10–20 mg/day	Xerostomia, nausea, drowsiness, and insomnia
Escitalopram	Lexapro	10 mg/day	10–20 mg/day	Nausea, insomnia, drowsiness, and headache
Clonidine	Catapres, Catapres TTS	0.1 mg/day	0.1–0.4 mg/day	Drowsiness, dizziness, hypotension, dry mouth
Gabapentin[a]	Neurontin	300 mg at bedtime	900 mg/day, divided in three daily doses (up to 2400 mg/day)	Somnolence and dizziness (can decrease with gradual increase in dosing)
Pregabalin[a]	Lyrica	75 mg twice daily	150–300 mg/day	Peripheral edema, dizziness, drowsiness, ataxia, headache, fatigue, weight gain, infection, diplopia, and tremor

[a]Dosage adjustments recommended in patients with renal impairment.

[b]Dosage adjustment recommended in patients with hepatic impairment.

[c]FDA approved for the treatment of moderate to severe hot flashes associated with menopause.

HA, headache.

data are available, the same precautions and contraindications as estrogen products should be assumed.[5]

Nonhormonal and Alternative Treatments

KEY CONCEPT Since publication of the WHI study, there has been an increase in the use of alternative and nonhormonal therapies for the management of menopausal symptoms, particularly for women with CHD and/or breast cancer risk factors. A wide range of therapies, both prescription and herbal, have been studied with limited success.

LO 7

Nonhormonal and alternative therapies (Table 50–3) have been studied for symptomatic management of VMS.[13] The limited and often conflicting evidence demonstrates that these agents are only modestly effective and also have associated adverse effects.

SSRIs and SNRIs reduce the frequency of hot flashes by increasing serotonin in the central nervous system. Of the SSRIs, paroxetine mesylate has the most published data demonstrating a reduction in hot flashes and is the only SSRI approved to treat moderate to severe VMS, while treating other symptomatic complaints such as depression and anxiety.[13,39] Other SSRIs such as escitalopram, citalopram, fluoxetine, and sertraline may also be effective. These antidepressant medications offer a reasonable option for women who are unwilling to or cannot take hormonal therapies, particularly those who suffer from depression or anxiety.[13]

Gabapentin, pregabalin, and clonidine have also been studied for the management of menopausal symptoms. In RCTs, gabapentin at doses of 900 mg/day demonstrated significant reductions in severity and frequency of hot flashes compared with placebo. In an RCT, pregabalin was studied at a dose of 75 mg twice daily and 150 mg twice daily. Both doses were effective in decreasing hot flash scores but adverse effects were more common with higher doses.[40] Clonidine has been studied in several small RCTs

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's hot flashes, vaginal dryness, dyspareunia, and insomnia. The plan should include:

(a) A statement identifying the problem and its severity

(b) Goals of therapy

(c) A therapeutic plan based on individual patient-specific factors

(d) Subjective and objective monitoring parameters

(e) A follow-up evaluation to assess for adverse effects and adherence and to determine whether the goals of therapy have been achieved

Patient Encounter Part 4

The patient has been in good health for the past 3 years. She reports adherence with her medications, a healthy diet and exercise routine, and her medical conditions are controlled. However, 2 months ago, she was diagnosed with a VTE secondary to being sedentary on a long airplane flight (14 hours). She is concerned that her hormone therapy may have caused the VTE.

Educate the patient regarding the risk of VTE and hormone therapy.

at doses of 0.1 to 0.4 mg/day and has demonstrated reductions in hot flashes but to a lesser extent than gabapentin.[39]

Phytoestrogens are plant sterols that are structurally similar to human and animal estrogen. Soy protein is a common source of phytoestrogens. There are differences among classes of phytoestrogens and biologic potencies vary, making it difficult to recommend specific dosing. The most commonly studied phytoestrogen is the isoflavone class. Because the effect of phytoestrogens on breast cancer and other female-related cancers is unknown, these products should not be considered in women with a history of estrogen-dependent cancers. After reviewing hundreds of studies, the North American Menopause Society (NAMS) determined that soy-based isoflavones are modestly effective in relieving menopausal symptoms.[13,41] The efficacy of soy isoflavones on bone, cognitive improvement, and cardiovascular health has not been proven.

Black cohosh has been one of the most studied alternative therapies for VMS. The mechanism of action, safety profile, drug–drug interactions, and adverse effects of black cohosh remain unknown. However, there have been case reports of hepatotoxicity with its use. In RCTs conducted for 6 months or less, there was no difference in black cohosh and placebo in reducing VMS.[13,39,42] Caution should be exercised if considering the use of this product, and it is not recommended for more than a 6-month period of time. Other alternative treatments that have been utilized include (but not limited to) dong quai, red clover leaf, kava, and evening primrose oil. These have not been shown to be effective in the treatment of menopausal symptoms and may have significant adverse effects.[13]

LO 7

Overall, alternative and nonhormonal therapies are less effective in treating VMS than HT, but do offer another option for women experiencing menopausal symptoms who cannot or are unwilling to take HT. SSRIs, SNRIs, and gabapentin have the best evidence for efficacy. Women should weigh the benefits and risks of all therapies, and discuss these options with their health care providers.[13]

OUTCOME EVALUATION

Evaluating the outcomes of any therapy for menopausal symptoms focuses primarily on the woman's report of symptom resolution. Ask women to report the resolution or reduction of hot flashes, night sweats, and vaginal dryness and any improvement or change in sleep patterns. Also ask women taking hormonal therapies to report any breakthrough bleeding or spotting. If abnormal or heavy bleeding occurs, refer the woman to her primary care provider. Monitor subjective parameters such as adverse effects and adherence to the therapy regimen. In addition, monitor objective parameters, including blood pressure, at every outpatient visit; encourage yearly clinical breast examinations, mammograms, lipid panel, and thyroid-stimulating

Patient Encounter Part 5

It has been 6 months since this patient discontinued taking hormone therapy secondary to her VTE. She presents to her PCP for follow-up with a chief complaint of recurrent hot flashes. She also complains of recurrent vaginal dryness and dyspareunia.

Recommend the most appropriate therapy for her recurrent hot flashes and vulvovaginal atrophy.

Patient Care Process

Collect Information:

- Obtain the chief complaint and history of present illness regarding symptomatology of VMS.
- Obtain patient health and functional goals for the treatment of VMS.
- Obtain a medical history that includes past medical history, social history, family history, surgical history, allergies, and information from a hot flash diary if the patient keeps one.
- Obtain a thorough medication history, including the use of over-the-counter and herbal products.

Assess the Information:

- Evaluate for the presence of VMS.
- Rule out other medical conditions that could be contributing to symptoms and manage those conditions prior to initiating therapy for symptoms.
- If the patient is experiencing bothersome VMS, consider the use of HT only after assessing for risk factors for heart disease and breast cancer.
- If VMS are tolerable and/or the patient has risk factors for heart disease and/or breast cancer, consider alternative, nonhormonal treatments for VMS.
- Consider appropriate nonpharmacologic interventions.

Develop a Care Plan:

- Create a patient-centered pharmacologic plan in conjunction with the health care provider.
- Create a patient-centered nonpharmacologic plan.

Implement the Care Plan:

- Recommend the appropriate dose of a pharmacologic agent and duration, regimen, and route of administration that are patient-specific, and aim to utilize the lowest effective dose of HT.
- Document findings and recommendations.
- Discuss the importance of adhering to the medication regimen.
- Discuss methods of administration, potential adverse effects, and expectations of therapy.
- Discuss lifestyle or behavioral interventions that may help to alleviate VMS.

Follow-up: Monitor and Evaluate:

- Efficacy: monitor for reduction in VMS and improvement in vulvovaginal atrophy, sleep, and QOL.
- Safety: monitor for breakthrough bleeding and spotting, adverse effects of HT, blood pressure at every outpatient visit, yearly mammograms, yearly TSH, and endometrial studies in women with undiagnosed vaginal bleeding.
- Assess symptoms every 6 to 12 months, and consider tapering the HT dose and discontinuing treatment after 5 years. If VMS return, determine whether a longer tapering schedule is warranted or if long-term treatment is necessary. If treatment beyond 5 years is necessary, consider switching to a nonhormonal product.

hormone (TSH) determination, particularly for women with hypothyroidism on thyroid therapy, and conduct a BMD test as indicated. Also perform endometrial studies, as necessary, in women with undiagnosed vaginal bleeding. Last, evaluate the patient's overall QOL. Because the management of menopause is largely symptomatic, it is important to document symptoms at the beginning of therapy and monitor symptom improvement and potential adverse effects at each visit. Frequent follow-up, proper monitoring, and education will help to ensure that the woman achieves optimal results from any therapy chosen to treat menopausal symptoms.

LO 8

Abbreviations Introduced in This Chapter

BMD	Bone mineral density
CEE	Conjugated equine estrogens
CHD	Coronary heart disease
FDA	US Food and Drug Administration
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
GSM	Genitourinary syndrome of menopause
HDL	High-density lipoprotein
HERS	Heart and Estrogen/Progestin Replacement Study
HT	Hormone therapy
LDL	Low-density lipoprotein
LH	Luteinizing hormone
MPA	Medroxyprogesterone acetate
NAMS	North American Menopause Society
QOL	Quality of life
PCP	Primary care provider
RCT	Randomized controlled trial
SERMs	Selective estrogen receptor modulators
SSRI	Selective serotonin reuptake inhibitor
TG	Triglycerides
TSH	Thyroid-stimulating hormone
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
WHI	Women's Health Initiative
WHIMS	Women's Health Initiative Memory Study

REFERENCES

1. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998;280(7):605–613.
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321–333.
3. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004;291(14):1701–1712.
4. Nelson HD. Menopause. Lancet. 2008;371:760–770.
5. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause. 2017;24(7):728–753.
6. The North American Menopause Society. Management of postmenopausal osteoporosis: 2010 position statement of The North American Menopause Society. Menopause. 2010;17:25–54.
7. The North American Menopause Society. Treatment of menopause associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause. 2004;11(1):11–33.
8. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an endocrine society scientific statement. J Clin Endocrinol Metab. 2010;95(suppl 1):S1–S66.
9. The Writing Group on behalf of the Workshop Consensus Group. Aging, menopause, cardiovascular disease and HRT. Climacteric. 2009;12:368–377.
10. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on menopause. Endocr Pract. 2017;23(7):869–880.
11. Kalantaridou SN, Borgelt LM, Dang DK, Calis KA. Hormone therapy in women. In: Dipiro, JT, Talbert RL, Yee, GC et al, eds. Chapter 82 in Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill, 2017.
12. The North American Menopause Society. Algorithm and mobile app for menopausal symptom management and hormonal/nonhormonal therapy decision making: a clinical decision support tool. Menopause. 2015;22:1–7.
13. The North American Menopause Society. Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause. 2015;22(11):1155–1172.
14. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: The ESTHER Study. Circulation. 2007;115:840–845.
15. Estrogens. Clinical Pharmacology. Available from:https://www.clinicalkey.com/pharmacology/monograph/150?n=Conjugated%20Estrogens. Accessed January 3, 2018.
16. Medroxyprogestrone acetate. Clinical Pharmacology. Available from: https://www.clinicalkey.com/pharmacology/monograph/369?n=Medroxyprogesterone. Accessed January 3, 2018.
17. Archer DF, Dorin M, Lewis V, Schneider DL, Pickar JH. Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on endometrial bleeding. Fertil Steril. 2001;75(6):1080–1087.
18. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. JAMA. 2002;287:2668–2676.
19. Pickar JH, Yeh I, Wheeler JE, Cunnane MF, Speroff L. Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril. 2001;76(1):25–31.
20. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. Fertil Steril. 2001;75(6):1065–1079.
21. Bioidential hormones. The Endocrine Society position statement. 2006. http://www.menopause.org/bioidenticalHT_Endosoc.pdf. Accessed January 12, 2012.
22. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003;290(13):1729–1738.
23. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med. 2003;349:523–534.
24. Wassertheil-Smoller S Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. JAMA. 2003;289:2673–2684.
25. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465–1477.

26. Toh S, Hernández-Díaz S, Logan R, Rossouw JE, Hernán MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. Ann Intern Med. 2010;152:211–217.
27. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal hormone therapy and long-term all cause and cause specific mortality. JAMA 2017;318(10);927–938.
28. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the women's health initiative randomized trial. JAMA. 2003;289:3243–3253.
29. Chlebowski RT, Anderson GL, Gass M, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010; 304:1684–1692.
30. Calle EE, Feigelson HS, Hildebrand JS, Teras LR, Thun MK, Rodriguez C. Postmenopausal hormone use and breast cancer associations differ by hormone regimen and histologic subtype. Cancer. 2009;115:936–945.
31. Saxena T, Lee E, Henderson KD, et al. Menopausal hormone therapy and subsequent risk of specific invasive breast cancer subtypes in the California Teachers Study. Cancer Epidemiol Biomarkers Prev. 2010; 19:2366–2378.
32. Hays J, Ockene JK, Brunner RL, et al. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med. 2003;348(19):1839–1854.
33. Hlatky MA, Boothroyd D, Vittinghoff E, Sharp P, Whooley MA. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. JAMA. 2002;287(5):591–597.
34. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003;289(20):2663–2672.
35. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003;289(20):2651–2662.
36. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004;291(24):2959–2968.
37. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004;291(24):2947–2958.
38. Grady D. A 60-year-old woman trying to discontinue hormone replacement therapy. JAMA. 2002;287(16):2130–2137.
39. Cheema D, Coomarasamy A, El-Toukhy T. Non-hormonal therapy of postmenopausal vasomotor symptoms: a structured evidence-based review. Arch Gynecol Obstet. 2007;276(5):463–469.
40. Loprinzi CL, Qin R, Balcueva EP, et al. Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. J Clin Oncol. 2010;28:641–647.
41. NAMS 2011 Isoflavones Report. The role of soy isoflavones in menopausal health: report of the North American Menopause Society. Menopause. 2011;18:732–753.
42. Leach MJ, Moore V. Black cohosh (Cimicifuga spp.) for menopausal symptoms. Cochrane Database Syst Rev. 2012;9:CD007244.

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51 Erectile Dysfunction

Cara Liday

LEARNING OBJECTIVES

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

LO

1. Explain the pathophysiology of erectile dysfunction (ED).
2. Recognize risk factors and medications associated with the development of ED.
3. Identify the goals of therapy when treating ED.
4. Describe current nonpharmacologic and pharmacologic options for treating ED, and determine an appropriate first- and second-line therapy for a specific patient.
5. Identify patients with significant cardiovascular risk and recommend an appropriate treatment approach for their ED.
6. Compare and contrast the benefits and risks for the current phosphodiesterase type 5 (PDE5) inhibitors.
7. Assess reasons for PDE5 failure and determine an optimal approach to improve treatment efficacy.

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection sufficient for sexual intercourse. ED is the most prominent sexual problem in men, and it can lead to lower quality of life and self-esteem.[1] Patients may also develop libido or ejaculatory disorders, but these are not considered ED.

EPIDEMIOLOGY AND ETIOLOGY

ED increases with age. Few men report erection problems before age 40, but ED increases to 61% in men aged 40 to 69 years and 77% in men older than 70 years.[2] The increase in incidence could be due to physiologic changes that occur with aging, the onset of chronic disease states associated with ED, increased medication use, lifestyle factors, or a combination of the above.

PATHOPHYSIOLOGY

The penis consists of three components, two dorsolateral corpora cavernosa and a ventral corpus spongiosum that surrounds the penile urethra and distally forms the glans penis.

In the flaccid state, a balance exists between blood flow into and out of the corpora cavernosa. With sexual stimulation, nerve impulses from the brain travel down the spinal cord triggering a reduction in sympathetic tone and an increase in parasympathetic activity. This leads to an increased production of nitric oxide (NO), which enhances the activity of guanylate cyclase. This results in increased production of cyclic guanosine monophosphate (cGMP). The enzyme phosphodiesterase type 5 (PDE5) is responsible for the catabolism of cGMP within the cavernosal tissue. Vasoactive peptide and prostaglandins E_1 and E_2 stimulate increased production of cyclic adenosine monophosphate (cAMP). Both cAMP and cGMP reduce calcium concentrations within smooth muscle cells of the penile arteries and the sinusoidal spaces, leading to smooth muscle relaxation and increased blood flow. As the spaces become engorged, pressure increases, subtunical venules are compressed by the tunica albuginea, and the penis becomes rigid and elongated (Figure 51–1).

Detumescence, or return of the penis to a flaccid state, occurs with sympathetic discharge after ejaculation. Norepinephrine contracts smooth muscle leading to a reduction in blood inflow, decompression of the sinusoidal spaces, and enhanced outflow.

Testosterone also plays a significant albeit complex role in erectile function. In addition to stabilization of intracavernosal levels of NO synthase, the enzyme responsible for triggering the NO cascade, testosterone is responsible for much of a man's libido. In general, there is not a strong association between normal or low serum testosterone levels and erectile function.[4]

Normal penile erections are complex events that require the full function of the vascular, neurologic, hormonal, and psychogenic systems. Anything that affects the function of these systems may lead to ED. KEY CONCEPT ED can be classified as organic, psychogenic, or a mixture of these. Organic dysfunction includes abnormalities in the vascular, hormonal, or neurologic systems or may be medication-induced (Tables 51–1 and 51–2). It is estimated that 10% to 25% of ED cases are due to medications. Note that many of the risk factors for ED are the same as those for cardiovascular (CV) disease, including hypertension, diabetes, dyslipidemia, smoking, obesity, metabolic syndrome, and sedentary behavior. In many patients, ED is the first indication of the endothelial dysfunction associated with CV, with a time between onset of ED and a CV event of 2 to 5 years.[6] The presence of ED risk factors leads to the assumption that the patient has organic dysfunction. Most commonly, medical conditions that impair arterial flow into or out of the erectile tissue or affect the innervation will be strongly associated with ED. Patients with diabetes mellitus have exceptionally high rates of ED as a result of vascular disease and

LO 1

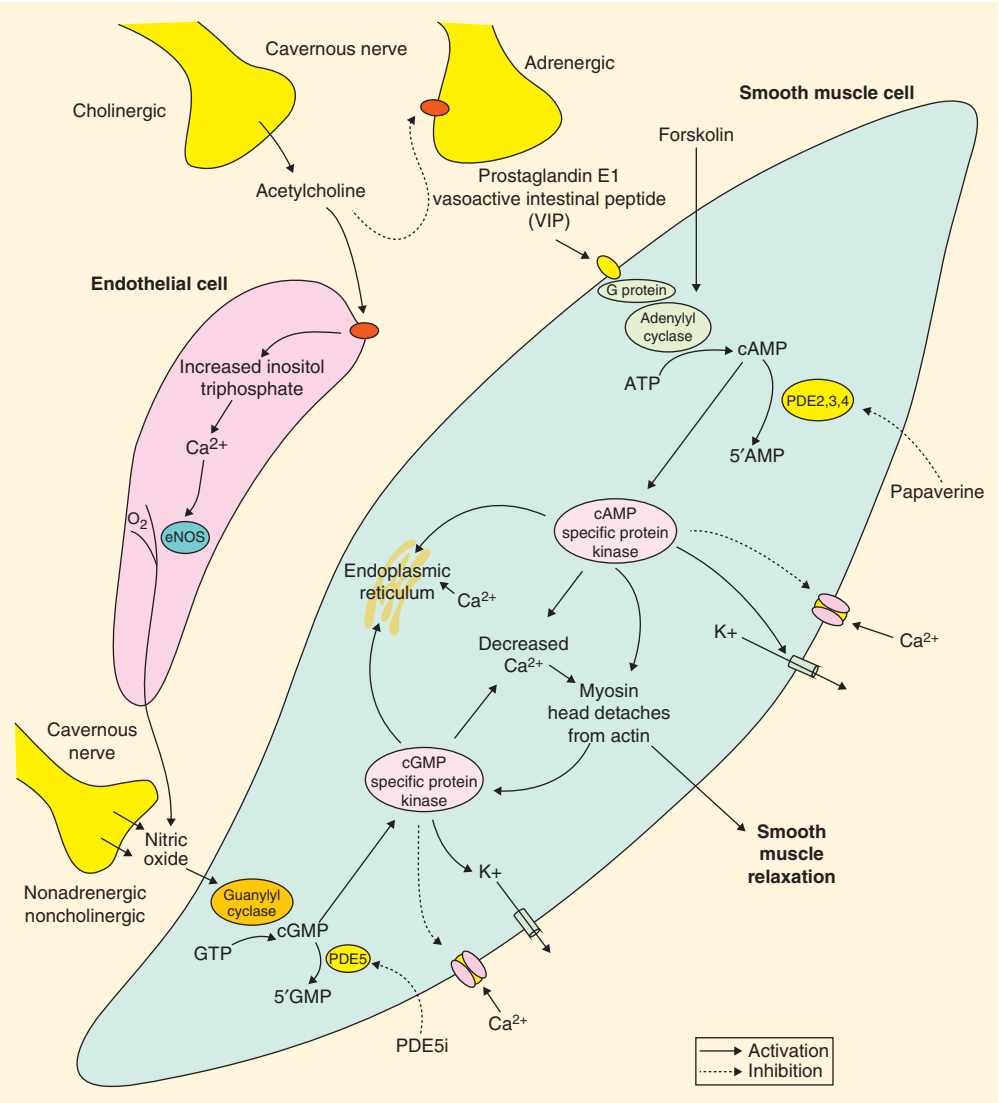

FIGURE 51–1. Molecular mechanism of penile smooth muscle relaxation. Cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), activate their specific protein kinases, which leads to sequestration of intracellular calcium by the endoplasmic reticulum. The resultant decrease in intracellular calcium leads to smooth muscle relaxation. Sildenafil inhibits the action of phosphodiesterase (PDE) type 5 and increases the intracellular concentration of cGMP. Papaverine is a nonspecific (PDE) inhibitor. (ATP, adenosine triphosphate; eNOS, endothelial nitric oxide synthase; GTP, guanosine triphosphate.) (Reproduced, with permission, from Lue T. Physiology of penile erection and pathophysiology of erectile dysfunction. In: Wein AJ, Kavoussi LR, Partin AW, et al, eds. Campbell-Walsh Urology, 11th ed. Philadelphia: Elsevier; 2016:630.)

neuropathy. Additionally, a relationship has been found between low testosterone levels and an increased incidence of metabolic syndrome and type 2 diabetes.[7]

Psychogenic dysfunction occurs if a patient does not respond to psychological arousal. Common causes include performance anxiety, strained relationships, lack of sexual arousability, and overt psychiatric disorders such as depression and schizophrenia. KEY CONCEPT Many patients may initially have organic dysfunction, but develop a psychogenic component as they try to cope with their inability to achieve an erection.[1]

CLINICAL PRESENTATION AND DIAGNOSIS OF ED

The introduction of oral medications and direct-to-consumer advertising has made patients feel more comfortable approaching practitioners for treatment advice. Despite this, some patients may only discuss their dysfunction when questioned directly by their provider or if their partner initiates the interaction.

TREATMENT

Desired Outcomes

ED is not a life-threatening condition, but if left untreated, it can be associated with depression, loss of self-esteem, poor self-image, and marital discord.[9] The primary goal of therapy is achievement of erections suitable for intercourse and improvement in patient and partner quality of life. Additionally, the ideal therapy should have minimal side effects, be convenient to administer, have a quick onset of action, and have few or no drug interactions.

LO 3

General Approach to Treatment

KEY CONCEPT Before initiating treatment for ED, a physical examination and thorough medical, social, and medication

Table 51–1

Factors Associated with ED[1,5]

Chronic Medical Conditions
Hypertension
Diabetes mellitus
Benign prostatic hyperplasia
Coronary and peripheral vascular disease
Neurologic disorders (eg, Parkinson disease and multiple sclerosis)
Endocrine disorders (hypogonadism, pituitary, adrenal, and thyroid disorders)
Psychiatric disorders
Dyslipidemia
Renal failure
Liver disease
Penile disease (Peyronie disease or anatomic abnormalities)
Surgical Procedures
Perineal or vascular surgeries
Radical prostatectomy
Lifestyle
Smoking
Excessive alcohol consumption
Obesity
Poor overall health and reduced physical activity
Trauma
Pelvic fractures or surgeries
Spinal cord or brain injuries

LO 2

Table 51–2

Medication Classes Associated with ED[3,5]

Antihypertensives
β-Blockers (excluding nebivolol)
Thiazide diuretics
Centrally acting agents (clonidine, methyldopa, and reserpine)
Spironolactone
α-Blockers
CNS Depressants
Opioid analgesics
Benzodiazepines
Hypnotics
Lipid Medications
Gemfibrozil
HMG-CoA reductase inhibitors
Antidepressants/Antipsychotics
Tricyclic antidepressants
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors
Lithium
Anticonvulsants
Carbamazepine
Phenytoin
Gastrointestinal Agents
Histamine 2-receptor antagonists
Proton pump inhibitors
Antiandrogens and Hormones
5α-Reductase inhibitors
Progesterone and estrogen
Corticosteroids
Recreational Drugs
Ethanol
Cocaine
Marijuana
Opiates

Clinical Presentation and Diagnosis

Possible Signs and Symptoms

- Marital difficulties
- Low self-confidence or morale; depression
- Full or partial inability to achieve erections
- Erections sufficient for intercourse, but early detumescence
- The problem may have a slow or acute onset, or may wax and wane.

Diagnosis

- ED may be the presenting symptom of other chronic disease states.
- The following should be performed to determine areas that can cause or exacerbate ED and to assess the patient's ability to safely perform intercourse:
  - Medical history with emphasis on cardiovascular and psychiatric disorders, diabetes, trauma, and surgical procedures
  - Social history including nutrition and history of smoking, recreational drug use, exercise, and alcohol consumption
  - Medication history including prescription, nonprescription, and herbal or dietary supplements

Physical Examination

- Review for hypogonadism (gynecomastia, testicular atrophy, reduced body hair, increase in body fat)
- Digital rectal examination to determine whether prostate is enlarged
- Vital signs
- Abnormalities of the penis; impaired vasculature or nerve function to the penis

Labs

- Fasting glucose or HbA_{1c}
- Serum testosterone if signs of hypogonadism
- Fasting lipid panel
- Further cardiac testing if warranted

Determine Severity

- Use an abridged, five-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool.[8]
- How do you rate your confidence that you could get and keep an erection?
- When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
- During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
- During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
- When you attempted sexual intercourse, how often was it satisfactory for you?
- Questions scored 1 to 5, very low to very high, respectively. Score of 21 or less indicates ED likely.

Table 51–3

The Princeton III Consensus Recommendations for Cardiovascular Risk Assessment and the Management of Erectile Dysfunction[6,10]

Risk	Risk Description	Treatment Recommendation
Low	Able to perform exercise of moderate activity without symptoms Successful revascularization (CABG, stent, angioplasty) Asymptomatic, well-controlled hypertension Mild valvular heart disease Left ventricular dysfunction/heart failure (NYHA classes I and II) Uncomplicated previous MI	May initiate or resume sexual activity and begin ED treatment without further evaluation
Intermediate	Has three or more risk factors for CV disease Mild or moderate, stable angina Had a recent MI within the past 2–8 weeks Moderate heart failure (NYHA Class III) Noncardiac sequelae of atherosclerotic disease (PAD, stroke, TIA)	Further evaluation using exercise stress testing is required before resuming sexual activity. After completion, will be reassigned to low or high risk category
High	Moderately or severely symptomatic Unstable or refractory angina, despite treatment Uncontrolled hypertension Severe heart failure (NYHA Class IV) Recent MI without intervention (< 2 weeks) High-risk cardiac arrhythmia Obstructive hypertrophic cardiomyopathy with severe symptoms Moderate or severe valvular heart disease	Sexual activity should be deferred until cardiac condition stabilized

CABG, coronary artery bypass grafting; CV, cardiovascular; NYHA, New York Heart Association; PAD, peripheral arterial disease; PDE, phosphodiesterase; TIA, transient ischemic attack; MI, myocardial infarction.

histories with emphasis on cardiac disease must be taken to assess for ability to safely perform sexual activity and to assess for possible drug interactions. The Princeton Consensus was developed to estimate risk associated with sexual activity and determine the safety of ED treatment.[6,10] In patients with intermediate or high CV risk, additional testing should occur to determine whether sexual activity is safe (Table 51–3).

LO 5

KEY CONCEPT Treatment options for ED include medical devices, pharmacologic treatments, lifestyle modifications, surgery, and psychotherapy. Reversible causes of ED should be identified first and treated appropriately. Additionally, combining different treatment modalities, that is, devices and pharmacologic options, may increase efficacy.

KEY CONCEPT When determining the best treatment for an individual, the role of the clinician is to inform the patient and his partner of all available options while understanding his medical history, desires, and goals. KEY CONCEPT The choice of treatment is primarily left up to the couple, but oral PDE5 inhibitors are considered first-line with vacuum erection devices (VEDs) as another noninvasive option. Ultimately, the choice of therapy should be individualized, taking into account patient and partner preferences, concomitant disease states, response, administration route, cost, tolerability, and safety. Common drug treatment regimens for ED are listed in Table 51–4.

▶ *Nonpharmacologic Therapy*

Lifestyle Modifications Control of risk factors and general lifestyle modifications should always be addressed first in the management of ED. A healthy diet, increase in regular physical activity, and weight loss are associated with higher IIEF scores and an improvement in erectile function.[11] The clinician should also recommend smoking cessation, reduction in excessive alcohol intake, and discontinuation of illicit drug use.

Psychotherapy Psychotherapy is an appropriate treatment approach for patients with psychogenic or mixed dysfunction. Counseling may include simple sex education and improved partner communication in addition to cognitive and behavioral therapy. Psychotherapy may help relieve anxiety and eliminate unrealistic expectations while enhancing pharmacologic efficacy.[9,12]

Vacuum Erection Devices VEDs induce erections by creating a vacuum around the penis; the negative pressure draws blood into the penis by passively dilating arteries and engorging the corpora. The erection is maintained with a constriction band placed at the base of the penis to reduce venous outflow (Figure 51–2). VEDs may be used as often as desired, but it is recommended that the constriction band not be left in place longer than 30 minutes at a time.

Patient Encounter 1, Part 1

A 68-year-old man with type 2 diabetes, hypertension, and obesity comes into your clinic for routine follow-up. When reviewing his history, he describes problems with his erections. After further questioning, you determine that his erectile dysfunction has progressively gotten worse over the last year. He is quite emotional and states that the problem is distressing and has caused significant marital discord.

Based on the available information, how would you classify his ED?

What additional information do you need before establishing an appropriate treatment regimen and determining his ability to safely perform intercourse?

Table 51–4

Common Drug Treatment Regimens for ED

Route of Administration	Generic Name	Brand Name	Typical Dosing Range[a]	Maximum Dosing Frequency
Oral	Sildenafil	Viagra	25–100 mg 1 hour prior to intercourse	Once daily
	Tadalafil	Cialis	5–20 mg 30 minutes prior to intercourse or daily dose of 2.5–5 mg	Once daily
	Vardenafil	Levitra, Staxyn	5–20 mg 1 hour prior to intercourse	Once daily
	Avanafil	Stendra	100–200 mg 15 minutes prior to intercourse	Once daily
Intracavernosal	Alprostadil	Caverject, Caverject Impulse, Edex	1.25–60 mcg 5–20 minutes prior to intercourse[b]	3 times weekly, 24 hours between injections
Intraurethral	Alprostadil	MUSE	125–1000 mcg 5–10 minutes prior to intercourse[b]	2 times daily
Intramuscular	Testosterone cypionate	Depo-Testosterone	50–400 mg every 2–4 weeks	Once weekly
	Testosterone enanthate	Delatestryl	50–400 mg every 2–4 weeks	Once weekly
	Testosterone undecanoate	Aveed	750 mg on day 1 and week 4; then every 10 weeks	After titration once every 10 weeks
Topical	Testosterone patch	Androderm	2–6 mg/day applied at night to back, abdomen, upper arms, or thighs	Once daily
	Testosterone gel	AndroGel 1%, Testim, Vogelxo	5–10 g gel per day (50–100 mg testosterone) in morning to shoulders, upper arms, abdomen (AndroGel 1% only)	Once daily
		AndroGel 1.62%	40.5–81 mg/day in morning to shoulders or upper arms	Once daily
		Natesto	11 mg intranasally 3 times daily; 6–8 hours apart (2 pump actuations, 1 per nostril)	3 times daily
		Fortesta	10–70 mg/day in morning to thigh (1–7 pumps)	Once daily
	Testosterone solution	Axiron	30–120 mg/day in morning to axilla (1–4 pumps)	Once daily
Buccal	Testosterone	Striant	30 mg every 12 hours to gum region above incisor; rotate to alternate sides with each dose	2 times daily
Subcutaneous implantable pellet	Testosterone	Testopel	150–450 mg (150 mg for every 25 mg testosterone propionate required weekly)	Every 3–6 months

[a]Use the lowest effective dose to limit adverse effects.

[b]Initial dose, to achieve erection lasting 1 hour, must be titrated in physician's office.

MUSE, medicated urethral system for erection.

Onset of action is slow, which limits spontaneity. In addition, patients and partners may complain of a cold, lifeless, discolored penis that has a hinge-like feel. Painful ejaculation or inability to ejaculate are additional adverse effects. VEDs are relatively contraindicated in persons with sickle cell disease and should be used with caution in those on oral anticoagulants or who have bleeding disorders.

VEDs are highly effective treatment modalities for ED and are considered a first- or second-line therapy. They are generally more acceptable to older patients in stable relationships and with infrequent sexual encounters. Efficacy rates are as high as 90% in obtaining an erection sufficient for intercourse, and although satisfaction rates are as high as 94%, the discontinuation rate after 2 years is close to 50%.[13] A double pumping technique in which the vacuum is applied for 1 to 2 minutes, removed, then reapplied for another 3 to 4 minutes may improve comfort levels and rigidity. Higher efficacy rates can also be achieved by combining VEDs with other therapies.

Prostheses Penile prostheses are semirigid malleable or inflatable rods, which are inserted surgically into the corpus cavernosa (see Figure 51–3). The malleable rods are rigid at all times, but may be bent into position by the patient when desired. The inflatable prostheses are preferred due to a more "natural" erection as they remain flaccid until the pump within the scrotum moves fluid from a reservoir to the cylinders within the penis. Detumescence is achieved when the fluid is then transferred back to the reservoir by activating a release button.

Patient satisfaction rates can be as high as 100%, with partner satisfaction rates slightly lower, but prostheses are the most invasive treatment available so are considered last-line therapy.[13]

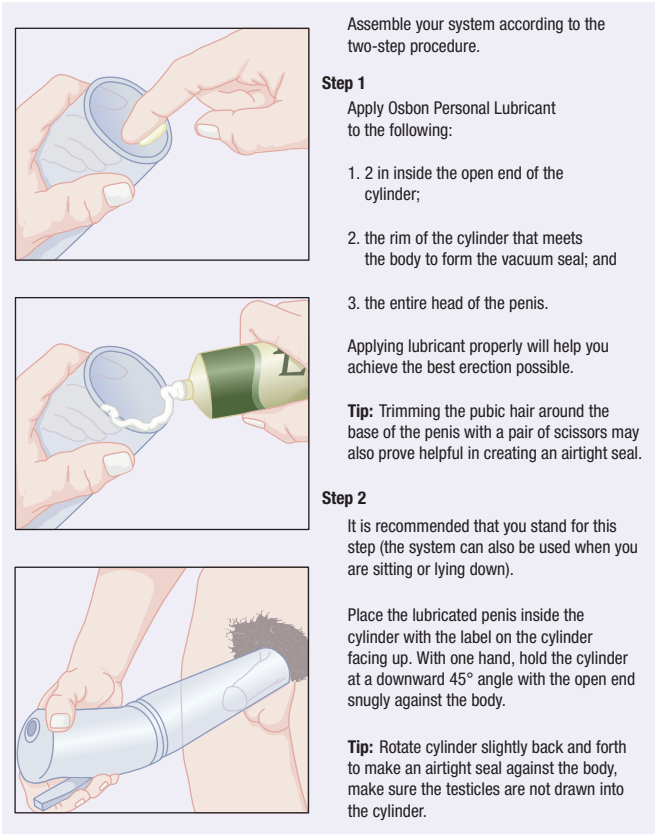

FIGURE 51–2. Technique for using a vacuum erection device. (From Lee M, Roohollah S. Erectile dysfunction. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:1319.)

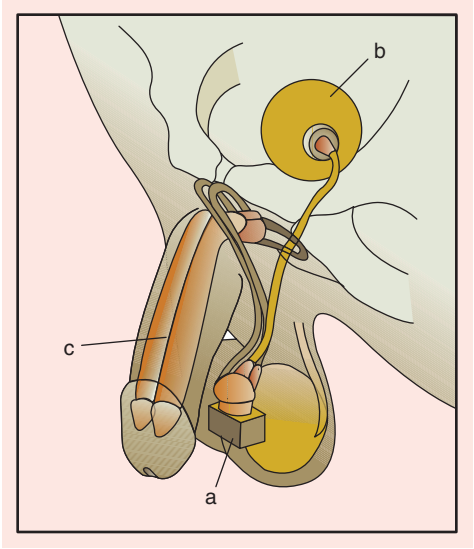

FIGURE 51–3. Example of a surgically implanted penile prosthesis. (a, activation mechanism; b, reservoir with fluid for inflating prosthesis; c, inflatable rods in corpora.) (From Lee M, Roohollah S. Erectile dysfunction. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:1331.)

Complications include mechanical failure and infection. Failure rates are less than 5% while infection occurs in 2% to 3% with primary implantation.[13]

▶ *Pharmacologic Therapy*

Phosphodiesterase Type 5 Inhibitors Avanafil, sildenafil, tadalafil, and vardenafil act by selectively inhibiting PDE5, which is responsible for degradation of cGMP. With prolonged cGMP activity, smooth muscle relaxation is induced, leading to an erection (see Figure 51–1). However, the PDE5 inhibitors are only effective in the presence of sexual stimulation to drive the NO/cGMP system, making them facilitators of an erection, not initiators.

LO 6 KEY CONCEPT Effectiveness of the four available PDE5 inhibitors is essentially comparable, but differences exist in onset, duration of action, absorption with a fatty meal, and, to a small degree, incidence of side effects and drug interactions (Table 51–5). Review of available data for each individual agent shows a 60% to 75% response rate depending on the dose of agent used and the etiology of dysfunction.[1,5] Although efficacy rates appear to be similar between agents, there are some data to suggest that continuation rates are higher and patient preference greater with tadalafil due to its longer duration of efficacy.[14] The PDE5 inhibitors are considered first-line therapies due to high efficacy rates, convenience of dosing, and minimal severe adverse effects.

The most dramatic difference among the four agents is tadalafil's extended duration of action (18 hours), earning it the nickname "the weekend pill." All are approved for as-needed dosing. Tadalafil has also been approved for use as a daily medication at a lower dose (2.5–5 mg) than the as-needed dose with similar efficacy. It also has an indication for treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia with a daily dose.

The most common side effects experienced with PDE5 inhibitors include headache, facial flushing, nasal congestion, dyspepsia, myalgia, back pain, and, rarely, priapism. Vardenafil and sildenafil may also cause blurred vision, difficulty in discriminating blue from green, bluish tones in vision, or difficulty seeing in dim light due to cross-reactivity with PDE type 6 in the retina. Labeling for all PDE5 inhibitors includes a warning about rare nonarteritic ischemic optic neuropathy in which blood flow is blocked to the optic nerve. If patients experience sudden or decreased vision loss, they should call a health care provider immediately. PDE5 inhibitors have also been associated with acute hearing impairment although a causal relationship has not been established.[1]

In addition to the inherent risk of renewing sexual activity, PDE5 inhibitors can lead to significant hypotension. Patients taking organic nitrates are at highest risk, as these drugs potentiate the drop in blood pressure. All four PDE5 inhibitors are absolutely contraindicated in patients taking any form of nitrate, whether scheduled or sublingual for acute situations. Additionally, caution should be used when combining a PDE5 inhibitor with α-blockers. Vardenafil contains a precautionary statement about the possibility of QT prolongation. Drug interactions and cautions vary slightly between agents and are described in Table 51–5.

LO 7 Up to a third of patients will not respond to therapy with PDE5 inhibitors. To achieve the greatest effect, patients must be fully informed of the onset and duration of effect, impact of high-fat meals, the need for sexual stimulation, and explanation

LO 6

Table 51–5

Comparison of PDE Inhibitors

	Sildenafil (Viagra)	Tadalafil (Cialis)	Vardenafil (Levitra, Staxyn)	Avanafil (Stendra)
Available strengths	25-, 50-, 100-mg tabs	2.5-, 5-, 10-, 20-mg tabs	2.5-, 5-, 10-, 20-mg tabs	50, 100, 200 mg
Initial dosage in healthy adults	50 mg up to once daily taken 1 hour prior to sexual activity	10 mg up to once daily taken 30 minutes prior to sexual activity or 2.5 mg daily at the same time each day	10 mg up to once daily taken 1 hour prior to sexual activity	100 mg up to once daily taken 15 minutes prior to sexual activity
Dosing range for healthy adults	25–100 mg	5–20 mg	5–20 mg	50–200 mg
Dosage in the elderly	25 mg	10–20 mg	5 mg	50–200 mg
Dosage in renal impairment	50 mg (moderate[a]) 25 mg (severe[b])	5–10 mg (moderate[a]) 5 mg (severe[b])	5–20 mg	50–200 mg[c]
Dosage in hepatic impairment	25 mg	10 mg[c]	5 mg[c]	50–200 mg[c]
Time to onset	60 minutes	30–60 minutes	60 minutes	15 minutes
Onset delayed by high-fat meal?	Yes	No	Yes	No
Duration of effect	Up to 4 hours	Up to 36 hours	Up to 4 hours	Up to 4 hours
Half-life	3–4 hours	18 hours	4–6 hours	5 hours
Metabolism	CYP3A4 (major) CYP2C9 (minor)	CYP3A4	CYP3A4 (major) CYP3A5 (minor) CYP2C (minor)	CYP3A4 (major) CYP2C9 (minor)
Clinically relevant drug interactions	Nitrates, α_1-blockers,[d] protease inhibitors, azole antifungals, erythromycin, grapefruit	Nitrates, α_1-blockers,[d] protease inhibitors, azole antifungals, erythromycin	Nitrates, α_1-blockers,[d] antiarrhythmic agents,[e] grapefruit, erythromycin	Nitrates, α_1-blockers,[d] protease inhibitors, azole antifungals, erythromycin, grapefruit

[a]Moderate renal impairment = creatinine clearance (CrCl) 31 to 50 mL/min (0.51–0.83 mL/s).

[b]Severe renal impairment = CrCl less than 30 mL/min (0.50 mL/s).

[c]Mild to moderate only—contraindicated in severe disease.

[d]Selective α_1-blockers (such as alfuzosin, silodosin, and tamsulosin) are appropriate in combination. If nonselective, initiate with lowest dose possible.

[e]Vardenafil can cause QT-interval prolongation; this effect in combination with certain antiarrhythmic agents can lead to life-threatening arrhythmias.

CYP, cytochrome P-450 isoenzyme.

that a single trial is not adequate. It is estimated that six to eight attempts with a medication and specific dose may be needed before successful intercourse.[5]

Alprostadil Alprostadil is a prostaglandin E_1 analog that induces an erection by stimulating adenyl cyclase, leading to increased cAMP, smooth muscle relaxation, rapid arterial inflow, and increased penile rigidity (see Figure 51–1). Alprostadil is available as an intracavernosal injection (Caverject or Edex) or an intraurethral suppository (MUSE, medicated urethral system for erection), with the injectable dose showing greater efficacy.[5,13] Both forms of alprostadil are considered more invasive than oral medications or VEDs and are therefore second-line therapies.

MUSE consists of a urethral pellet of alprostadil with an applicator (Figure 51–4). Onset of action is within 5 to 10 minutes and it is effective for 30 to 60 minutes. Initial dose titration should occur in a physician's office to ensure correct dose and prevent adverse events. Success rates are between 30% and 66%, with higher doses showing the most consistent response.[13] Aching in the penis, testicles, legs, and perineum; warmth or burning sensation in the urethra, minor urethral bleeding or spotting, priapism; and light-headedness are all possible adverse effects. In addition, partners may experience burning or itching, and use is contraindicated with a pregnant partner unless using a condom.

Intracavernous alprostadil injection is the more effective route and is the only Food and Drug Administration (FDA)-approved injection for ED. The onset of action is similar to intraurethral alprostadil, but duration varies with dose and must be titrated in a physician's office to achieve an erection lasting no more than 1 hour. Papaverine and phentolamine are nonapproved intracavernosal agents which are only used in combination. Injections should be performed into one side directly into the corpus cavernosum, and then the penis should be massaged to distribute the drug to both corpora (Figure 51–5). Education is extremely important with intracavernosal injections. Patients must be adequately informed of technique, expectations, side effects, and when to seek help. Intracavernosal injections are effective in 60% to 80% of patients, but side effects, lack of spontaneity, and fear of needles limit their widespread use as first-line therapy, and therefore this therapy is most appropriate for patients in long-term stable relationships.[1,5] Adverse effects include pain with injection, bleeding or bruising at the injection site, fibrosis, or priapism. Use with caution in patients with sickle cell disease, those on anticoagulants, or those who have bleeding disorders, due to an increased risk of priapism and bleeding.

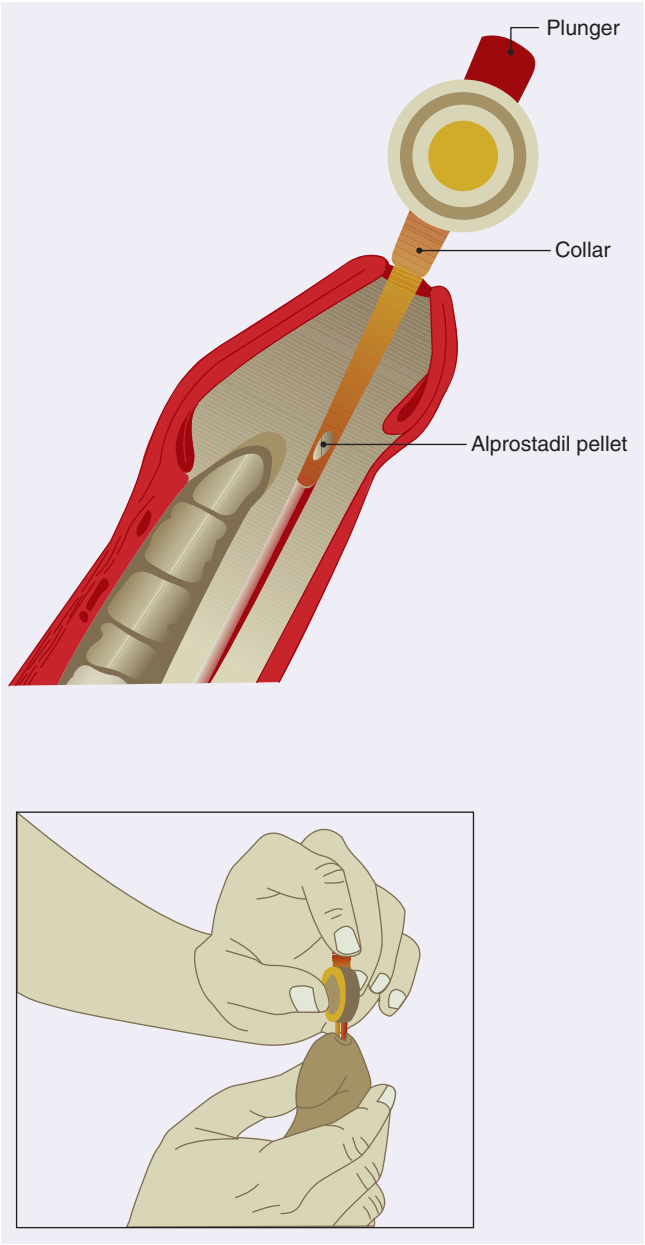

FIGURE 51–4. Technique for administration of intraurethral alprostadil with a mediated urethral system for erection applicator. (From Lee M, Roohollah S. Erectile dysfunction. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:1330.)

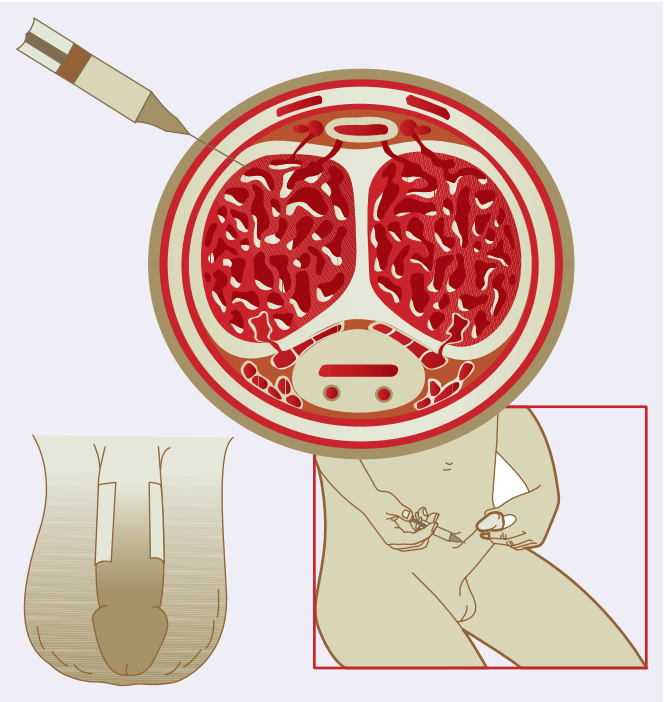

FIGURE 51–5. Technique for administration of intracavernosal injections. (From Lee M, Roohollah S. Erectile dysfunction. In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:1329.)

Testosterone Supplementation KEY CONCEPT Androgens are important for general sexual function and libido, but testosterone supplementation is only indicated in patients with documented low serum testosterone levels. In patients with hypogonadism, testosterone replacement is the initial treatment of choice, as it corrects decreased libido, fatigue, muscle loss, sleep disturbances, and depressed mood. However, testosterone is contraindicated in patients with prostate cancer, erythrocytosis, uncontrolled heart failure, or sleep apnea.

Testosterone supplementation may improve ED symptoms, but is not universally effective. Initial supplementation should occur for 3 months with reevaluation and the addition of another ED therapy if needed at that time. Dosage forms include intramuscular, an implanted pellet, topical patches or gel, nasal spray, and a buccal tablet.

Injectable testosterone cypionate and enanthate offer the most inexpensive replacement option. There are several drawbacks associated with parenteral testosterone, including the need to administer deep intramuscular injections every 2 to 4 weeks. Testosterone undecanoate offers the benefit of an extended dosing interval of 10 weeks, but is a more expensive injectable option. Concentrations of hormone are well above physiologic values within the first few days, and then decline and eventually dip below physiologic levels prior to the next dose. These changes in concentration may lead to mood swings and a reduced sense of well-being.[15] Implantable subcutaneous testosterone pellets are a longer-acting and convenient alternative which are placed every 3 to 6 months.

Treatment with topical products is attractive to patients due to convenience, but they tend to be more expensive than the injections. Testosterone patches and gels are administered daily and result in serum levels within the physiologic range during the 24-hour dosing period.[16] Care must be taken with the use of the gel to prevent transfer of testosterone to children and females by washing hands thoroughly, allowing the site to dry, and covering immediately. Newer formulations for the axilla and thigh may reduce this risk. It is recommended to avoid swimming or showering for 2 to 3 hours after patch or gel application. The most common side effects of topical testosterone are dermatologic reactions.

Oral testosterone products are also available for supplementation. Unfortunately, testosterone has poor oral

Patient Encounter 1, Part 2

PMH: Type 2 diabetes for 15 years, not controlled and is unmotivated to improve. Hypertension for 8 years, currently controlled. Dyslipidemia for 15 years, uncontrolled.

SH: Works in an office 40 hours/week; 3–4 alcoholic drinks daily; has a 25-pack per year smoking history with occasional marijuana use. No regular exercise and eats fast food regularly.

Meds: Metformin 1000 mg orally twice daily; insulin glargine 60 units subcutaneously once daily; lisinopril/HCTZ 20/25 mg orally once daily; simvastatin 20 mg orally once daily; has tried herbal products as well as "online" medications for ED with inconsistent success.

ROS: (–) Morning, nocturnal, or spontaneous erections suitable for intercourse; (–) nocturia, urgency, incomplete bladder emptying, dribbling; (–) symptoms of prostatitis; (–) chest pain or anginal symptoms; (+) significant life stressors; (+) mild pain in feet

PE:

VS: BP 135/78, P 85, RR 18, Wt 249 lb (113 kg), Ht 70 in (178 cm)

CV: Normal examination

Labs: Lipid pofile: total cholesterol, 240 mg/dL (6.21 mmol/L), HDL 38 mg/dL (0.98 mmol/L), LDL163 (4.22 mmol/L), triglycerides 246 mg/dL (2.78 mmol/L); fasting glucose 189 mg/dL (10.5 mm/L); HbA_{1c} 9% (0.09; 74 mmol/mol Hgb), total testosterone 300 ng/dL (24 nmol/L); SCr 0.9 mg/dL (80 µmol/L)

Given this additional information, what are his risk factors for ED?

Identify treatment goals for this patient.

Perform a cardiovascular risk assessment to determine risk.

What pharmacologic and nonpharmacologic alternatives are available for this patient?

Patient was referred to his cardiologist and it was determined that he may safely resume sexual activity at this time. Based on the information available, which of the available options will be your treatments of choice based on concomitant disease states and medications, degree of invasiveness, side effects, ease of use, and side-effect profile?

What are the safety and efficacy monitoring parameters for the chosen treatment?

Describe the education that should be given to the patient regarding his use of herbal and possibly counterfeit treatment for ED.

bioavailability and undergoes extensive first-pass metabolism. Alkylated derivatives such as methyltestosterone and fluoxymesterone have been formulated, but this modification makes them considerably more hepatotoxic and therefore undesirable.

An alternative to the oral route is the buccal mucoadhesive system. This system adheres to the inside of the mouth and testosterone is absorbed through the oral mucosa and delivered to the systemic circulation with no first-pass effect. Side effects unique to this dosage form include oral irritation, bitter taste, and gum edema.

General side effects of testosterone include gynecomastia, dyslipidemia, polycythemia, and acne. Weight gain, hypertension, edema, and exacerbations of heart failure also occur due to sodium retention. The undecanoate formulation also carries a risk of serious pulmonary oil microembolism reactions and anaphylaxis after any dose; therefore, patients must be monitored for 30 minutes after the injection. Before initiating testosterone, the patient should undergo evaluation for benign prostatic hypertrophy and prostate cancer. Routine follow-up includes yearly prostate-specific antigen, digital rectal examination, hemoglobin and liver function, in addition to assessment of response.

Patient Encounter 2

A 62-year-old man presents with a history of hypertension, dyslipidemia, coronary artery disease, and recently diagnosed ED. When in the office for a routine follow-up, he asks about treatment options for his ED.

Meds: Losartan/hydrochlorothiazide 50/25 mg orally once daily, metoprolol XL 100 mg orally once daily, amlodipine 5 mg orally once daily, atorvastatin 40 mg orally once daily, aspirin 81 mg orally once daily.

ROS: (–) Morning, nocturnal, or spontaneous erections suitable for intercourse; (–) nocturia, or urgency; (–) chest pain

PE:

VS: BP 173/96 mm Hg, P 69, Wt 214 lb (97 kg), Ht 69 in (175 cm)

Labs: Lipid panel, complete metabolic panel, testosterone within normal limits

Based on the information provided, what is your assessment of the patient's ED?

What should be recommended as the next step in treatment of his ED?

OUTCOME EVALUATION

Successful therapy for ED results in an increase in erections suitable for intercourse and, most importantly, in an improvement in the patient's quality of life. Ideally, the therapy chosen is free of significant adverse effects, discomfort, and inconvenience. Laboratory evaluation and a physical examination are not necessary for evaluation of effectiveness but may be necessary for adverse event monitoring.

Evaluate satisfaction and effectiveness after a 4-week trial. Some therapies will require multiple visits over the long term to determine the correct dose and to detect adverse effects. If the initial therapy is not effective, the patient must be further evaluated to determine whether the initial assessment of comorbid disease states, type of dysfunction, and patient goals were appropriate. After providing further education and determination of realistic goals, providers may then increase the dose of medication, switch to another therapy, or add a therapy if indicated.

Patient Care Process

Collect Information:

- Assess the patient's specific symptoms to determine the type of dysfunction.
- Ask specific questions related to onset and frequency of dysfunction, and status of sexual relationships. Assess severity with the IIEF-5 questionnaire.
- Perform complete full histories, physical examination, and laboratory tests (see Clinical Presentation and Diagnosis, Tables 51–1 and 51–2).
- Assess cardiovascular risk (see Table 51–3).

Assess the Information:

- Evaluate medications, concomitant disease states, and lifestyle factors which could exacerbate ED or indicate a need to defer sexual activity.
- Based on histories, determine whether the patient has either compelling indications for or contraindications to specific therapies.
- Review relevant laboratory and cardiac tests (eg, testosterone, A1c, complete metabolic panel, treadmill).
- Assess the efficacy, safety, and adverse effects of current treatment.

Develop a Care Plan:

- Treat underlying diseases, discontinue medications, and eliminate risk factors which can exacerbate ED.
- PDE5 inhibitors are first-line treatment unless contraindicated, not tolerated, or ineffective, but treatment should be individualized.
- Give supplementation if patient has low testosterone.

Implement the Care Plan:

- Initiate PDE5 inhibitor or patient treatment of choice and provide education regarding:
  - ED
  - Lifestyle
  - Treatment of associated disease states
  - Drug therapy—mechanisms of action and adverse effects
  - Device technique

Follow-up: Monitor and Evaluate:

- Follow-up in 4 to 6 weeks or more frequently to assess effectiveness and safety of therapy including specific warning signs (eg, vision changes, fibrosis, pain, priapism, or hypotension).
- Reeducate on lifestyle, associated disease states, expectations, and methods for increasing efficacy with therapy.
- Increase dosage, switch to alternate therapy, or add alternate therapy if needed.

Abbreviations Introduced in This Chapter

cAMP	cyclic adenosine monophosphate
FDA	Food and Drug Administration
cGMP	Cyclic guanosine monophosphate
IIEF	International Index of Erectile Function
MUSE	Medicated urethral system for erection
NO	Nitric oxide
PDE5	Phosphodiesterase type 5
VED	Vacuum erection device

REFERENCES

1. McMahon CG. Erectile dysfunction. Intern Med J. 2014;44:18–26.
2. Wagle KC, Carrejo MH, Tan RS. The implications of increasing age on erectile dysfunction. Am J Mens Health. 2012;6(4):273–279.
3. Morgentaler A. A 66-year-old man with sexual dysfunction. JAMA. 2004;291:2994–3003.
4. Rizk PJ, Kohn TP, Pastuszak AW, et al. Testosterone therapy improves erectile function and libido in hypogonadal men. Curr Opin Urol 2017;27:1–5.
5. Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013; 381:153–165.
6. Nehra A, Jackson G, Miner M, et al. The Princeton III consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87:766–778.
7. Shabsigh R, Arver S, Channer KS, et al. The triad of erectile dysfunction, hypogonadism and the metabolic syndrome. Int J Clin Pract. 2008;62:791–798.
8. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Dysfunction (IIEF-5) as a diagnostic tool for erectile dysfunction. IntJ Impot Res. 1999;11:319–326.
9. Simopoulos E, Trinidad A. Male erectile dysfunction: integrating psychopharmacology and psychotherapy. Gen Hosp Psychiatry. 2013;35:33–38.
10. Kostis JB, Jackson G, Rosen R. Sexual dysfunction and cardiac risk (the Second Princeton Consensus Conference). Am J Cardiol. 2005;96(2):313–321.
11. Gupta BP, Murad MH, Clifton MM, et al. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction. Arch Intern Med. 2011;171:1797–1803.
12. Gareri P, Castagna A, Francomano D, et al. Erectile dysfunction in the elderly: an old widespread issue with novel treatment perspectives. Int J Endo. 2014;2014:1–15.
13. Hatzimouratidis K, Eardley I, Giuliano F, et al. EAU guidelines on erectile dysfunction, premature ejaculation, penile curvature and priapism. 2016. European Association of Urology website. Available at: https://uroweb.org/wp.../EAU-Guidelines-Male-Sexual-Dysfunction-2016-3.pdf. Accessed August 15, 2017.
14. Morales AM, Casillas M, Turbi C. Patients' preference in the treatment of erectile dysfunction. Int J Impot Res. 2011;23:1–8.
15. Traish AM, Miner MM, Morgentaler A, Zitzmann M. Testosterone deficiency. Am J Med. 2011;124:578–587.
16. Wagner G, Saenz de Tejada I. Update on male erectile dysfunction. BMJ. 1998;316:678–682.

52 Benign Prostatic Hypertrophy

Mary Lee and Roohollah Sharifi

LEARNING OBJECTIVES

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

1. Explain the pathophysiology of benign prostatic hypertrophy (BPH).
2. Recognize the symptoms and signs of BPH.
3. List the desired treatment outcomes for BPH.
4. Identify factors that guide selection of a particular α_1-adrenergic antagonist for an individual patient.
5. Compare and contrast α_1-adrenergic antagonists versus 5α-reductase inhibitors in terms of mechanism of action, treatment outcomes, adverse effects, and interactions.
6. Describe the indications, advantages, and disadvantages of various combination drug regimens that include an α_1-adrenergic antagonist, 5α-reductase inhibitor, anticholinergic agent, tadalafil, or mirabegron.
7. Describe the indications for surgical intervention.
8. Apply the patient care process to develop an individualized treatment plan.

INTRODUCTION

The prostate is an organ, which is of the shape and size of a horse chestnut, that encircles the portion of the proximal posterior urethra that is located at the base of the urinary bladder. The prostate produces secretions, which are part of the ejaculate.

Benign prostatic hypertrophy (BPH) is the most common benign neoplasm in men who are at least 40 years of age. BPH can produce lower urinary tract symptoms (LUTS), a collection of obstructive and irritative voiding symptoms that are consistent with impaired emptying of urine from and defective storage of urine in the bladder, respectively. Medications are a common mode of treatment to reduce symptoms and/or delay complications of BPH.

EPIDEMIOLOGY AND ETIOLOGY

BPH first presents as benign prostatic hyperplasia, a histologic disease in many elderly men which increases in prevalence with advancing patient age. Benign prostatic hyperplasia may progress to BPH, which is clinically evident, and then to benign prostatic obstruction, which produces LUTS. Of patients with histologic disease, only about 50% of patients develop an enlarged prostate on digital palpation and 25% of patients exhibit clinical voiding symptoms.[1,2] It is estimated that 8% of men 40 years of age, increasing to 35% of men 60 to 69 years of age, have voiding symptoms consistent with BPH, and 20% to 30% of all male patients who live to the age of 80 years will require a **prostatectomy** for severe voiding symptoms of BPH.[2]

Two chief etiologic factors for BPH include advanced patient age and the stimulatory effect of androgens.

- Prior to 40 years of age, the prostate in the adult male is approximately 15 to 20 g. However, in men who have reached 40 years of age, the prostate undergoes a growth spurt, which continues as the men advance in age. BPH can result in clinically symptomatic LUTS.
- The testes and adrenal glands produce 90% and 10%, respectively, of circulating testosterone. Testosterone enters prostate cells, where predominantly Type II 5α-reductase converts testosterone to dihydrotestosterone, which combines with a cytoplasmic receptor. The complex enters the nucleus and induces changes in protein synthesis that promote glandular tissue growth of the prostate. Thus 5α-reductase inhibitors (eg, finasteride and dutasteride) directly interfere with one of the major etiologic factors of BPH.
- The prostate is composed of two types of tissue: (a) glandular or epithelial tissue, which produces prostatic secretions, including prostate-specific antigen (PSA), and (b) muscle or stromal tissue, which can contract around the urethra and bladder outlet when stimulated. Whereas androgens stimulate glandular tissue growth, they have no direct effect on stromal tissue. Stromal tissue growth may be stimulated by estrogen. Because testosterone is converted to estrogen in peripheral tissues in males, testosterone may be associated indirectly with stromal hyperplasia. Stromal tissue is innervated by α_{1A}-adrenergic receptors. When stimulated, prostatic stroma contracts around the urethra, narrowing the urethra and causing obstructive voiding symptoms.

PATHOPHYSIOLOGY

LO 1

KEY CONCEPT LUTS and signs of BPH are due to static, dynamic, and/or detrusor factors. The static factor refers to anatomic obstruction of the bladder neck caused by an enlarged prostate gland. As the gland grows around the urethra, the prostate

occludes the urethral lumen. The dynamic factor refers to excessive stimulation of α_{1A}-adrenergic receptors in the smooth muscle of the prostate, urethra, and bladder neck, which results in smooth muscle contraction. This reduces the caliber of the urethral lumen and causes obstructive voiding symptoms. The detrusor factor refers to bladder detrusor muscle hypertrophy in response to prolonged bladder outlet obstruction. To further explain, detrusor muscle fibers undergo hypertrophy so that the bladder can generate higher pressure to overcome bladder outlet obstruction. The hypertrophic detrusor muscle becomes irritable, contracting abnormally in response to small amounts of urine in the bladder. This causes storage voiding symptoms (urinary frequency, nocturia, urgency, or urinary incontinence). If obstruction is not treated, the bladder muscle will decompensate and be unable to empty completely; postvoid residual urine volume (PVR) will increase.

In an enlarged gland, the epithelial/stromal tissue ratio is 1:5.[3] Androgens stimulate epithelial, but not stromal tissue hyperplasia. Hence, androgen antagonism does not induce a complete reduction in prostate size to normal. This explains one of the limitations of 5α-reductase inhibitors.

Stromal tissue is the primary locus of α_1-adrenergic receptors in the prostate. An estimated 98% of the α-adrenergic receptors in the prostate are found in prostatic stromal tissue. Of the α_1-receptors found in the prostate, 70% of them are of the α_{1A}-subtype and the remainder are of the α_{1B} and α_{1D} subtypes.[4] In some patients, excessive α_1-adrenergic stimulation of stromal tissue may cause significant LUTS even though the prostate is only slightly enlarged. This explains why α_1-adrenergic antagonists are effective for managing symptoms of BPH independent of prostate size.[5]

More recently, atherosclerosis of the pelvic vascular supply to the prostate and bladder has been linked to BPH. Specifically, atherosclerosis leads to hypoxia, which stimulates prostate stromal tissue to increase release of growth factors.[6] Also, in experimental rat models, chronic inflammation may also stimulate prostate gland growth.[7]

The natural history of untreated BPH is unclear in patients with mild symptoms. It is estimated that up to 38% of untreated men with mild symptoms will have symptom improvement over a 2.5- to 5-year period.[8] It may be that such patients attribute their symptoms to aging, grow tolerant of their symptoms, or adopt behavioral changes in their lifestyle that minimize their voiding symptoms. On the other hand, a significant portion of patients with mild symptoms will likely experience disease progression. Patients with moderate to severe symptoms can experience decreased quality of life as daily activities are reduced because of LUTS. Also, such patients may develop complications of BPH. Predictors of disease progression include an enlarged prostate of at least 30 g (1.05 oz) or PSA of 1.4 ng/mL (1.4 mcg/L) or greater.[9] Finally, erectile dysfunction commonly develops in patients with BPH. Effective treatment of BPH symptoms often improves sexual function without initiating specific treatment for erectile dysfunction.[10]

Patient Encounter 1

A 65-year-old man with a BPH and an AUA Symptom Score of 22, urinary hesitancy, a slow urinary stream, urinary frequency, and nocturia presents to the clinic. He wakes up two times every night to void. A DRE reveals a prostate of 40 g (1.40 oz). His PSA is 1.8 ng/mL (1.8 mcg/L). A urinary flow rate is 7 mL/s and PVR is 100 mL.

What stage of BPH does this patient have?

How should the patient be managed?

TREATMENT

Desired Outcomes[9]

LO 3

- KEY CONCEPT Reducing or eliminating obstructive and irritative voiding symptoms. Drug treatment with an α_1-adrenergic antagonist or 5α-reductase inhibitor is expected to decrease the American Urological Association (AUA) Symptom Score (Table 52–1) by 30% to 50% (or at least by three or more points), improve peak and mean urinary flow rate by at least 1 to 3 mL/s, and decrease PVR to normal (< 50 mL total) when compared with pretreatment baseline values.
- Slowing disease progression. When compared with baseline, symptoms and serum blood urea nitrogen (BUN) and creatinine should improve, stabilize, or decrease to the normal range with treatment.
- Preventing disease complications and reducing the need for surgical intervention.
- Avoiding or minimizing adverse treatment effects.
- Providing economical therapy.
- Maintaining or improving quality of life.

Table 52–1

Questions to Determine the AUA Symptom Score

Directions for the patient: The patient should be asked to respond to each question based on the absence or presence of symptoms over the past month. For each question, the patient can respond using a 1–5 scale, where 0 = not at all or none; 1 = less than 1 time in 5; 2 = less than half of the time; 3 = about half of the time; 4 = more than half of the time; and 5 = almost always

Directions for the clinician: After the patient completes the questionnaire, the scores for individual items should be tallied for a final score. Scores of 0–7 = mild symptoms; scores of 8–19 = moderate symptoms; scores more than 20 = severe symptoms

Questions to Assess Obstructive Voiding Symptoms

1. How often have you had a sensation of not emptying your bladder completely after you finished urinating?
2. How often have you found you stopped and started again several times when you urinated?
3. How often have you had a weak urinary stream?
4. How often have you had to push or strain to begin urinating?

Questions to Assess Irritative Voiding Symptoms

5. How often have you found it difficult to postpone urination?
6. How often have you had to urinate again < 2 hours after you finished urinating?
7. How many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

AUA, American Urological Association.

Data from AUA Practice Guidelines Committee. AUA guideline on the management of benign prostatic hyperplasia (2010, reaffirmed 2014). www.auanet.org/content/guidelines-and-quality care/clinical-guidelines.cfm?sub=bph. Last accessed July 31, 2017.

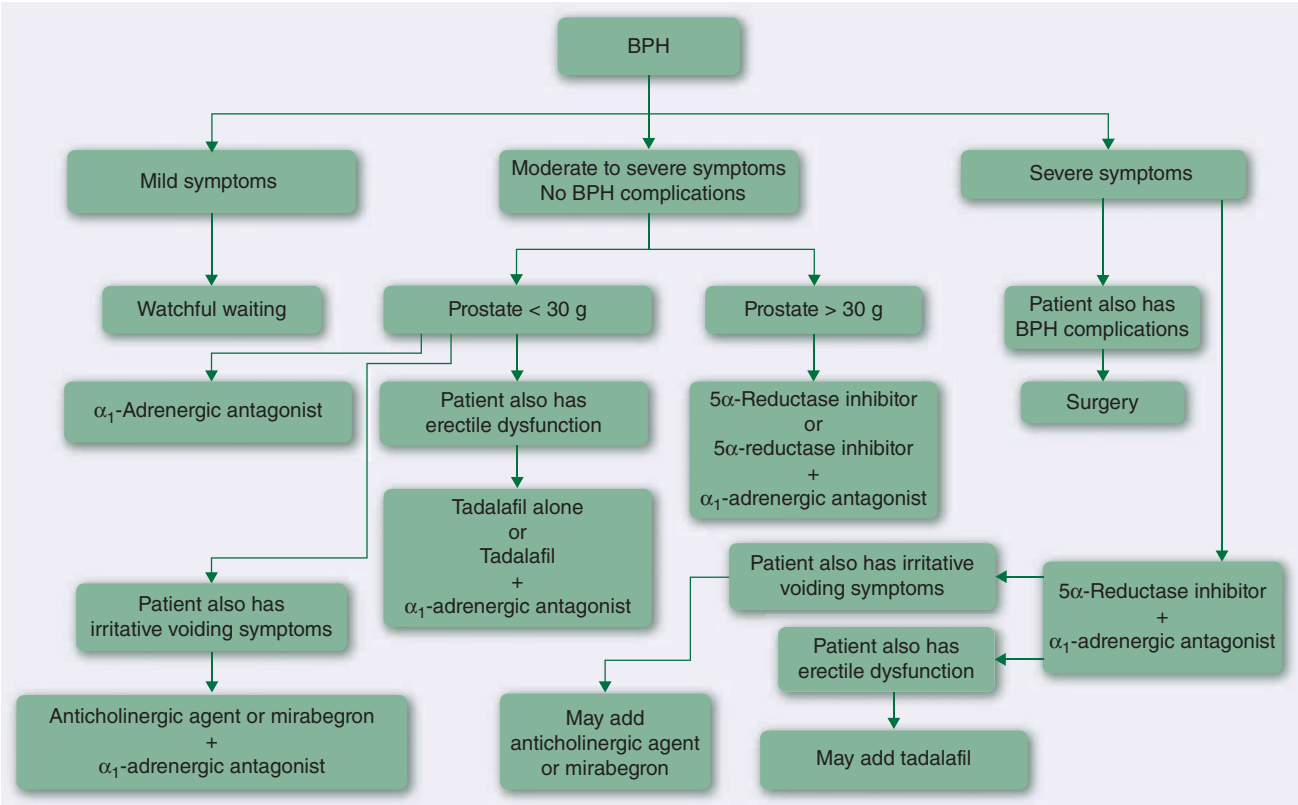

FIGURE 52–1. Algorithm for selection of treatment for BPH based on symptom severity and presence of disease complications.

General Approach to Treatment

Until recently, the principal approach to treatment focused on reducing BPH symptoms (Figure 52–1). However, treatment should also slow disease progression and decrease complications of BPH, particularly in those patients at high risk (Table 52–2).[9,11]

KEY CONCEPT For patients with mild symptoms (AUA Symptom Score of 7 or less) that the patient does not consider to be bothersome, watchful waiting is a reasonable approach to treatment (Table 52–3). The patient is instructed to schedule return visits to the clinician every 6 to 12 months. At each visit,

Table 52–2

Objective Tests Used to Assess the Severity and Complications of BPH

Test	How the Test Is Performed	Normal Test Result	Test Result in Patients with BPH
DRE of the prostate	Physician inserts an index finger into the patient's rectum and palpates the prostate	Prostate is soft, symmetric, mobile; size is 15–20 g (0.5–0.7 oz)	Prostate is enlarged, > 20 g (0.7 oz); no areas of induration or nodularity
Peak and mean urinary flow rate	Patient drinks water until bladder is full; patient empties bladder; volume of urine output and time to empty the bladder are measured; the flow rate (mL/s) is calculated	Peak and mean urinary flow rate are at least 10 mL/s	Peak and mean urinary flow rates are < 10 mL/s
PVR	Measurement of urine left in the bladder after the patient has tried to empty his bladder; assessed by urethral catheterization or ultrasonography	PVR should be 0 mL	PVR > 50 mL is a significant amount of retained urine; this is associated with recurrent urinary tract infection
Urinalysis	Midstream urine is analyzed microscopically for white blood cells and bacteria	Urine should have no white cells or bacteria in it	Urine with white blood cells and bacteria is suggestive of inflammation and infection; if positive, urine is sent for bacteriologic culture
Prostate needle biopsy	Transrectally, a biopsy needle is inserted into the prostate; tissue core is sent to a pathologist for analysis	A normal prostate should have no evidence of BPH or prostate cancer	The biopsy is consistent with BPH
PSA	Blood test for this enzyme, which is secreted by the prostate	< 4 ng/mL (4 mcg/L)	A PSA > 1.5 ng/mL (1.5 mcg/L) is a surrogate marker for an enlarged prostate > 30 g (1.05 oz)

BPH, benign prostatic hypertrophy; DRE, digital rectal examination; PSA, prostate-specific antigen; PVR, postvoid residual urine volume.

Table 52–3

Staging the Severity of BPH Based on AUA Symptom Score and Example Signs of Disease

	AUA Symptom Score	Signs of Disease
Mild	≤ 7	Enlarged prostate on DRE, peak urinary flow rate ≤ 10 mL/s
Moderate	8–19	All of the above, PVR > 50 mL, irritative symptoms
Severe	≥ 20	All of the above plus one or more complications of BPH

The AUA Symptom Score focuses on seven items (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) and asks that the patient quantify the severity of each complaint on a scale of 0 to 5. Thus the score can range from 0 to 35. A decrease in score of 3 points or more is considered a clinically significant improvement.

AUA, American Urological Association; BPH, benign prostatic hyperplasia; DRE, digital rectal examination; PVR, postvoid residual urine volume.

the patient's symptoms are reassessed using the AUA Symptom Scoring Index, and results are compared against the baseline (see Table 52–1). In addition, the patient is educated about implementing nonpharmacologic measures to reduce voiding symptoms (see section on Nonpharmacologic Therapy) and avoiding factors that worsen LUTS (Table 52–4). A digital rectal examination (DRE) is repeated annually. If the patient's symptoms are unchanged, watchful waiting is continued. If the patient's symptoms worsen, specific treatment is initiated.[9] Watchful waiting is effective in approximately 65% of patients with mild LUTS after 5 years.[9,11]

KEY CONCEPT For patients with moderate to severe symptoms and no complications of BPH, the patient is usually offered drug treatment first. α_1-Adrenergic antagonists are preferred over 5α-reductase inhibitors because the former have a faster onset of action (days to a few weeks) and improve symptoms independent of prostate size. α_1-Adrenergic antagonists are preferred for patients with LUTS, who also have a small prostate (< 30 cm^3 [approximately 30 g or 1.05 oz]).

5α-Reductase inhibitors have a delayed onset of peak clinical effect of 6 months and are most effective in patients with moderate to severe LUTS and larger size prostate glands (> 30 g or 1.05 oz). Because of the delay in clinical effect, a 5α-reductase inhibitor is often taken with an α_1-adrenergic antagonist.

With either medication, treatment must be continued as long as the patient responds (Table 52–5).[9]

KEY CONCEPT Combinations of medications to treat moderate or severe symptoms of BPH are more expensive and can cause more adverse effects than single drug treatment. Therefore, combination medication regimens are reserved for patients who have voiding symptoms that do not respond to an adequate trial of single drug treatment or patients who are at high risk of developing complications of BPH. Refer to the section on Combination Therapy for a detailed description of various regimens and their advantages and disadvantages.

LO 7

KEY CONCEPT Surgery is indicated for patients who are at risk of disease progression (ie, those with large prostates [> 30 g or 1.05 oz]), have moderate-severe symptoms and who are unresponsive to or intolerant of drug treatment, or have complications of BPH disease.[9] Although potentially curative, surgery can result in significant morbidity, including erectile dysfunction, **retrograde ejaculation**, **urethral stricture**, urinary incontinence, bleeding, or urinary tract infection. The gold standard is prostatectomy, which can be performed transurethrally using electrocautery or as an open surgical procedure. A transurethral prostatectomy

Table 52–4

Drugs and Diseases That Can Cause Irritative or Obstructive Voiding Symptoms[12]

Pharmacologic Class	Example Drugs	Mechanism of Effect
Androgens	Testosterone	Stimulate prostate enlargement to cause obstructive voiding symptoms
α-Adrenergic agonists	Phenylephrine, pseudoephedrine	Stimulate contraction of prostatic and bladder neck smooth muscle to cause obstructive voiding symptoms
Anticholinergic agents	Antihistamines, phenothiazines, tricyclic antidepressants, antiparkinsonian agents	Block detrusor muscle contraction, thereby impair bladder emptying
Caffeine	Caffeine	Acts like a diuretic to increase urine output
Calcium channel blocker	Nifedipine, diltiazem	Blocks detrusor muscle contraction, and thereby impairs bladder emptying
Diuretics	Thiazides diuretics, loop diuretics	Produce polyuria
Opiates	Morphine, hydromorphone, meperidine	Decrease bladder motility
Sedatives	Benzodiazepines, ethanol	Can cause functional incontinence
Disease[6,12]	**Example Diseases**	**Mechanism of Effect**
Diabetes mellitus		Results in glucosuria, which can cause urinary frequency; also can be associated with a neuropathy of the bladder which can produce irritative symptoms.
Neurologic disorder	Parkinson disease, multiple sclerosis, brain tumors, spinal cord injury	Associated with neurogenic bladder which can produce irritative symptoms
Urethral stricture		Reduces urethral caliber which can cause obstructive symptoms
Meatal stenosis		Blocks urethral opening which can cause obstructive symptoms
Obesity		Causes stress urinary incontinence
Cigarette smoking		Unknown

Clinical Presentation and Diagnosis of BPH

General

In early stages of disease, the patient may complain of obstructive voiding symptoms. If untreated, the disease may progress and the patient may complain of irritative voiding symptoms or acute urinary retention, which can be painful due to maximal distention of the urinary bladder. Also, the patient may be symptomatic of disease complications.

Symptoms

LO 2

Patients may complain of obstructive voiding symptoms (eg, urinary hesitancy, decreased force of urinary stream, straining to void, incomplete bladder emptying, and intermittency) and/or irritative voiding symptoms (eg, urinary frequency, nocturia, and urgency with or without incontinence). A patient with LUTS will typically seek out medical care once the symptoms curb their daily activities, are bothersome to the patient or his significant other, or cause embarrassment. Severity of symptoms should be assessed by the patient using a standardized instrument (eg, the AUA Symptom Scoring Index; Table 52–1). However, a patient's perception of the bothersomeness of his voiding symptoms may not match with the AUA Symptom Score. In this case, after thorough evaluation of the signs and complications of BPH disease, the physician and patient should discuss the bothersomeness of the symptoms and decide together on the most appropriate course of treatment.[1,9]

It should be noted that LUTS is not specific for BPH. LUTS may be due to other urologic disorders including prostate cancer, prostatitis, or neurogenic bladder.

Signs

LO 2

Enlarged prostate on DRE; check for prostate nodules or induration, which would suggest prostate cancer instead of BPH as the cause of the patient's voiding symptoms.

- Distended urinary bladder
- Rule out meatal stenosis or urethral stricture, which could cause voiding symptoms similar to LUTS.
- Check anal sphincter tone as an indirect assessment of peripheral innervation to the detrusor muscle of the bladder.

Complications of Untreated BPH

Upper and lower urinary tract infection, urosepsis, urinary incontinence refractory urinary retention, chronic renal failure, bladder diverticula, bladder stones, or recurrent gross hematuria.

Medical History

- Check the patient's general health, including previous surgery, presence of diabetes mellitus, or medications that may cause or worsen voiding symptoms.
- Have the patient provide a diary of his voiding pattern for the past week: date and time of each voiding, volume voided, and whether or not the patient had urinary leakage during the day.

Laboratory Tests

- Serum PSA: The combination of PSA and DRE of the prostate can be used to screen for prostate cancer, which could also cause an enlarged prostate. Also, PSA is a surrogate marker for an enlarged prostate due to BPH.[9]
- Urinalysis to rule out infection as a cause of the patient's voiding symptoms; also check urinalysis for microscopic hematuria, which typically accompanies BPH.
- Plasma BUN and serum creatinine may be increased as a result of long-standing bladder outlet obstruction. These tests are not routinely performed but rather are reserved for those patients in whom renal dysfunction is suspected.

Other Diagnostic Tests (Table 52–2)

- Decreased peak and mean urinary flow rate (< 10–15 mL/s) on uroflowmetry; decreased urinary flow rate is not specific for BPH; it can also be due to other urologic disorders (eg, urethral stricture, meatal stenosis, or bladder hypotonicity).
- Increased PVR greater than 50 mL
- DRE to check for an enlarged prostate (> 15–20 g [0.5–0.7 oz]).
- A focused neurological examination to check the integrity of innervation to the urinary bladder (that is responsible for bladder emptying).
- Transurethral cystoscopy reveals an enlarged prostate, which decreases urethral lumen caliber; information from this procedure helps the surgeon decide on the best surgical approach.
- Transrectal ultrasound of the prostate; a transrectal probe is inserted to evaluate prostate size and best surgical approach.
- Transrectal prostate needle biopsy to be done if the patient has areas of nodularity or induration on DRE; tissue biopsy can document the presence of prostate cancer.
- LO 2 Computerized tomography of the urinary tract (CT urogram) with contrast will show a thickened bladder wall, hydronephrosis, and retention of contrast in the bladder if the patient has chronic bladder outlet obstruction; this is only indicated in patients with recurrent hematuria, recurrent urinary tract infection, and urolithiasis.
- Filling cystometry provides information on bladder capacity, detrusor contractility, and the presence of uninhibited bladder contractions, which could also cause LUTS.

is typically reserved for prostates of intermediate size (30 g [1.05 oz] to 80 g [2.83 oz]), whereas an open prostatectomy is used for very large prostates (> 80 g [2.83 oz]) or when the patient has BPH and other associated urologic disorders, for example, large bladder stones or bladder diverticula, that can be surgically treated at the same time.[5,9] The newer bipolar technique for performing a TURP, which uses saline irrigating solution, has reduced the incidence of dilutional hyponatremia, a common adverse effect of the older monopolar technique, which uses glycine or sterile water irrigating solution.[6] The outcomes of prostatectomy include an almost immediate improvement of LUTS, an increase of peak urinary flow rate by 6 to 15 mL/s, and a PVR decrease of 30 to 80 mL. The need for reoperation is less than 1%.[6]

LO 5

Table 52–5

Comparison of α-Adrenergic Antagonists, 5α-Reductase Inhibitors, Anticholinergic Agents, Tadalafil, and Mirabegron for Treatment of BPH

Characteristic	α-Adrenergic Antagonists	5α-Reductase Inhibitors	Anticholinergic Agents	Tadalafil	Mirabegron
Relaxes prostatic smooth muscle	Yes	No	No	Yes	No
Reduces size of enlarged prostate	No	Yes	No	No	No
Useful in patients with enlarged prostates	Yes (works independent of the size of the prostate)	Yes	Yes	Yes	No[a]
Efficacy in relieving voiding symptoms and improving flow rate	++	+	+, irritative symptoms	+	+, irritative symptoms
Reduces the frequency of BPH-related complications	No	Yes	No	No	No
Reduces the frequency of BPH-related surgery	No	Yes	No	No	No
Frequency of daily dosing	Once or twice daily, depending on the agent and the dosage formulation	Once daily	Once or twice daily, depending on the agent	Once daily	Once daily
Requirement for up-titration of dose	Yes (for terazosin and doxazosin immediate-release); no (for alfuzosin or silodosin; possibly for doxazosin extended-release and tamsulosin)	No	Yes, depending on the agent	No	Yes, but minimal
Peak onset of action	Days to 6 weeks, depending on need for dose titration	6 months	Days	Days	2–8 weeks
Decreases PSA	No	Yes	No	No	No
Cardiovascular adverse effects	Yes, hypotension	No	Yes, tachycardia	Yes, hypotension	Yes, hypertension, tachycardia
Drug-induced sexual dysfunction	Ejaculation disorders	Decreased libido, erectile dysfunction, ejaculation disorders	Yes, erectile dysfunction	No	No
Significant drug interactions	Antihypertensives Calcium channel blockers β-adrenergic antagonists CYP 3A4 inhibitors CYP 3A4 inducers	CYP 3A4 inhibitors (dutasteride only)	Drugs with anticholinergic effects/side effects Drugs that prolong QT interval CYP 3A4 inhibitors CYP 3A4 inducers	Nitrates Drugs that prolong QT interval CYP 3A4 inhibitors CYP 3A4 inducers α-Adrenergic antagonists	CYP2D6 substrates Drugs that prolong the QT interval

[a]Mirabegron is not FDA-approved for BPH.

BPH, benign prostatic hyperplasia; CYP, cytochrome P-450; PSA, prostate-specific antigen.

To minimize complications of prostatectomy,[13] or in patients who are taking anticoagulants, minimally invasive surgical procedures, such as transurethral incision of the prostate, transurethral needle ablation, transurethral microwave thermotherapy, or transurethral laser ablation, are options.[14,15] A variety of ablative laser energy sources are used to vaporize tissue: holmium, potassium-titanyl-phosphate (KTP or green light), or diode. The choice of energy source is largely determined by the surgeon's level of training, the patient's anatomy, and potential risks for the patient. The potential advantages of minimally invasive surgical procedures include less blood loss, shorter periods of catheterization postoperatively, and no need for hospitalization. However, minimally invasive surgical procedures are associated with a higher reoperation rate than a prostatectomy.[16]

Nonpharmacologic Therapy (Behavioral Modification)

To reduce nocturia, patients should be instructed to stop drinking fluids 3 or 4 hours before going to bed and then void before going to sleep. During the day, timed voidings every 2 to 3 hours, double voiding, toilet mapping (knowing the location of toilets on the way to and from various destinations), or voiding before a long trip may be helpful. Patients should avoid excessive intake of caffeine-containing beverages, sugar-sweetened drinks, and alcohol because these may cause urinary frequency. Patients should avoid taking nonprescription medications that can worsen obstructive voiding symptoms (eg, antihistamines or decongestants) (see Table 52–4). Patients who take a diuretic

should avoid taking it in the evening. Patients are also advised to stop smoking and lose excessive weight. An alteration in the testosterone:estrogen ratio occurs in overweight men because of testosterone conversion to estrogen in adipose tissue, which may contribute to the development of BPH.[17]

Although a variety of herbal agents are used for symptomatic management, including pygeum (African plum), secale cereale (rye pollen), serenoa repens, and hypoxis rooperi (South African star grass), objective evidence of efficacy is lacking.[18]

Pharmacologic Therapy

▶ α_1-Adrenergic Antagonist Monotherapy[19]

KEY CONCEPT α_1-Adrenergic antagonists reduce the dynamic factor causing BPH symptoms. These drugs competitively antagonize α_1-adrenergic receptors, thereby causing relaxation of the bladder neck, prostatic urethra, and prostate smooth muscle.[9,19] A secondary mechanism of action may be that α_1-adrenergic antagonists induce prostatic apoptosis.[20]

All α_1-adrenergic antagonists are considered equally effective in relieving symptoms.[9,19] See Table 52–6. In various clinical trials, 30% to 80% of patients experience improvement in the AUA Symptom Score by 30% to 45%, and 20% to 40% of patients experience urinary flow rate increases of 2 to 3 mL/s. The onset of action is days to weeks, with peak clinical effects observed in several weeks. An adequate clinical trial is at least 2 to 4 weeks of continuous treatment at a full maintenance dose with any of these agents.[9] Durable responses have been demonstrated for many years with continued use. However, some patients will develop disease progression despite treatment. α_1-Adrenergic antagonists are hepatically metabolized. Therefore, in patients with significant hepatic dysfunction, these drugs should be used in the lowest possible dose. With the exception of silodosin, these drugs do not require dosage modification in patients with renal dysfunction.

LO 4

α_1-Adrenergic antagonists can be distinguished by several characteristics:

- *Uroselectivity*. Pharmacologic uroselectivity refers to preferential inhibition of α_{1A}-receptors, which predominate in the prostatic stroma, prostatic urethra, and bladder neck.[19,21] Pharmacologically uroselective α_{1A}-adrenergic antagonists, tamsulosin and silodosin, have the potential to produce less hypotension than other α_1-adrenergic antagonists, because the former have a lower propensity to antagonize α_{1B}-adrenergic receptors in the peripheral vasculature. Silodosin has significantly greater α_{1A}-adrenergic selectivity than tamsulosin and is preferred when a patient has minimal tolerance for any blood pressure–lowering adverse effects.[19,22]

  Despite the potential of inhibiting α-adrenergic receptors in both the prostate and peripheral vasculature, usual doses of alfuzosin, a functionally uroselective α_1-adrenergic antagonist, produce effective relaxation of prostatic smooth muscle with minimal vascular vasodilation.[19]

- KEY CONCEPT Both pharmacologically and functionally uroselective agents appear to be clinically uroselective, in that they improve BPH symptoms with a low potential to cause cardiovascular adverse effects in humans. They are preferred in patients who usually have low blood pressure or those taking multiple antihypertensives.[21,22]

  Pharmacologic and functional uroselectivity are dose-related phenomena. Large daily doses of tamsulosin, silodosin, or alfuzosin may cause loss of uroselectivity, with resultant hypotension and dizziness in some patients.[23]

  Despite the blood pressure–lowering property of α_1-adrenergic antagonists, they are not recommended to be used alone to treat patients with both BPH and essential hypertension. In the ALLHAT study,[24] where doxazosin was compared with other agents for treatment of essential hypertension, it was associated with a higher incidence of congestive heart failure. Therefore, in patients with both hypertension and moderate to severe LUTS, it is recommended that an appropriate antihypertensive be added to an α_1-adrenergic antagonist.

- *Need for up-titration of daily dose*. Up-titration is required for immediate-release terazosin and doxazosin. It is minimally required for extended-release doxazosin and tamsulosin. It is not required for extended-release alfuzosin or silodosin. The need for up-titration with a particular α_1-adrenergic antagonist delays its onset of peak action.

- *Plasma half-life*. α_1-Adrenergic antagonists with short plasma half-lives (eg, prazosin, which is a first generation α_1-adrenergic antagonist) require multiple doses during the day. This is challenging for most patients, and thus prazosin is not recommended for BPH.[9]

- *Dosage formulation*. Immediate-release formulations of terazosin and doxazosin are quickly absorbed and produce high peak plasma levels. Modified- or extended-release formulations of doxazosin, alfuzosin, tamsulosin, and silodosin produce lower peak levels, but more sustained therapeutic plasma levels, than immediate-release formulations and have less potential for producing hypotensive episodes. This allows for initiation of treatment with a therapeutic dose, a faster onset of peak clinical effects, and once daily dosing.[19]

- *Adverse effects*. Hypotensive adverse effects of α_1-adrenergic antagonists can range from asymptomatic blood pressure reductions to dizziness and syncope. This adverse effect occurs in approximately 2% to 14% of treated patients and is most commonly associated with immediate-release terazosin and doxazosin; is less commonly associated with extended-release alfuzosin and extended-release doxazosin; and least commonly associated with tamsulosin and silodosin.[9,19,23] To minimize first-dose syncope from terazosin and doxazosin immediate-release, a slow up-titration from a subtherapeutic dose of 1 mg/day to a therapeutic dose is essential. The first dose should be given at bedtime so that the patient can sleep through the peak serum concentration of the drug when the adverse effect is most likely to occur. A 3- to 7-day interval between each dosage increase should be allowed, and the patient should be maintained on the lowest effective dose of an α_1-adrenergic antagonist. If the patient is noncompliant with his regimen or he skips or interrupts treatment, the α_1-adrenergic antagonist should be restarted using the usual starting dose and then retitrated up. The patient should not be instructed to simply double up on missed doses or resume treatment with the currently prescribed daily dose, as this can lead to significant hypotension or syncope.

Reversible delayed, absent or retrograde ejaculation occur with all α_1-adrenergic antagonists. This is due to pharmacologic blockade of peripheral α_{1A}-adrenergic receptors in the vas deferens and seminal vesicles, which results in decreased antegrade flow of semen to the ejaculatory ducts, or at the bladder neck.[25,26]

Table 52–6

Comparison of Pharmacologic Properties of α_1-Adrenergic Antagonists

	Terazosin	Doxazosin	Alfuzosin	Tamsulosin	Silodosin
Brand name	*	Cardura Cardura-XL	Uroxatral	Flomax	Rapaflo
Generation	Second	Second	Second	Third	Third
Uroselective	No	No	Functionally (Clinically)	Pharmacologically	Pharmacologically
Need for up-titration	Yes	Yes (with immediate-release); possibly (with extended-release)	No	Minimal	No
Daily oral dose (mg)	5–20	2–8, immediate-release; 4–8, extended-release	10	0.4–0.8; (0.8 mg/day dose has not consistently produced clinical improvement over 0.4 mg/day)	8
Recommended dose reduction in patients with renal dysfunction	None needed	None needed	Manufacturer recommends caution in patients with severe renal insufficiency. No specific dosing recommendations provided	If creatinine clearance > 10 mL/min (0.17 mL/s), none needed. Tamsulosin has not been studied in patients with creatinine clearance < 10 mL/min (0.17 mL/s)	If creatinine clearance 30–50 mL/min (0.50–0.83 mL/s), use 4 mg/day. Contraindicated in patients with creatinine clearance < 30 mL/min (0.50 mL/s)
Recommended dose reduction in patients with hepatic dysfunction	Manufacturer provides no specific recommendation. Terazosin should be used cautiously as it undergoes extensive hepatic metabolism	Manufacturer provides no specific recommendation. Doxazosin should be used cautiously as it undergoes extensive hepatic metabolism	Contraindicated in patients with moderate/severe hepatic impairment. Alfuzosin should be used cautiously in patients with mild hepatic impairment	Patients with mild/moderate hepatic impairment require no dosage adjustment. Tamsulosin has not been studied in patients with severe hepatic impairment	Patients with mild/moderate hepatic impairment require no dosage adjustment. Contraindicated in patients with severe hepatic impairment
Best time to take doses	At bedtime	Immediate-release: anytime during the day; however, it is typically given at bedtime Extended-release: anytime during the day	After meals for best oral absorption	On an empty stomach for best oral absorption. If taken 30 minutes after a meal, as recommended by the manufacturer, extent of absorption is reduced, thereby further reducing the potential for hypotensive adverse effects	Take with a meal, which decreases extent of absorption. Theoretically, this would help decrease hypotensive adverse effects
Special administration instructions	None	Do not crush, cut, or chew extended release tablet	Do not crush or chew tablet	Do not crush, chew, or open capsule	May open capsule and sprinkle on applesauce. Must swallow (not chew) applesauce within 5 minutes of preparation. Follow with a full cup of water.
Half-life (hours)	12	22	5	10	13
Formulation	Immediate-release	Immediate-release and extended-release	Extended-release	Modified-release	Modified-release
Cardiovascular adverse effects	++	++	+	0 to +	0 to +
Ejaculation disorders	+	+	+	++	++
Rhinitis	+	+	+	+	+
Malaise	+	+	+	+	+
Major substrate for CYP 3A4	No	Yes	Yes	Yes	Yes

+ minimal; ++ moderate; * terazosin is only available as a generic formulation.

The incidence appears to be dose-related and highest with daily doses of tamsulosin 0.8 mg and silodosin 8 mg, occurring in up to 26% and 28% of treated patients, respectively.[25,27,28] Ejaculation disorders generally do not necessitate discontinuation of treatment as some elderly patients may not be sexually active. Although this adverse effect may decrease a younger patient's satisfaction with the quality of sexual intercourse, ejaculation disorders are not harmful to the patient.

Nasal congestion and malaise occur with α_1-adrenergic antagonists and are an extension of the pharmacologic blockade of α_{1B}-adrenergic receptors in the vasculature of the nasal mucosa and in the central nervous system, respectively. Tolerance often develops to these adverse effects and they rarely require discontinuation of treatment. Avoid use of topical or oral decongestants, as these may exacerbate obstructive voiding symptoms. Cautious use of antihistamines with anticholinergic adverse effects is also recommended in patients with severe BPH and large PVRs, as these drugs may precipitate acute urinary retention.

Floppy iris or small pupil syndrome has been reported with α_1-adrenergic antagonists, most often with selective α_{1A} adrenergic antagonists.[9] In response to tamsulosin, the iris dilator muscle relaxes and the pupil constricts. Pupillary constriction interferes with the surgical procedure and increases the risk of intraoperative and postoperative complications. As a result, when the α_1-adrenergic antagonist–treated patient undergoes cataract surgery, the iris can become flaccid, floppy, or billow out. The iris can prolapse into the incision.[29,30] A patient who plans to undergo cataract surgery is advised to inform his ophthalmologist that he is taking an α_1-adrenergic antagonist. Although the drug will not need to be held or discontinued, the ophthalmologist can plan to use certain surgical techniques to deal with the drug's effect on the iris dilator muscle.[29] Likewise, prior to initiating an α_1-adrenergic antagonist, a patient who needs cataract surgery should have this ophthalmologic procedure performed first, if possible.[30]

- *Potential for drug interactions*. Hypotensive adverse effects of terazosin and doxazosin can be additive with those of diuretics, antihypertensives, and phosphodiesterase type 5 inhibitors (eg, sildenafil). In patients at greatest risk for hypotension, or in those patients who tolerate hypotension poorly, including those with poorly controlled coronary artery disease or severe orthostatic hypotension, tamsulosin or silodosin appear to be the safest choice. In patients who cannot tolerate adverse effects of any α_1-adrenergic antagonist, a 5α-reductase inhibitor or prostatectomy could be considered, particularly if the prostate is enlarged and greater than 30 g (1.05 oz). When initiating a phosphodiesterase type 5 inhibitor, patients who are taking α_1-adrenergic antagonists should be stabilized first on a fixed dose of the α_1-adrenergic antagonist, and then patients should be started on the lowest effective dose of phosphodiesterase type 5 inhibitor to minimize the likelihood of hypotensive effects.[31]

▶ *5α-Reductase Inhibitor Monotherapy*

KEY CONCEPT 5α-Reductase inhibitors reduce the static factor, which results in shrinkage of an enlarged prostate by approximately 15% to 25% after 6 months of continuous treatment. They inhibit 5α-reductase, which is responsible for intraprostatic conversion of testosterone to dihydrotestosterone, the active androgen that stimulates prostate tissue growth. Two subtypes of 5α-reductase, Type I and II, are present in the prostate; the majority is the Type II isoenzyme.[6,32] Finasteride is a selective Type II isoenzyme inhibitor, whereas dutasteride is a nonselective inhibitor of both isoenzymes. When compared with finasteride, dutasteride produces a faster and more complete inhibition of 5α-reductase in prostate cells. However, no difference in clinical efficacy has been demonstrated between these two agents.[9,32,33] Thus finasteride and dutasteride are considered therapeutically equivalent (Table 52–7). It should be noted that 5α-reductase inhibitors may also cause apoptosis of prostate cells, which could contribute to a reduction in prostate gland size.[34]

Table 52–7

Comparison of Pharmacologic Properties of 5α-Reductase Inhibitors

	Finasteride	Dutasteride
Brand name	Proscar	Avodart
Subtype inhibition of the 5α-reductase enzyme	Type II	Types I and II
Percentage decrease of serum dihydrotestosterone level	70–76	90–95
Time to peak onset of reduction in serum dihydrotestosterone level	6 months	1 month
Percentage decrease of intraprostatic dihydrotestosterone	85–90	> 95
Half-life	6.2 hours	5 weeks
Daily dosage (mg)	5	0.5
Dosage formulation	Tablet	Capsule
Instructions for drug administration	Take with or without meals	Take with or without food. Do not open or chew capsules. Swallow capsule whole
Recommended dose reduction in patients with renal dysfunction	None needed	None needed
Recommended dose reduction in patients with hepatic dysfunction	Manufacturer provides no specific recommendation. Finasteride should be used cautiously as it undergoes extensive hepatic metabolism	Manufacturer provides no specific recommendation. Dutasteride should be used cautiously as it undergoes extensive hepatic metabolism

Patient Encounter 2

A 60-year-old man is diagnosed with moderate LUTS secondary to BPH. Because he also has erectile dysfunction and is sexually active, tadalafil 5 mg daily was prescribed. After a month of treatment, the patient reports that he doesn't seem to notice any improvement in his voiding symptoms.

What assessments should be performed?

Let us assume that the patient was adherent to the prescribed regimen and was not taking any other medications or have any medical disorders that could contribute to LUTS. How should the patient be managed?

Finasteride and dutasteride are considered equally effective in relieving LUTS by 15% to 30% in 30% to 70% of patients, increasing the urinary flow rate by 1 to 2 mL/s, and decreasing PVR by 18% to 28%, which is less improvement than that seen with α_1-adrenergic antagonists.[35] A minimum of 6 months is required to evaluate the full clinical effectiveness of treatment. This is a disadvantage in patients with moderate to severe symptoms, as it will take that long to determine whether the drug is or is not effective. Durable responses have been demonstrated in responding patients treated continuously for years. Unlike α_1-adrenergic antagonists, long-term use of 5α-reductase inhibitors is used to prevent BPH-related complications and disease progression. 5-α-Reductase inhibitors have been shown to reduce both the incidence of acute urinary retention by 57% and the need for prostate surgery by 55% in patients with significantly enlarged prostate glands (> 40 g [1.4 oz]) when used continuously for at least four consecutive years.[36,37]

These agents are hepatically metabolized. No specific recommendations for dosage modification are available in patients with significant hepatic dysfunction. No dosage adjustment is needed in patients with renal impairment.

Sexual dysfunction, including decreased libido, erectile dysfunction, ejaculation disorders, and gynecomastia, occurs in 5% to 15% of treated patients.[38] The frequency of sexual dysfunction peaks generally 1 year after the start of treatment,[27] and the incidence of such adverse effects tends to be higher for dutasteride than for finasteride.[33] Recently, a postfinasteride syndrome of persistent sexual dysfunction even after discontinuation of finasteride has been described.[26] Some have suggested that the sexual dysfunction is more likely due to age-related sexual dysfunction, which developed in a patient who coincidentally had been taking finasteride. More studies are needed before any conclusions can be made. Also, dutasteride has been shown to increase insulin resistance in adipose tissue,[39] and may be associated with an increased risk of congestive heart failure.[40] Finally, the 5α-reductase inhibitors are associated with a dose-related increased risk of osteoporosis.[41] Further study is needed to establish cause–effect relationships for these possible adverse effects.

These agents reduce the incidence of prostate cancer by 25%, but are suspected to increase the risk of developing moderate to high grade cancer, if prostate cancer does develop.[42]

Exposure to 5α-reductase inhibitors is contraindicated in pregnant females, as the drugs may cause feminization of a male fetus. Pregnant females should not handle these drugs unless they are wearing gloves.

During continuing treatment of BPH, the patient should undergo an annual repeat PSA and DRE. These agents decrease PSA by a mean of 50% after 6 months of continuous use. A rising PSA level suggests that the patient has worsening BPH, new-onset prostate cancer, or that the patient is noncompliant with his regimen of 5α-reductase inhibitor. An abnormal DRE suggestive of prostate cancer would reveal a nodule or area of induration on the prostate. In such a case, a prostate biopsy is required to rule out prostate cancer.

► *Tadalafil*

Tadalafil is expensive; therefore, the best candidates for treatment are those with BPH and erectile dysfunction, or those patients with LUTS that is not responsive to α-adrenergic antagonists. Tadalafil may be prescribed alone, or along with an α_1-adrenergic antagonist or 5α-reductase inhibitor. Its mechanism is probably due to relaxation of smooth muscle of the urethra, prostate, and bladder neck, which is mediated by increased production of cyclic guanosine monophosphate and hence, nitric oxide, which increases perfusion of the pelvic organs, including the prostate.[43] Tadalafil is comparable to α_1-adrenergic antagonists in relieving LUTS and decreasing the AUA Symptom Score by 3.8 points after 12 weeks; however, it does not produce a clinically significant increase in urinary flow rate or reduce PVR.[43] The usual recommended dose is 5 mg by mouth daily; the dose should be reduced to 2.5 mg daily if the creatinine clearance is 30 to 50 mL/min (0.50–0.83 mL/s). Tadalafil should be avoided if the creatinine clearance is less than 30 mL/min (0.50 mL/s). Tadalafil is contraindicated in patients on nitrates by any route of administration. If the patient is sexually active, tadalafil should not be used in patients with unstable angina, uncontrolled or high-risk arrhythmias, persistent hypotension, poorly controlled hypertension, or New York Heart Association Classification IV congestive heart failure; or patients who have had a myocardial infarction within the past 2 weeks.[44] Common adverse effects include headache, dizziness, flushing, back pain, myalgia, and cyanopsia (Table 52–8).

Although other phosphodiesterase type 5 inhibitors share the same mechanism of action as tadalafil and can improve the AUA Symptom Score, tadalafil is preferred because of its longer plasma half-life, which is theoretically beneficial in the management of BPH, a chronic disease.

► *Anticholinergic Agents*

Irritative voiding symptoms are due to involuntary detrusor muscle contraction in response to small volumes of urine in the bladder. The detrusor muscle is innervated with muscarinic receptors. M_2 receptors comprise 75% of all muscarinic receptors; however, their physiologic function, along with that of M_4 and M_5 receptors, is not well understood. M_3 receptor stimulation is associated with abnormal detrusor contractions, which can cause irritative voiding symptoms.[45]

Anticholinergic agents are indicated when a patient has bothersome irritative voiding symptoms despite treatment with an α_1-adrenergic antagonist. Typically, an anticholinergic agent is added sequentially to an established α_1-adrenergic antagonist regimen. The ideal patient for the combination has a urinary flow rate of at least 10 mL/s and a PVR less than 50 mL. A recent meta-analysis showed that the addition of an anticholinergic agent to an α_1-adrenergic antagonist improved irritative symptoms more than what was observed with the α_1-adrenergic antagonist alone.[46] No cases of urinary retention were reported.

Table 52–8

Summary of Adverse Effects of α-Adrenergic Antagonists, 5α-Reductase Inhibitors, Anticholinergic Agents, and Tadalafil and Management Suggestions

Drug Class	Adverse Reaction	Management Suggestion
α-Adrenergic antagonist	Hypotension	Start with lowest effective dose, give doses at bedtime, and slowly up-titrate at 0.5- to 1-week intervals to a full therapeutic dose, if using immediate-release terazosin or doxazosin. Use tamsulosin, silodosin, extended-release doxazosin, or alfuzosin, as alternatives to immediate-release products, particularly in patients with low blood pressure at baseline or in those taking other antihypertensives.
	Malaise	Educate the patient that this is a common adverse effect; tolerance may develop to malaise. Usually does not require discontinuation of treatment.
	Nasal congestion	Educate the patient that this is a common adverse effect; tolerance may develop to rhinitis. Usually does not require discontinuation of treatment. Avoid decongestants.
	Ejaculation disorders	Educate the patient that this is a common adverse effect and it is not harmful.
	QT interval prolongation	This is a rare but potentially serious adverse effect of alfuzosin only. The patient will most likely have chest pain, dizziness, loss of energy, and pass out. The patient should discontinue the medication and seek immediate notification of the prescriber.
5α-Reductase inhibitor	Gynecomastia	Educate the patient that this may be painful or bothersome, but not harmful.
	Decreased libido	If the patient is sexually active, sexual counseling may be helpful. May be reversible despite continued use of the 5α-reductase inhibitor.
	Erectile dysfunction	The addition of sildenafil or another erectogenic drug may be helpful. May be reversible despite continued use of the 5α-reductase inhibitor.
	Ejaculation disorders	Educate the patient that this may occur but it is not harmful. May be reversible despite continued use of the 5α-reductase inhibitor.
Anticholinergic agent	Dry mouth	Educate the patient that this is a common adverse effect. If drinking fluids and sucking on sugarless hard candy are not effective, the health care provider may switch to another agent in the same class or possibly reduce the daily dose.
	Constipation	This is a common adverse effect. Educate the patient to drink plenty of fluids and eat a high-fiber diet.
	Confusion, drowsiness	If this occurs, consider switching to another agent in the same class with less potential to cross the blood–brain barrier, eg, trospium.
	Acute urinary retention	Do not use anticholinergic agents in patients with a PVR > 250 mL as they are high risk of developing this adverse effect, which is a urologic emergency.
	Increased risk of heat stroke	By decreasing perspiration, patients who are in hot climates and who do not have access to air conditioning, are at risk of heat stroke. Use of anticholinergic agents in elderly who are exposed to these conditions should be avoided.
Tadalafil	Headache	Educate the patient that this is a common adverse effect. It is usually mild, temporary, and does not require treatment discontinuation. If necessary, acetaminophen is usually effective.
	Dizziness	Educate the patient that this is a common adverse effect and does not require treatment. If the patient is taking other blood pressure–lowering medications, stabilize blood pressure on these medications before starting tadalafil.
	Flushing	This is a reversible, dose-related adverse effect that does not require treatment discontinuation.
	Nasal congestion	This is an extension of the vasodilatory effects of tadalafil. It is reversible, dose-related, and does not require treatment discontinuation.
	Visual loss	This can occur any time after tadalafil is started. It is usually painless. The patient should discontinue tadalafil and seek immediate medical attention.
	Back pain	If severe, the patient should report this to the clinician. It may require discontinuation of tadalafil.
	Dyspepsia	Heartburn-like symptoms may occur. Usually, it is mild and does not require treatment.
	Back pain or myalgia	This occurs more often with tadalafil than with the other phosphodiesterase inhibitors. It usually resolves once the drug is stopped. If not severe, tadalafil may be continued as the adverse effect may resolve with continued tadalafil use.
Mirabegron	Hypertension	May need to initiate or adjust existing antihypertensive medications. Educate patient to monitor blood pressure while taking this medication.
	Tachycardia	Educate the patient that this is a common adverse effect. However, if increased pulse rate or palpitations are associated with low blood pressure, chest pain, or difficulty breathing, the patient should seek medical attention.
	Headache	Educate the patient that this is a common adverse effect. It is usually mild, temporary, and does not require treatment discontinuation. If necessary, a low dose of acetaminophen is usually effective.
	Constipation	This is a common adverse effect. Educate the patient to drink plenty of fluids and eat a high-fiber diet.
	Dizziness	Educate the patient that this is a common adverse effect. The patient should monitor blood pressure and seek medical attention if dizziness is moderate or severe.
	Angioedema	In addition to swelling of the face, lips, tongue, and throat, the patient may have shortness of breath and wheezing. This is an allergic reaction that requires immediate discontinuation of the drug and notification of the prescriber. The patient should not continue taking mirabegron unless the prescriber approves doing so.
	QT interval prolongation	This is a rare but potentially serious adverse effect. The patient will most likely have chest pain, dizziness, loss of energy, and pass out. The patient should discontinue the medication and seek immediate notification of the prescriber.

Many anticholinergic agents are available. Darifenacin is the only M_3 uroselective anticholinergic agent. Because M_3 receptors are present in the gastrointestinal tract, and eye, darifenacin can cause constipation, xerostomia, and mydriasis. Refer to the chapter on Urinary Incontinence and Pediatric Enuresis for a discussion of the properties of anticholinergic agents.

If irritative symptoms do not improve after starting an anticholinergic agent, up-titrating the dose or switching to another anticholinergic agent may be helpful. Patients at the highest risk of anticholinergic agent-induced acute urinary retention include those with a PVR of 250 mL or more, low urinary flow rate, or previous history of acute urinary retention.[47] Also, the medication profile of patients should be checked for overall anticholinergic burden, which increases the likelihood of anticholinergic adverse effects, including dry mouth, tachycardia, constipation, confusion, and drowsiness. Finally, elderly patients have a high risk of cognitive impairment from anticholinergic agents, especially those with a history of stroke, head trauma, Parkinson disease, and Alzheimer disease.[47]

▶ *Mirabegron*

In the urinary bladder, 95% of all β-adrenergic receptors are of the β_3 type. Receptor stimulation relaxes the detrusor muscle, but does not interfere with the bladder's contractility.[48]

Mirabegron is a β_3-adrenergic agonist. It causes release of norepinephrine which stimulates β_3-adrenergic receptors. The detrusor muscle relaxes and urine storage in the bladder is improved. Thus, mirabegron reduces irritative voiding symptoms.[48] Although not Food and Drug Administration (FDA)-approved for this indication, mirabegron is an alternative to an anticholinergic agent in patients who poorly tolerate or are at high risk of anticholinergic adverse effects, or when irritative voiding symptoms do not respond to an anticholinergic agent. Mirabegron is typically added to an α_1-adrenergic antagonist.[47] The usual dose is 50 mg by mouth daily. Doses greater than 100 mg have shown no greater efficacy than 50 mg.[47] If the creatinine clearance is 15 to 29 mL/min (0.25–0.49 mL/s), the dose should be reduced to 25 mg daily. Mirabegron should be avoided if the creatinine clearance is less than 15 mL/min (0.25 mL/s) or in patients with poorly controlled hypertension. Common adverse effects of mirabegron include headache, hypertension, tachycardia, constipation, and nasopharyngitis.

▶ *Combination Therapy*

LO 6

KEY CONCEPT A combination of an α_1-adrenergic antagonist and 5α-reductase inhibitor may be considered in symptomatic patients who do not respond to an adequate trial of monotherapy or in symptomatic patients at high risk of BPH complications, that is, those with an enlarged prostate of at least 30 g (1.05 oz.).[9] In such patients, combination therapy will relieve voiding symptoms and also may reduce the risk of developing BPH-related complications by 64% and reduce the need for prostatectomy by 67% after continued use for a minimum of 4 years.[36,37]

The benefit of combination therapy with any α_1-adrenergic antagonist and any 5α-reductase inhibitor is well established. A recent study suggests that initiating a combination regimen in patients with moderate LUTS due to BPH may produce persistent improvements in AUA Symptom Score and urinary flow rate and may reduce the risk of clinical progression after 1 year than treatment with an α_1-adrenergic antagonist alone.[49] To streamline and reduce the cost of treatment regimens, it has been suggested that the α_1-adrenergic antagonist may be discontinued after the first 3 to 12 months of combination therapy; however, the long-term efficacy of doing so remains to be established.[50] Because combination therapy is also associated with low adherence, a commercially available combination formulation of dutasteride 0.5 mg and tamsulosin 0.4 mg is available. In summary, combination therapy generally requires long-term use of an α_1-adrenergic antagonist and 5α-reductase inhibitor, which is more expensive, and is associated with lower adherence and more adverse effects than a single drug regimen. Therefore, clinicians should discuss the advantages and disadvantages of such a combination regimen with the patient before a final decision is made (see Table 52–5).[9]

Several other combination therapy regimens have also been used for moderate to severe LUTS due to BPH. Unlike that of the previously described combination, the published evidence to support newer combinations is limited. One rationale for combined use is that drugs working by different mechanisms to reduce LUTS may provide additional benefit. Tadalafil has been combined with an α_1-adrenergic antagonist or with a 5α-reductase inhibitor. To minimize an additive blood pressure–lowering effect, a uroselective α_{1A}-adrenergic antagonist may be preferred when combined with tadalafil. Similarly, tadalafil can offset erectile dysfunction that commonly occurs with finasteride or dutasteride. As tadalafil is expensive, combination therapy with tadalafil is generally reserved for patients with both moderate or severe LUTS due to BPH and erectile dysfunction.

For patients with moderate or severe irritative voiding symptoms due to BPH that are not responsive to an α_1-adrenergic antagonist alone, an anticholinergic agent may be added. The combination increases urine storage in the bladder and decreases voiding frequency and urgency. Patients at low risk of acute urinary retention should be carefully selected for such combination therapy. These include patients with PVRs less than 50 mL and those with a urinary flow rate of at least 10 mL/s.

For patients who poorly tolerate anticholinergic adverse effects, an alternative is mirabegron, which has been added to an α_1-adrenergic antagonist. A combination of tamsulosin and mirabegron has reduced urinary urgency and frequency and increased urine storage in the bladder when compared to tamsulosin alone.

Patient Encounter 3

A 66-year-old man who has severe obstructive voiding symptoms secondary to BPH presents to clinic. A DRE reveals a prostate of 45 g (1.6 oz) and a PSA of 1.8 ng/mL (1.8 mcg/L). He is started on doxazosin-XL 8 mg daily by mouth. After 1 month, the patient complains that his symptoms have not significantly improved. However, he says that since he started on this medication, he feels lightheaded and dizzy. This patient is also taking hydrochlorothiazide 25 mg daily and valsartan 160 mg daily. A pill count shows that he has been adherent to the prescribed regimen of all of his medications.

Explain the patient's response to doxazosin. Be sure to address the lack of responsiveness as well as adverse effects.

What additional information is needed to develop an individualized treatment plan for this patient?

What treatment options should be considered for this patient?

OUTCOME EVALUATION

KEY CONCEPT Once the peak effects of drug treatment are expected to occur, monitor the drug for effectiveness. This is approximately 2 to 4 weeks after the start of an α_1-adrenergic antagonist, anticholinergic agent, tadalafil, or mirabegron; and 3 and 6 months after the start of a 5α-reductase inhibitor. Assess symptom improvement using the AUA Symptom Scoring Index. A reduction in symptom score by a minimum of 3 points is anticipated. However, it should be noted that the AUA Symptom Score may not match the patient's perception of the bothersomeness of his voiding symptoms. If the patient perceives his symptoms as bothersome, independent of the AUA Symptom Score, consideration should be given to modifying the patient's treatment regimen. Similarly, a patient may regard his symptoms as not bothersome even though the AUA Symptom Score is high. At baseline and during treatment, the clinician should objectively assess symptoms, and check urinary flow rate, PVR, and for the absence of complications of BPH. If the patient shows a response to treatment, instruct the patient to continue the drug regimen and have the patient return at 6-month intervals for monitoring. If the patient shows an inadequate response to treatment, the dose of α_1-adrenergic antagonist can be increased (except for alfuzosin and silodosin) or another drug can be added to reduce the patient's symptoms or until the patient experiences adverse drug effects.

For the α_1-adrenergic antagonists, the severity of hypotensive-related adverse effects, which may manifest as dizziness or syncope, may require a dosage reduction, slower up-titration of the dose, or drug discontinuation. Other adverse effects of α_1-adrenergic antagonists are nasal congestion, malaise, headache, and ejaculation disorders. None of these generally require discontinuation of treatment, and these often improve as treatment continues. For the 5α-reductase inhibitors, the most bothersome adverse effects are decreased libido, erectile dysfunction, and ejaculation disorders. In sexually active males, erectile dysfunction may be improved with erectogenic drugs; however, this adverse effect may necessitate discontinuation of treatment. The adverse effects of anticholinergics are dose-related, and may be poorly tolerated and require drug discontinuation. Whereas tadalafil is well tolerated, mirabegron may increase blood pressure, necessitating the initiation or modification of an existing antihypertensive regimen.

LO 8

Patient Care Process

Collect Information:

- Review the medical history and physical examination.
- Conduct a medication history for medications or dietary supplements that could be contributing to his voiding symptoms (Table 52–4). Identify allergies to medications and other substances. List current medications that the patient may be taking for LUTS and identify dose, start date, response to treatment, and adverse effects of treatment (Tables 52–5 through 52–8).
  - Speak with the patient to identify lifestyle habits, preferences and health beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on the medical history, determine whether the patient has compelling indications for specific medications for BPH, (eg, does the patient also have erectile dysfunction?).
- Based on medical history, signs and symptoms, AUA Symptom Score (Table 52–3), and presence of complications of BPH disease, classify BPH as mild, moderate, or severe.
- Review available laboratory tests, especially serum electrolytes, renal function, and urinalysis.
- Assess the patient's adherence to lifestyle modification measures.
- Assess the efficacy and safety of, and patient adherence to current pharmacotherapy.
- Identify any significant adverse drug effects or interactions from current pharmacotherapy.

Develop a Care Plan:

- If the patient's AUA Symptom Score is in the range of 8–35 despite existing pharmacotherapy for BPH, modify the existing regimen. Consider increasing the dose of the drug, if feasible, or adding a drug to the existing regimen.
- If the patient is not on current pharmacotherapy for BPH but has mild LUTS, initiate lifestyle modifications. If LUTS is moderate to severe, drug therapy is also indicated. Choose medications and doses that are optimal for the patient.

Implement the Care Plan:

- Review lifestyle modification measures that reduce LUTS and reinforce adherence.
- Educate the patient about new or changes to drug therapy, best time to take daily doses, potential adverse effects, and how to self-manage and report adverse effects that might occur.
- Address any patient concerns about BPH and its management.
- Determine whether the patient has insurance coverage or whether recommended agents are included on this patient's insurance formulary.
- Educate the patient on the importance of adherence to the prescribed drug regimen.

Follow-up: Monitor and Evaluate:

- After starting an α_1-adrenergic antagonist, tadalafil, an anticholinergic agent, or mirabegron, assess effectiveness and safety of therapy in 1 month, and then at 6 months. At each visit, repeat the AUA Symptom Scoring Index, check for disease progression, repeat urinary flow rate and PVR, and assess adverse effects of treatment. As long as the patient continues to respond and tolerates the medication well, repeat all assessments at yearly intervals thereafter.
- After starting a 5α-reductase inhibitor, assess effectiveness and safety of therapy at the end of the third and sixth month.

Initial failure to respond to α_1-adrenergic antagonists occurs in 20% to 70% of treated patients. It is likely in these patients that the static factor may predominate as the cause of symptoms in these patients. In these patients, adding a 5α-reductase inhibitor may be helpful. Initial failure to respond to 5α-reductase inhibitors occurs in 30% to 70% of treated patients. It is likely that the dynamic factor may predominate as the cause of symptoms in these patients. Switching to or adding an α_1-adrenergic antagonist may be helpful. In contrast, drug treatment failures after an initial good response to drug therapy will likely be an indication of progressive BPH disease. In such patients, modifying the drug regimen or surgical intervention may be indicated.

Table 52–8 summarizes the adverse effects of the agents used to treat BPH and includes management suggestions for these situations.

Abbreviations Introduced in This Chapter

AUA	American Urological Association
BPH	Benign prostatic hyperplasia
BUN	Blood urea nitrogen
DRE	Digital rectal examination
FDA	Food and Drug Administration
LUTS	Lower urinary tract symptoms
PSA	Prostate-specific antigen
PVR	Postvoid volume
TURP	Transurethral resection of the prostate

REFERENCES

1. Thorner DA, Weiss JP. Benign prostatic hyperplasia: symptoms, symptom scores, and outcome measures. Urol Clin North Am. 2009;36:417–429.
2. Berry SJ, Coffey DS, Walsh PC, et al. The development of human benign prostatic hyperplasia with age. J Urol. 1984;132:474–479.
3. Shapiro E, Becich MJ, Hartano V, et al. The relative proportion of stromal and epithelial hyperplasia as related to the development of clinical BPH. J Urol. 1992;147:1293–1297.
4. Pool JL, Kirby RS. Clinical significance of α_1-adrenoceptor selectivity in the management of benign prostatic hyperplasia. Int Urol Nephrol. 2001;33:407–412.
5. Hollingsworth JM, Wilt TJ. Lower urinary tract symptoms in men. BMJ. 2014;349:g4474.
6. Kim EH, Larson JA, Andriole GL. Management of benign prostatic hyperplasia. Annu Rev Med. 2016;67:137–151.
7. Kessler OJ, Keisari Y, Servadio C, Abramovici A. Role of chronic inflammation in the promotion of prostatic hyperplasia in rats. J Urol. 1998;159:1949–1953.
8. Isaacs JT. Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. Prostate. 1990;3(suppl):1–7.
9. Management of Benign Prostatic Hyperplasia (published 2010, reviewed and validity confirmed 2014). AUA Practice Guidelines Committee. Available from: http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-(2010-reviewed-and-validity-confirmed-2014). Accessed July 30, 2017.
10. Mirone V, Sessa A, Giuliano F, et al. Current benign prostatic hyperplasia treatment: impact on sexual function and management of related sexual adverse effects. Int J Clin Pract. 2011;65:1005–1013.
11. Flanigan RC, Reda DJ, Wasson JH, et al. 5-year outcomes of surgical resection and watchful waiting for men with moderately symptomatic BPH: a department of Veterans Affairs cooperative study. J Urol. 1998;160:12–16.
12. Rosenberg MT, Witt ES, Miner M, Barkin J. A practical primary care approach to lower urinary tract symptoms caused by benign prostatic hyperplasia (BPH-LUTS). Can J Urol. 2014;21(suppl 2):12–24.
13. Parker DC, Simhan J. Management of complications after surgical outlet reduction for benign prostatic obstruction. Can J Urol. Oct 2015;22(suppl 1):88–92.
14. Blankstein U, Van Asseldonk B, Elterman DS. BPH update: medical versus interventional management. Can J Urol. 2016;23(suppl 1):10–15.
15. Lerner LB, Rajender A. Laser prostate enucleation techniques. Can J Urol. 2015;22(suppl 1):53–59.
16. Djavan B, Eckersberger E, Handl M, et al. Durability and retreatment rates of minimally invasive-treatments of benign prostatic hyperplasia: Aa cross-analysis of the literature. Can J Urol. 2010;17:5249–5254.
17. Brown CT, Emberton M. Self management for men with lower urinary tract symptoms. Curr Urol Rep. 2009;10(4):261–266.
18. Keehn A, Taylor J, Lowe FC. Phytotherapy for benign prostatic hyperplasia. Curr Urol Rep. 2016;17:53.
19. Lepor H. Alpha-blockers for the treatment of benign prostatic hyperplasia. Urol Clin North Am. 2016;43:311–323.
20. Liao CH, Guh JH, Chueh SC, Yu HJ. Anti-angiogenic effects and mechanism of prazosin. Prostate. 2011;71:976–984.
21. Oelke M. Latest developments in the assessment and treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: what is clinically relevant. Clin Drug Investig. 2015;35(suppl 1):S3–S6.
22. Rossi M, Roumequere T. Silodosin in the treatment of benign prostatic hyperplasia. Drug Des Devel Ther. 2010;4:291–297.
23. Bird ST, Delaney JA, Brophy JM, et al. Tamsulosin treatment for benign prostatic hyperplasia and risk of severe hypotension in men aged 40–85 years in the United States: risk window analyses using between and within patient methodology. BMJ. 2013;347:f6320.
24. Davis BR, Cutler JA, Gordon DJ, et al, for the ALLHAT Research Group. Rationale and design for the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). Am J Hypertens. 1996;9(4 Pt 1):342–360.
25. Wilt T, MacDonald R, Rutks I. Tamsulosin for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2002;(4):CD002081.
26. Herberts M, Butcher M, Kohler T. The effect of LUTS/BPH and treatments on ejaculatory function. Curr Urol Rep. 2016;17:48.
27. Welliver C, Essa A. Sexual side effects of medical and surgical benign prostatic hyperplasia treatments. Urol Clin North Am. 2016;43:393–404.
28. Capogrosso P, Serino A, Ventimiglia E, et al. Effects of silodosin on sexual function-realistic picture from the everyday clinical practice. Andrology. 2015;3:1076–1081.
29. Friedman AH. Tamsulosin and the intraoperative floppy iris syndrome. JAMA. 2009;301:2044–2045.
30. Bell CM, Hatch WV, Fischer HD, et al. Association between tamsulosin and serious ophthalmic adverse events in older men following cataract surgery. JAMA. 2009;301(19):1991–1996.
31. Nieminen T, Tammela TLJ, Koobi T, Kahonen M. The effects of tamsulosin and sildenafil in separate and combined regimens on detailed hemodynamics in patients with benign prostatic enlargement. J Urol. 2006;176 (6 Pt 1):2551–2556.
32. Nickel JC, Gilling P, Tammela TL, et al. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). BJU Int. 2011;108:388–394.
33. Kaplan SA, Chung DE, Lee RK, et al. A 5-year retrospective analysis of 5-alpha-reductase inhibitors in men with benign

prostatic hyperplasia: finasteride has comparable urinary symptom efficacy and prostate volume reduction, but less sexual side effects and breast complications than dutasteride. Int J Clin Pract. 2012;66:1052–1055.
34. Rittmaster RS, Norman RW, Thomas LN, et al. Evidence for atrophy and apoptosis in the prostates of men given finasteride. J Clin Endocrinol Metab. 1996;81(2):814–819.
35. Tacklind J, Fink HA, MacDonald R, et al. Finasteride for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2010 Oct 6; 10:CD006015. doi.10.1002/1465/ 858CD006015.pub3.
36. McConnell JD, Roehrborn CG, Bautista OM, et al. The long term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med. 2003;349:2389–2398.
37. Roehrborn CG, Siami P, Barkin J, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4 year results from the CombAT study. Eur Urol. 2010;57:123–131.
38. Glina S, Roehrborn CG, Esen A, et al. Sexual function in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: results of a 6-month, randomized, double-blind, placebo-controlled study of tadalafil coadministered with finasteride. J Sex Med. 2015;12:129–138.
39. Upreti R, Hughes KA, Livingstone DE, et al. 5α-reductase type I modulates insulin sensitivity in men. J Clin Endocrinol Metab. 2014;99:E1397–E1406.
40. Loke YK, Ho R, Smith M, et al. Systematic review evaluating cardiovascular events of the 5-alpha-reductase inhibitor-dutasteride. J Clin Pharm Ther. 2013;38:405–415.
41. Lin WL, Hsieh YW, Lin CL, et al. A population-based nested case-control study: the use of 5-alpha reductase inhibitors and the increased risk of osteoporosis diagnosis in patients with benign prostatic hyperplasia. Clin Endocrinol. 2015;82:503–508.
42. Andriole GI, Bostwick DG, Brawley OW, et al. Effect of dutasteride on the risk of prostate cancer. N Engl J Med. 2010;362:1192–1202.
43. Lythgoe C, Vary KT. The use of PDE-5 inhibitors in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia. Curr Urol Rep. 2013;14:585–594.
44. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 2012;87:766–778.
45. Andersson KE. Antimuscarinic mechanisms and the overactive detrusor: an update. Eur Urol. 2011;59:377–386.
46. Filson CP, Hollingsworth JM, Clemens JQ, et al. The efficacy and safety of combined therapy with α-blockers and anticholinergics for men with benign prostatic hyperplasia: a meta-analysis. J Urol. 2013;190:2153–2160.
47. Osman N, Aldamanhori R, Mangera A, Chapple CR. Antimuscarinics, β-3 agonists, and phosphodiesterase inhibitors in the treatment of male lower urinary tract symptoms—an evolving paradigm. Urol Clin North Am. 2016;43:337–349.
48. Schauer I, Madersbacher S. Medical treatment of lower urinary tract symptoms/benign prostatic hyperplasia: anything new in 2015. Curr Opin Urol. 2015;25:6–11.
49. Roehrborn CG, Oyarzabal Perez I, Roos EP, et al. Efficacy and safety of a fixed dose combination of dutasteride and tamsulosin treatment (Duodart) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naïve men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results. BJU Int. 2015;116(3):450–459.
50. Nickel JC, Barkin J, Koch C, et al. Finasteride monotherapy maintains stable lower urinary tract symptoms in men with benign prostatic hyperplasia following cessation of alpha blockers. Can Urol Assoc J. 2008;2(1):16–21.

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53 Urinary Incontinence and Pediatric Enuresis

Sum Lam and Gladys El-Chaar

LEARNING OBJECTIVES

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

LO

1. Explain the pathophysiology of the major types of urinary incontinence (UI): urge, stress, overflow, and functional.
2. Recognize the signs and symptoms of the major types of UI in individual patients.
3. List the treatment goals for a patient with UI.
4. Compare and contrast available therapeutic agents for managing UI; identify factors that guide drug selection for an individual patient.
5. Formulate a monitoring plan and provide patient counseling for a patient on a given treatment regimen based on patient-specific information.
6. Explain the pathophysiology of pediatric enuresis.
7. List treatment goals; compare and contrast available management strategies for managing pediatric enuresis.
8. Formulate a patient-specific monitoring plan and implement patient counseling for a patient on a given treatment regimen.
9. Describe nonpharmacologic treatment approaches for pediatric enuresis.

URINARY INCONTINENCE

INTRODUCTION

Urinary incontinence (UI) is defined as the complaint of involuntary leakage of urine.[1] It is often associated with other bothersome lower urinary tract symptoms such as urgency, increased daytime frequency, and **nocturia**. Despite its prevalence in both genders, UI remains an underreported health problem that can negatively impact an individual's quality of life. Patients with UI may sense a loss of self-control, independence and self-esteem, and often modify their activities for fear of an "accident." Patients with UI may also suffer from other consequences, including perineal dermatitis and infections, pressure ulcers, urinary tract infections (UTIs), and falls. In the United States, the estimated national cost of urge urinary incontinence (UUI) in 2007 was $66 billion, with projected costs of $83 billion in 2020.[2]

EPIDEMIOLOGY AND ETIOLOGY

The true prevalence of UI is unclear because of varying definitions of UI and reporting bias.[3]

- About 44% of noninstitutionalized persons aged 65 and older reported UI[4]
- 7% to 37% of women aged 20 to 39 report some degree of UI
- 9% to 39% of women aged 60 and older report daily UI
- 11% to 34% of older men report some degree of UI
- 2% to 11% of older men reporting daily UI
- In the noninstitutionalized setting, more than 50% of elderly women and more than 25% of elderly men reported UI
- 46% of short-term and 76% of long-term nursing home residents report UI[4]

UI can result from abnormalities within (intrinsic to) and outside of (extrinsic to) the urinary tract. Within the urinary tract, abnormalities may occur in the urethra (including the bladder outlet and urinary sphincters), the bladder, or a combination of both structures. Focusing on abnormalities in these two structures, a simple classification scheme emerges for all but the rarest intrinsic causes of UI. KEY CONCEPT Accurate diagnosis and classification of UI type is critical to the selection of appropriate drug therapy.

LO 1 PATHOPHYSIOLOGY

Stress Urinary Incontinence[5]

Stress urinary incontinence (SUI) occurs most frequently in women and is related to the underactivity of urethra and/or urethral sphincters, leading to inadequate resistance to impede urine flow from the bladder. SUI occurs when intraabdominal pressure is elevated by exertional activities like exercise, running, lifting, coughing, and sneezing. SUI is usually episodic, associated with small volume leakage and rarely causes nocturia or **enuresis**. The etiology for urethral underactivity is not completely understood, although the loss of the trophic effects of estrogen on the uroepithelium at menopause is thought to be

Patient Encounter 1, Part 1

A 60-year-old woman presents to the clinic complaining of a strong, sudden urge to urinate every 2 to 3 hours while awake. Every day she makes about 8 to 10 trips to a bathroom, and gets up once or twice each night to urinate. She reports no clothes-wetting accidents so far, but is fearful that "it will happen someday in the public." She has stopped "window shopping and walking program" in a huge mall near her house. The activity was her favorite pastime after retirement until 2 months ago when she almost experienced a wetting accident. Since then, she has avoided several social and family events. At this clinic visit, she denies any urinary leakage when she coughs, laughs, or exercises. She is diagnosed with overactive bladder without urinary incontinence. Patient prefers to try an oral drug that is administered once daily. She dislikes the feeling of dry mouth. She has prescription coverage, as well as a secondary private prescription insurance plan for out-of-pocket deductibles and copayments.

What information is suggestive of overactive bladder?

What additional information is necessary to differentiate overactive bladder from stress, overflow, and functional urinary incontinence? Are there any exacerbating factors?

What additional information do you need to know before creating a treatment plan for this patient?

important. The peak of SUI prevalence in the perimenopausal years supports this hypothesis. Clearly established risk factors for SUI include the following:

- Pregnancy (increased risk with increased parity)
- Childbirth (vaginal delivery)
- Menopause
- Cognitive impairment
- Obesity
- Increasing age

SUI is exceedingly rare in males unless the sphincter mechanism is compromised by surgery or trauma. The most common surgeries predisposing to SUI in males are radical prostatectomy for prostate cancer and transurethral resection of the prostate for benign prostatic hyperplasia (BPH).

Urge Urinary Incontinence[5]

UUI is related to the overactivity of detrusor muscle in the bladder, which contracts inappropriately during the filling (urinary storage) phase and generates **urgency**. The bladder contractions are due to the stimulation of muscarinic cholinergic receptors, especially M2 and M3 subtypes. UUI is associated with large volume leakage, sometimes complete bladder emptying, nocturia and enuresis; thus UUI may disrupt sleep. Overactive bladder (OAB) is a symptom syndrome with or without associated UUI.[6]

Most women with UUI or OAB have no identifiable causes (idiopathic), while in men similar symptoms are associated with benign prostatic hyperplasia (see Chapter 52). Overactivity may be myogenic and/or neurogenic. Clearly established risk factors for UUI include:

- Older age
- Neurologic disorders (eg, stroke, Parkinson disease, multiple sclerosis, and spinal cord injury)
- Bladder outlet obstruction (eg, benign or malignant prostatic enlargement or hyperplasia)
- **Hysterectomy**
- Recurrent UTIs

Overflow Urinary Incontinence[5]

Overflow urinary incontinence (OUI) is a less common form of UI in men or women. It is related to urethral overactivity and/or bladder underactivity. In short, the bladder is filled to capacity at all times but cannot empty, causing urine to leak out episodically. If caused by bladder underactivity, the progressively weakened detrusor muscle eventually loses the ability to voluntarily contract, which leads to incomplete voiding and large residual urinary volume after **micturition**. Both myogenic and neurogenic factors have been associated with impaired bladder contractility that leads to OUI. Common neurogenic factors are diabetes, lower spinal cord injury, multiple sclerosis, or radical pelvic surgery.

If OUI is due to urethral overactivity, incomplete bladder emptying occurs because the resistance of the urethra and/or sphincters cannot be overcome by detrusor contractility. In men, this most frequently occurs in cases of long-term chronic bladder outlet obstruction due to BPH, prostate cancer, or abdominal-pelvic surgeries. In women, urethral overactivity is rare, but may result from **cystocele** formation or surgical overcorrection for SUI. In both genders, systemic neurologic diseases such as multiple sclerosis or spinal cord injury may be the etiology.

Functional UI[5]

Functional UI is generally caused by extrinsic factors to the urinary tract, such as:

- Immobility (due to pain, physical limitations)
- Inadequate or delayed access to toileting facilities
- Neurologic impairment (Parkinson disease, multiple sclerosis, spinal cord injury, stroke, apathy due to depression)
- UTIs
- Postmenopausal **atrophic urethritis**, and/or vaginitis

LO 2

Clinical Presentation of Stress Urinary Incontinence (SUI) Related to Urethral Underactivity[5]

General

Usually occurs during activities like exercise, running, lifting, coughing, or sneezing; much more common in females.

Symptoms

Urine leakage volume is proportional to activity level; not associated with nocturia. No SUI with physical inactivity, especially when supine. May develop urgency and frequency as a compensatory mechanism (or independently as a separate component of bladder overactivity).

Diagnostic Tests

Observation of urethral meatus (opening) while patient coughs or strains.

LO 2

Clinical Presentation of Urge Urinary Incontinence (UUI) Related to Bladder Overactivity[5]

General

If sensory input from the lower urinary tract is absent, may have bladder overactivity and urine leakage without urgency. Patient with overactive bladder (OAB) may not have UUI.

Symptoms

Patients with OAB typically present with symptoms of urgency, frequency, nocturia with or without UUI.

Diagnostic Tests

Urodynamic studies are the gold standard for diagnosis. UTI must be ruled out by urinalysis and urine culture.

LO 2

Clinical Presentation of Overflow Urinary Incontinence (OUI) Related to Urethral Overactivity and/or Bladder Underactivity[5]

General

Rare type of UI in both genders. Urethral overactivity is usually due to prostatic enlargement (males) or cystocele formation or surgical overcorrection for SUI (females). Bladder underactivity is usually due to a weakened detrusor muscle.

Symptoms

Lower abdominal fullness, hesitancy, straining to void, decreased force of stream, interrupted stream, sense of incomplete bladder emptying. May have urinary frequency and urgency, as well as abdominal pain if acute urinary retention occurs.

Signs

Increased postvoid residual urine volume.

- Diabetes mellitus (glucosuria leading to polyuria)
- Diabetes insipidus (polyuria due to decreased antidiuretic hormone [ADH])
- Pelvic malignancy (extrinsic pressure on urinary tract structures causing obstruction)
- Constipation or fecal impaction
- Congenital malformations of the urinary tract system

Mixed and Drug-Induced UI[5]

Mixed urinary incontinence (MUI) occurs when two or more types of UI coexist in a given patient, which may lead to diagnostic and therapeutic difficulties. Patients may experience worsening of symptom due to the opposing effects of treatments indicated for specific and different types of UI.

KEY CONCEPT Many medications can influence the lower urinary tract system, and can precipitate or aggravate existing voiding dysfunction that leads to UI (Table 53–1).

CLINICAL PRESENTATION AND DIAGNOSIS

Guidelines are available for the assessment, diagnosis, and management of UI or OAB.[6-10] In general, obtaining a complete medical history and performing a targeted physical examination are essential to correctly classify the type(s) of UI. The degree of annoyance perceived by the patient due to urinary symptoms must be assessed. However, it may not correlate well with quantitative tests such as symptom frequency/severity, use of absorbent products, and postvoid residual (PVR) urine volume (Table 53–2). Major components of the physical examination include the following:[5]

- Abdominal examination for distended bladder, organomegaly, and masses
- Neurologic evaluation of perineum and lower extremities to evaluate lumbosacral nerve function (includes digital rectal

Table 53–1

Medications Influencing Lower Urinary Tract Function

Medication	Effect
Diuretics	Polyuria, frequency, urgency
α-Adrenoceptor antagonists	Urethral relaxation: may relieve obstruction in males, induces/worsens SUI in females
α-Adrenoceptor agonists	Urethral constriction: aggravates obstruction in males (may cause urinary retention), potential SUI treatment in females
Calcium channel blockers (dihydropyridines)	Urethral constriction (may cause urinary retention), especially in males
Opioid analgesics	Impaired bladder contractility (may cause urinary retention)
Sedative-hypnotics	Functional UI due to immobility, delirium, sedation
Psychotherapeutics with anticholinergic properties; anticholinergics	Urinary retention due to impaired bladder contractility or potential UUI treatment
TCAs	Combination of anticholinergic and α-adrenoceptor blocking activities can lead to unpredictable effects on UI
Ethanol	Polyuria and frequency (via effects on ADH), functional UI (delirium, sedation), urgency
ACEIs	Cough leading to SUI (ARBs do not induce cough)
Cyclophosphamide	Hemorrhagic cystitis due to acrolein metabolite (prevent with MESNA)

ACEIs, angiotensin-converting enzyme inhibitors; ADH, antidiuretic hormone (or vasopressin); ARB, angiotensin II receptor blocker; MESNA, sodium 2-mercaptoethanesulfonate; SUI, stress urinary incontinence; TCA, tricyclic antidepressant; UI, urinary incontinence; UUI, urge urinary incontinence.

Table 53–2

Items to Address during Diagnostic Evaluation of UI

Item	Comments
Urine Leakage	
Use of absorbent products	Type(s), quantity, times of day worn
Urine leakage per episode	Dribbling, small or large volumes, intermittently; consistent or varied quantities
Precipitants	Physical activity, excessive fluid intake, drug(s)
Times of day	Daytime/nighttime/both
Symptoms	
Urgency	Frequency, severity, duration from urge onset to micturition
Frequency	Daytime/nighttime/both, how often
Nocturia	How often, proportion associated with UI
Obstructive symptoms	Type(s) (hesitancy, strain to void, decreased force of stream, start and stop stream, sense of incomplete emptying), severity
Lower abdominal fullness	Frequency, severity
Comorbidities	
Current medication use	See Table 53–1. Remember CAMs, OTCs
Evidence of preexisting or new-onset:	
Diabetes mellitus	
Metastatic or genitourinary malignancy	
Multiple sclerosis or other neurologic disease	
CNS disease above the pons	Usually UUI
Spinal cord injury	UUI or OUI, depending on level and degree of completeness of injury
Recent nongenitourinary surgery	Functional UI
Previous local surgery/radiation	Prostate surgery, lower abdominal cavity surgery (direct injury versus denervation), radiation (direct injury)
Gynecologic history	Childbirth (vaginal versus cesarean section), prior gynecologic surgery, hormonal status (pre- versus peri- versus postmenopausal)
Pelvic floor disease	Constipation, diarrhea, fecal incontinence, dyspareunia, sexual dysfunction, pelvic pain
UTI	Dysuria, CVA tenderness, frequency
Gross Hematuria	Possible bladder or other genitourinary cancer

CAM, complementary and alternative medications; CVA, costovertebral angle; OTC, over-the-counter; OUI, overflow urinary incontinence; UTI, urinary tract infection; UUI, urge urinary incontinence.

examination to check rectal tone, reflexes, ability to perform a voluntary pelvic muscle contraction in females; size and surface quality of prostate in males)

- Pelvic examination in women for evidence of prolapse of bladder, small bowel, rectum, or uterus, or signs of estrogen deficiency
- Genital/prostate examination in men
- Urinalysis, PVR urine volume
- Direct observation of urethral meatus (opening) when patient coughs/strains (urine spurt consistent with SUI) (cough stress test)
- Perineal examination for skin maceration, redness, breakdown, ulceration, and evidence of fungal skin infection

Clinicians could inquire about UI and OAB with open- and closed-ended questions:[11]

- Do you leak urine when you cough, sneeze, laugh, etc?
- Do you have to get up more than once at night to urinate?
- Do you feel the urge to urinate frequently?
- How many times do you typically urinate from waking in the morning until going to bed in the evening?
- How many times do you typically wake up to urinate from going to sleep at night until waking in the morning?
- How often do you have a sudden compelling desire to urinate, which is difficult to postpone?
- How often do you leak urine because you cannot postpone the sudden desire to urinate?

TREATMENT

Desired and realistic treatment outcomes should be individualized and discussed with each patient. KEY CONCEPT The treatment goals for UI may change with time, and often require reaching a compromise between efficacy and tolerability of drug therapy.

Desired Outcomes

LO 3

- Restoration of continence
- Reduction of the number of UI episodes (daytime and nighttime) and nocturia
- Prevention or delaying of complications associated with UI (eg, pressure ulcers, skin conditions)
- Minimization of adverse effects and costs related to treatment
- Improvement in quality of life

Nonpharmacologic Treatment

At the primary care level, nonsurgical, nonpharmacologic intervention constitutes the chief approach to the management of UI. It has no adverse reactions, is minimally invasive, and can be utilized adjunctively with other treatment modalities. KEY CONCEPT Nonpharmacologic treatment gives at least an additive effect in efficacy when combined with drug therapy, and can allow the use of lower drug doses. It is ideal for patients who fit the following scenarios:

- Being medically unfit for surgery
- Planning for pregnancies/childbirths, which can compromise the long-term results of certain types of continence surgery

- Having OUI whose condition is not amenable to surgical or drug treatment
- Avoiding drug therapy or surgery due to safety concern or patient preference

These approaches include lifestyle/behavioral modifications, fluid management, scheduled voiding regimens, pelvic floor muscle rehabilitation (PFMR; common term "Kegel exercises"), external neuromodulation, anti-incontinence devices, acupuncture, and supportive interventions.[3,5,12,13] Many of these are best utilized through attendance at multidisciplinary UI clinics staffed by specialized health care providers. Weight loss of 5% to 10% in overweight or obese women has an efficacy similar to that of other nonpharmacologic treatments for treating SUI. Therefore, weight loss and exercise are recommended for obese women with any of the three types of UI.[8,10]

Bladder training and prompted voiding improve symptoms of UUI and MUI. PFMR is an effective treatment for adult women with SUI and MUI.[8] Combination therapy with PFMR plus behavioral training achieved better outcomes than drug therapy in women with UUI. However, these methods require motivation from patients. Medical conditions, such as cognitive dysfunction, may interfere with active participation and compromise efficacy. Regular follow-ups are important for monitoring outcomes and for providing reassurance and support. Lifestyle/behavioral interventions should be continued during drug therapy in patients with UI, even if the results have not fully achieved the desired outcomes. PFMT is strongly recommended for SUI; bladder training may be recommended for UUI; and the combination of both is strongly recommended for MUI.[8,10]

External neuromodulation may include nonimplantable electrical stimulation, percutaneous tibial nerve stimulation, or extracorporeal magnetic stimulation. This treatment option is typically prescribed when traditional PFMR has failed. Anti-incontinence devices, such as bed alarms, catheters, pessaries, penile clamps, and external collection devices, are reserved for special situations depending on patient's symptoms, cognition, mobility status, and overall health status. Supportive interventions such as physical therapy may be beneficial for patients with muscle weakness and slow gait that hinder their ability to reach to the toilet in a timely manner. Lastly, absorbent products provide greater patient confidence in dealing with unpredictable urine loss.[5]

Surgery is rarely an initial treatment for UI; only considered in patients with significantly bothersome symptoms, and when nonsurgical options are undesired or ineffective. Surgery is not as helpful for bladder underactivity, but it can be used to manage urethral overactivity due to BPH and bladder outlet obstruction (via endoscopic incision using a cystoscope). It is most effective for SUI by stabilizing the urethra and bladder neck and/or augmenting urethral resistance. Common approaches are injection of periurethral bulking agents and midurethral sling procedure. In males, SUI is best treated by implanting an artificial urinary sphincter.[5]

Posterior tibial nerve stimulation is an office-based percutaneous treatment for UUI or OAB. Therapy consists of weekly 30-minute treatments with a needle placed posterior to the medial malleolus of the ankle over the course of 3 months. Efficacy appears similar to or slightly better than oral pharmacotherapy.[5]

Surgical treatment for UUI generally consists of implantation of a sacral nerve stimulator (neuromodulation) or endoscopic office based injection of botulinum toxin A directly into the smooth or striated muscle.[5] The injections are performed in the office generally with local anesthesia. The duration of effect of the toxin is about 4 to 8 months after which repeat injection is necessary to maintain effect. Intravesical (bladder) botulinum toxin A injections increased bladder capacity/compliance and improved quality of life in patients with refractory OAB.[5]

Patients with UUI and an elevated PVR urine volume may require intermittent self-catheterization along with frequent voiding between catheterizations. Surgical placement of a suprapubic catheter may be necessary in cases when intermittent catheterization is not possible. Catheterization can be combined with pharmacologic treatment for symptom relief.[5]

Patient Encounter 1, Part 2

PMH: Hypertension, congestive heart failure, diabetes mellitus type 2, mild dementia

FH: Noncontributory

SH: Retired business owner. Lives with husband. Two married daughters (ages 33 and 28 years) live in the same state. Drinks one glass of red wine with dinner everyday. Drinks one cup (16 oz) of coffee in the morning and one cup (8 oz) at lunch

All: NKDA

Meds: Enalapril 5 mg once daily, simvastatin 10 mg once daily, furosemide 40 mg daily, metformin 500 mg twice daily, donepezil 5 mg daily

ROS: Alert and pleasant. (–) UTI, (–) dysuria, lower abdominal fullness, or decreased force of stream, (+) nocturia

PE:

VS: BP 110/70 mm Hg, HR 85 beats/min, RR 20 breaths/min, T 36.8°C (98.3°F), Wt 209 lbs (95 kg), Ht 5'5" (165 cm)

HEENT: PERRLA; EOMI, TMs WNL

Neck/LN: Supple w/o LAD or masses

Lungs/Thorax: CTA

CV: RRR w/o murmurs, rubs, gallops

Abd: Soft, NT/ND w/o masses; (+) BS; bladder not palpable

GU: WNL; no atrophic vaginitis or uterine prolapse

MS/Ext: WNL, no edema

Neuro: DTRs 2+, CN II–XII intact

Labs: All within normal limits. SCr 1.0 mg/dL (88 µmol/L). LFTs within normal limits

Given this additional information, what is your assessment of the patient's condition?

What are the goals of pharmacotherapy for this patient?

What nonpharmacologic and pharmacologic options are available to the patient?

Pharmacologic Treatment

LO 4

The ideal treatment agent must have clinical efficacy, minimal side effects, minimal drug–drug or drug–disease interactions, convenient administration, and affordable cost. KEY CONCEPT Patient characteristics (eg, age, comorbidities, concurrent drug therapies, and ability to adhere to the prescribed regimen) can influence drug therapy selection.[5] Although a recent systematic review has shed light on the comparative data on newer agents,[14] selection of an initial agent should be based on patient individual characteristics.

▶ *Urge Urinary Incontinence*

Anticholinergic/Antimuscarinic

Antimuscarinic agents are the first-line pharmacologic treatment for UUI or OAB (Table 53–3).[6] They are effective in suppressing premature detrusor contractions, enhancing bladder storage, and relieving symptoms. When used with or without bladder training, these agents improved symptoms and quality of life in patients with UUI or OAB; however, they restore continence in less than 15% of patients and reduce episodes of incontinence by only 0.5 to 1 episodes per day.[14,15] They are considered equally effective based on statistical superiority over placebo or active controls.

All antimuscarinic agents have similar contraindications and precautions, including urinary retention, gastric retention, and uncontrolled narrow-angle glaucoma.[5] Older immediate release (IR) agents, such as oxybutynin and tolterodine, have been associated with higher rates of dry mouth, constipation, headache, dyspepsia, dry eyes, cognitive impairment, tachycardia, and urinary retention (Table 53–4). Older patients are especially susceptible to these adverse events. Significant dry mouth can be associated with dental caries, ill-fitting dentures, and swallowing difficulty. Chewing sugarless gum or use of saliva substitutes can help to alleviate dry mouth.

Orthostatic hypotension and sedation can be particularly troublesome to patients with cognitive impairment or at risk for falls. Issues with tolerability and multiple daily dose administration associated with IR products may jeopardize medication adherence and can prevent dose titration to achieve optimal clinical response. Thus, these IR products are not preferred in patients with functional limitations and/or those who are already taking complicated drug regimens. Nevertheless, adverse events are not universal and the severity varies with individuals. Older agents, when initiated at the lowest possible doses and gradually titrated, are reasonable to consider in cases when long-acting products are undesirable (eg, troubles with swallowing).

Extended-release (ER) agents (oxybutynin XL, tolterodine LA, trospium ER, darifenacin ER, fesoterodine ER) cause less dry mouth compared with IR products.[5,7] These products cannot be chewed, crushed, or divided, and must be swallowed whole. Oxybutynin transdermal patch and topical gel are alternatives for patients who cannot take or tolerate oral drugs; they have lower rates of dry mouth but are associated with application site reactions. Rotation of application sites can be helpful to minimize the side effects.

Patients receiving any antimuscarinic agent should be informed about sedation as a possible side effect and warned against operating heavy machinery, such as driving, especially during the initial phase of therapy. Patients with existing cognitive dysfunction or difficulty with balance should be monitored closely for mental status changes and risk for falls. Older individuals are more prone to experience constipation because they are more likely to take medications which affect bowel function. Patients should be advised to contact their physician if they experience severe abdominal pain or become constipated for 3 or more days. Clinicians should monitor potential drug interactions between antimuscarnic agents and acetylcholinesterase inhibitors, which are used to treat dementia (antagonism). Also, concomitant use with any other anticholinergic agents increases side effects.

KEY CONCEPT Antimuscarinic agents should be initiated at the lowest possible dose and gradually titrated upward based on clinical response; however, not to exceed the maximum recommended dose. A trial of at least 4 weeks is required to evaluate its efficacy. Consider switching to another agent if the patient reports intolerable side effects or inadequate symptom relief despite optimized dose and duration.

Mirabegron Mirabegron is a β_3-adrenergic agonist approved in June 2012 for the treatment of OAB with UUI. Like antimuscarinic agents, it reduces urinary frequency and incontinence episodes by less than one per day and is also considered the first-line drug therapy for OAB (see Table 53–3).[6,16] It increases bladder capacity by relaxing the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle. It requires 4 to 8 weeks of therapy for optimal efficacy.[16]

Mirabegron is available as ER tablets, and should be swallowed whole without chewing, dividing, or crushing. Most commonly reported adverse reactions are hypertension (7%–11%), nasopharyngitis (4%), UTI (3%–6%), and headache (3%–4%). Patient should be monitored for increased blood pressure and urinary retention, particularly in patients with bladder outlet obstruction or those who are taking anticholinergic drugs.[5] Currently, there is no direct comparison of mirabegron and antimuscarinics for efficacy or tolerability.

Older Agents[5] Tricyclic antidepressants (TCA), such as desipramine, nortriptyline, imipramine, and doxepin, are generally no more effective than oxybutynin IR. They may cause potentially serious adverse effects (eg, orthostatic hypotension, cardiac conduction abnormalities, dizziness, and confusion) and thus should be limited to individuals who have one or more indicated comorbidities (eg, depression or neuropathic pain), patients with MUI (because of their effect of decreasing bladder contractility and increasing outlet resistance), and possibly those with nocturnal incontinence associated with altered sleep patterns. Propantheline, flavoxate, dicyclomine, and hyoscyamine are not recommended due to lack of efficacy and/or significant adverse effects.[5]

▶ *Stress Urinary Incontinence*

The goal of pharmacologic therapy of urethral underactivity is to improve the urethral closure mechanism by:

- Stimulating α-adrenoceptors in the smooth muscle of the proximal urethra and bladder neck
- Enhancing the supportive structures underlying the urethral mucosa
- Enhancing the positive effects of serotonin and norepinephrine in the afferent and efferent pathways of the micturition reflex

In general, systemic pharmacologic therapy is not recommended for SUI.[8,10] PFMT is the first-line therapy in

Patient Encounter 1, Part 3

Based on the information presented, create a care plan for this patient's OAB. Your plan should include:

(a) A statement of the drug-related needs and/or problems

(b) A patient-specific detailed therapeutic plan, including patient counseling to enhance medication adherence, ensure successful therapy, and minimize adverse effects

(c) A plan for follow-up to evaluate therapeutic outcome and drug tolerability

Table 53–3

Approved Drugs for the Management of UUI

Parameter	Oxybutynin	Tolterodine	Trospium Chloride	Solifenacin	Darifenacin	Fesoterodine	Mirabegron
Dosage forms	IR tablets, solution SR-ER tablets, SR-TD patch, topical gel	IR tablets SR-LA capsules	IR tablets ER tablets	IR tablets	ER tablets	ER tablets	ER tablets
Dosing	IR: 2.5–5 mg 2–4 times daily (pediatrics 0.3–0.5 mg/kg/day in three doses) SR (oral): 5–30 mg once daily (pediatrics: 0.3–0.5 mg/kg/day) SR (TD): 3.9 mg/day patch applied twice weekly; available over-the-counter SR (gel): 1 sachet (100 mg) applied once daily	IR: 1 or 2 mg twice daily (pediatrics: 1 mg twice daily) ER: 2 or 4 mg once daily (pediatrics: 2 mg once daily)	IR: 20 mg twice daily ER: 60 mg once daily	5–10 mg once daily	7.5–15 mg once daily	4–8 mg once daily	25 mg once daily, then 50 mg once daily after 8 weeks
Kinetics	Active metabolite (*N*-desethyl) Not altered in renal or hepatic disease or advanced age	Active metabolite (5-hydroxymethyl) Polymorphic metabolism (CYP 2D6) Not altered in advanced age. Significantly altered in hepatic disease (decreased CL in cirrhosis) and renal disease (decreased CL)	Food: decreased F by 70%–80% Significantly altered in renal disease (decreased CL) but not in hepatic disease or advanced age	Metabolized via CYP 3A4 but only one active metabolite (4-hydroxy) Significantly altered in severe renal impairment, moderate hepatic impairment (Child-Pugh B), and advanced age (decreased CL in all)	Complex metabolism (polymorphic CYP 2D6, CYP 3A4) Not altered in advanced age, renal impairment, mild hepatic impairment (Child-Pugh A) Significantly altered in moderate hepatic impairment (Child-Pugh B) (decreased CL)	Prodrug (for 5-hydroxmethyl tolterodine) Inactive metabolites Not altered in advanced age Significantly altered in renal disease (decreased CL) and moderate hepatic impairment (Child-Pugh B) (decreased CL)	Terminal elimination half-life 50 hours Moderate inhibitor of CYP 2D6
Contraindications and precautions	Use with caution if CYP 3A4 inhibitors are also being taken (decreased oxybutynin CL)	Reduce dose 50% in those taking CYP 3A4 inhibitor(s) or with hepatic cirrhosis or with CrCl < 30 mL/min (0.50 mL/s) Antacid-SR (oral) prep, interaction (dose-dumping) (not seen with PPIs)	Give on empty stomach Do not use ER when CrCl < 30 mL/min (0.50 mL/s); use IR 20 mg once daily at bedtime	Do not exceed 5 mg/day if CrCl < 30 mL/min (0.50 mL/s), patient has moderate hepatic impairment, or patient is taking CYP 3A4 inhibitor(s) If severe hepatic impairment, do not use	Do not exceed 7.5 mg/day if patient is taking potent CYP 3A4 inhibitor(s) Use caution if patient is taking moderate CYP 3A4 inhibitor(s) or CYP 3A4 or 2D6 substrate(s) Do not chew, divide, or crush the ER tablets	Do not exceed 4 mg/day if CrCl < 30 mL/min (0.50 mL/s) or patient is taking potent CYP 3A4 inhibitor(s) If severe hepatic impairment, do not use	Limit dose to 25 mg once daily if severe renal impairment or moderate hepatic disease Avoid in end-stage renal disease or severe hepatic impairment, or more BP 180/110 mm Hg Monitor for increased BP and urinary retention Do not chew, divide, or crush

BP, blood pressure; CL, total body clearance; CrCl, creatinine clearance; ER, extended release; F, bioavailability; IR, immediate release; LA, long acting; PPIs, proton pump inhibitors; SR, sustained release; TD, transdermal.

Table 53–4

Adverse Event Incidence Rates with Approved Drugs for Bladder Overactivity[a]

Drug	Dry Mouth (%)	Constipation (%)	Dizziness (%)	Vision Disturbance (%)
Oxybutynin IR	71	15	17	10
Oxybutynin XL	61	13	6	14
Oxybutynin TDS	7	3	NR	3
Oxybutynin gel	10	1	3	3
Tolterodine	35	7	5	3
Tolterodine LA	23	6	2	4
Trospium chloride IR	20	10	NR	1
Trospium chloride XR	11	9	NR	2
Solifenacin	20	9	2	5
Darifenacin	24	18	2	2
Fesoterodine	27	5	NR	3
Mirabegron ER	3	3	3	NR

[a]All values constitute mean data, predominantly using product information from the manufacturers.

IR, immediate-release; LA, long-acting; NR, not reported; TDS, transdermal system; XL, extended-release; XR, extended-release.

women with SUI.[10] Nevertheless, SUI in women is frequently curable by surgery, thus obviating years of drug therapy that may not provide adequate symptom relief. Surgery (tension-free vaginal tape sling) is a more cost-effective therapy of SUI than duloxetine in women failing PFMR.[17] Automatic pelvic exercise devices, incontinence pessaries, and disposable intravaginal bladder support devices can also be considered for SUI.[10]

Estrogens[5] KEY CONCEPT Local vaginal estrogen preparations can effictvely relieve the genitourinary syndrome of menopause, including urinary complaints of frequency, urgency, and SUI.[18] Estrogen products are believed to work by a trophic effect on uroepithelial cells and underlying collagenous subcutaneous tissue, enhancement of local microcirculation by increasing the number of periurethral blood vessels, and enhancement of the number and/or sensitivity of α-adrenoceptors.

Since 1940s, estrogens administered by various routes (oral, transdermal, and local) have been used to manage SUI although recent trials showed them to be no better than placebo. Actually, oral hormone replacement therapy increases the risk of new-onset UI (SUI, UUI, MUI) while carrying numerous short- and long-term risks, including mastodynia, uterine bleeding, nausea, thromboembolism, cardiac/cerebrovascular ischemic events, and breast/endometrial cancer.[19] In contrast, local estrogens (estriol [not available in the United States] tablets, conjugated equine estrogen cream, estradiol rings, pessaries) have demonstrated subjective improvement in SUI and UI in general.[19] Local products, such as estrogen ring, may have dual effects: functioning like an incontinence pessary by supporting the bladder neck while simultaneously providing estrogen locally (Table 53–5).

α-Adrenoceptor Agonists[5] Phenylpropanolamine, ephedrine, and pseudoephedrine have been used alone or with estrogen for mild and moderate SUI. However, recent data showed that they are not better than placebo or PFMR.[18] Phenylpropanolamine has been removed from the market in the United States due to associated risk of ischemic stroke. Ephedrine, although still available by prescription, should not be used for SUI due to toxicity and lack of efficacy data. The major impediment to using α-adrenoceptor agonists is the extensive list of contraindications (see Table 53–5). Side effects of pseudoephedrine, an over-the-counter medication, include hypertension, headache, dry mouth, nausea, insomnia, and restlessness.

Duloxetine This selective serotonin-norepinephrine reuptake inhibitor is approved to treat SUI in Europe, but is off-label in the United States. It enhances central serotonergic and adrenergic tone, which is involved in ascending and descending control of urethral smooth muscle and the internal urinary sphincter, and thereby enhances urethral and urinary sphincter smooth muscle tone during the filling phase.[20] It may benefit incontinence and quality of life in men with SUI after radical prostatectomy.[21]

The use of duloxetine in SUI is complicated by intolerability (eg, high rates of nausea), numerous precautions or contraindications, CYP P450 drug–drug interactions, and possibility of withdrawal symptoms if abruptly discontinued.[20] Due to its modest benefit and intolerability issues, it may be considered only if there are comorbiditeis such as depression, anxiety, fibromyalgia, diabetic neuropathy, and chronic musculoskeletal pain.

The usual dosage is 40 to 80 mg/day (in one or two doses) for 12 weeks. Gradual dose titration (starting from 20 mg once daily for at least 1 week, then titrate no shorter than weekly interval) may help to reduce the risks of nausea, dizziness, and premature therapy cessation. Similarly, taper the dose to avoid withdrawal symptoms if duloxetine is discontinued. Dose reduction of 50% for 2 weeks before discontinuation or slow tapering over 4 to 6 months is reasonable.

▶ *Overflow Incontinence[5]*

There is no established effective pharmacologic therapy for OUI due to bladder underactivity (atonic bladder). A trial of bethanechol (25–50 mg three or four times daily) may be reasonable if contraindications do not exist. Bethanechol is a cholinomimetic that has uncertain efficacy but is associated with bothersome and potentially life-threatening side effects (muscle and abdominal cramping, hypersalivation, diarrhea, and bronchospasm), particularly in patient with preexisting conditions. α-Adrenoceptor antagonists, such as silodosin, prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin, may be beneficial for OUI by relaxing the bladder outflow tract and hence reducing outflow resistance. If pharmacologic therapy fails, intermittent urethral catheterization by the patient or caregiver three or four times per day is recommended. Less satisfactory alternatives include indwelling urethral or suprapubic catheters or urinary diversion. In OUI due to obstruction, such as BPH, the goal of treatment is to relieve the obstruction.

Table 53–5

Drugs Used for SUI[a]

Parameter	Estrogens	Pseudoephedrine	Duloxetine
Dosage forms	Avoid systemic (parenteral, oral, TD); use vaginal: tablet, cream, intravaginal ring	Tablets, solution	DR capsules
Dosing	Estradiol 25-mcg vaginal tablets (insert one PV daily for 14 days, then one PV twice weekly) Estradiol vaginal cream (0.1 mg/g) (2–4 g daily PV for 1–2 weeks; then 1 g PV daily or less frequently) CEE vaginal cream (0.625 mg/gm) (0.5–2 g daily PV; consider 3 weeks on, 1 week off; may be able to decrease frequency of use over time) Estradiol 2-, 12.4-, 24.8-mg vaginal rings (1 ring PV every 3 months)	15–60 mg three times daily	40–80 mg/day in one or two doses for 12 weeks (titrate and taper dosage)
Kinetics	Use local route to minimize systemic F and side effects Estradiol less likely to be absorbed; CEE 1 mg or more daily sufficiently absorbed to cause systemic side effects	Less than 1% of dose is metabolized (inactive metabolites) Primarily renal elimination of unchanged drug Would not expect hepatic impairment to have an effect (no data) Expect significant effect if renal impairment and no effect if advanced age (beyond decreased CrCl with age) (no data)	Extensive metabolism via CYP 2D6 and 1A2 (inactive metabolites) Not altered in advanced age, mild to moderate renal impairment (CrCl 31–80 mL/min [0.51–1.34 mL/s]), mild hepatic impairment (Child-Pugh A) Significantly altered in severe renal disease (CrCl < 30 mL/min [< 0.50 mL/s]) and moderate hepatic impairment (Child-Pugh B)
Contraindications/ precautions	Known or suspected breast or endometrial cancer Abnormal genitourinary bleeding of unknown etiology Active thromboembolism (or history of TE associated with previous estrogen use)	Hypertension, tachyarrhythmias, coronary artery disease, MI, cor pulmonale, hyperthyroidism, renal failure, narrow-angle glaucoma	Multiple drug–drug interactions possible with CYP 2D6 and 1A2 substrates/inhibitors Avoid if CrCl < 30 mL/min (0.50 mL/s) and in all patients with hepatic disease Can raise BP Do not discontinue abruptly (withdrawal syndrome) Suicide risk even in patients without psychiatric disease Avoid in uncontrolled narrow-angle glaucoma (causes mydriasis) Hepatotoxic; avoid in alcoholics even if signs/symptoms of hepatic disease are absent

[a]None of these agents are FDA approved for treatment of SUI. Duloxetine is approved in Europe only.

BP, blood pressure; CEE, conjugated equine estrogens; CrCl, creatinine clearance; CYP, cytochrome P-450; DR, delayed-release; F, bioavailability; MI, myocardial infarction; PV, per vagina; TD, transdermal; TE, thromboembolism.

► *Mixed Urinary Incontinence*[5]

MUI is usually a combination of UUI plus SUI with one dominant component. It accounts for one-third of UI cases in women. A reasonable management approach is a combination of lifestyle/behavioral modifications and PFMR with pharmacotherapy appropriate to the dominant type of UI. For instance, antimuscarinics can be offered in UUI-predominant cases, whereas duloxetine, local estrogen, and α-adrenoceptor agonists in SUI-predominant cases. In some cases, the less dominant form of UI may respond, but usually not to a degree that is considered adequate by the patient. Most experts feel that SUI-predominant MUI is best treated initially using the nonpharmacologic approach plus surgery for SUI. Unfortunately, these patients with MUI are expected to have a lower success rate with surgery compared to those with pure SUI. The urge component may get better, stay the same, or get worse after surgery. Unfortunately, there is no a priori way to predict the response in a given individual.

► *Nocturia*

Desmopressin Nocturia may be caused by a wide array of factors, such as uncontrolled diabetes mellitus, congestive heart failure, bladder/prostate diseases, and use of medications, especially diuretics. Desmopressin is a synthetic vasopressin analog in intransal formulation that was approved in March 2017 in the United States for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void. The product carries multiple contraindications which

may limit its use, especially in the elderly. Contraindications include hyponatremia, polydipsia, primary nocturnal enuresis, concomitant use of loop diuretics or glucocorticoids (systemic or inhaled), renal impairment, syndrome of inappropriate ADH secretion, concurrent illness that can cause fluid or electrolyte imbalance, moderate to severe heart failure, and uncontrolled hypertension. Intranasal desmopressin was approved based on clinical studies involving patients aged 50 years or older. The dose for patients younger than 65 years who are not at increased risk for hyponatremia is one spray (1.66 mcg) in either nostril nightly approximately 30 minutes before going to bed. In patients who are 65 years or older, or younger patients at risk for hyponatremia, the starting dose is 0.83 mcg nightly, which can be increased to 1.66 mcg after at least 1 week as needed.[22] Sublingual formulation was approved in Canada for nocturia. Desmopressin oral and sublingual formulations are indicated for primary nocturnal enuresis.

OUTCOME EVALUATION

- Monitor the patient for symptom relief. Has the treatment achieved the desired outcomes jointly developed by the health care team and the patient/caregiver? If so, to what degree? Inspect the daily diary completed by the patient/caregiver and quantitate the clinical response (eg, number of micturitions, number of incontinence episodes, and pad use) since the last visit. If a diary has not been used, ask the patient how many incontinence pads have been used and how they have been doing in terms of "accidents" since the last visit. If appropriate, administer a short-form instrument to measure the impact of symptoms, including quality of life. Compare the findings with previous results.
- Ask patients about adverse effects of drug therapy using a nonleading approach. Ask the patient/caregiver to judge their severity and what measures, if any, they have used to alleviate. Assess medication adherence (ask patient/caregiver about missed doses or do a pill count if the prescription containers are available at the visit).
- The balance of clinical response and tolerability should guide whether the drug dosage is increased, decreased, or left unchanged. Consider stopping/tapering off the regimen and initiate another drug option if bothersome adverse effects compromise patient safety and/or medication adherence.

LO 5

Patient Care Process: Urinary Incontinence

Collect Information:

- Identify urinary symptoms and ask the patient how the symptoms affect his or her daily living.
- Identify exacerbating factors and UI complications.
- Review concurrent medical conditions and obtain a thorough medication history, including use of prescription, nonprescription, and complementary/alternative drug products.
- Identify allergies, or serious adverse events related to the use of medications and other substances.
- Ask the patient and caregiver about their goals of therapy and socioeconomic factors that affect medication access and other aspect of care. In cognitively intact elderly patients, focus communications to elicit the preferences of the patient, not those of potential proxies.

Assess the Information:

- Assess the severity of urinary symptoms. Assess changes in quality of life (physical, psychological, social functioning, and well-being).
- Based on reported signs, symptoms, and exacerbating factors, determine whether a referral to specialized professional is required.
- Evaluate whether or not urinary symptoms could be disease-related or drug induced (see Table 53–1). Determine if any current or previous treatments are/were helpful for UI.

Develop a Care Plan:

- Help the patient and caregiver to set realistic goals of therapy.
- Consider whether lifestyle/behavioral modification, fluid management, and other nonpharmacologic treatment are feasible or desirable.
- Determine whether pharmacotherapy is indicated or desired by patient. Choose appropriate treatment regimen (drug choice, dosage, administration) for his or her type(s) of UI.
- Evaluate the patient for medication adherence, drug-related adverse events, allergies, and drug interactions with concomitant medications or disease states.

Implement the Care Plan:

- Educate the patient on lifestyle modifications that may improve symptoms: smoking cessation (for patients with cough-induced SUI), weight reduction (for those patients with SUI and UUI), constipation prevention in patients at risk, caffeine reduction, and diet/fluid modification. Note the timing and quantity of fluid intake, as well as possibility of avoiding foods or beverages that worsen UI.
- Provide patient education regarding the disease state, lifestyle modifications, and drug therapy (see Tables 53–3 and 53–5).
- Address any patient/caregiver concerns about disease state and its management, including timing of medication intake, potential adverse events, potential drug–drug or drug–disease interactions and importance of treatment adherence.

Follow-up: Monitor and Evaluate:

- Monitor for patient response in 1 or 2 weeks after therapy initiation.
- Develop a plan to assess efficacy after a minimum of 4 weeks.
- Determine whether the patient is experiencing any adverse effects or drug interactions.

PEDIATRIC ENURESIS

INTRODUCTION

UI, referred to as pediatric enuresis, is a common problem in children. In children less than 5 years of age, treatment is unnecessary because spontaneous cure is likely. Pediatric enuresis is subdivided into the following categories to clarify expectations of the condition and response to therapy:[23,24]

- Monosymptomatic enuresis: enuresis in children without other lower urinary tract symptoms or bladder dysfunction
- Primary enuresis: enuresis in children who have never been consistently dry throughout the night
- Secondary enuresis: enuresis in patients who have resumed wetting after a period of dryness of at least 6 months in duration
- Nonmonosymptomatic enuresis: enuresis in children with other lower urinary tract symptoms (eg, urgency, frequency, daytime incontinence, genital or lower urinary tract pain)

The emotional and developmental impacts from enuresis are significant and include social stigma and low self-esteem. Missing camp getaways and sleepovers can have a negative effect on peer relationships.[25]

EPIDEMIOLOGY AND ETIOLOGY

Five to seven million children and adolescents in the United States suffer from nocturnal enuresis; however, with each year of maturity, the percentage of bed-wetters declines by 15% without treatment due to maturation alone.[26] In the enuretic population, 80% to 85% are monosymptomatic, 5% to 10% are nonmonosymptomatic, and less than 5% have an organic cause.[27] Primary enuresis is twice as common as secondary enuresis.[27] The prevalence of enuresis is as follows:

- At 5 years of age: 15% to 25%
- At 12 years of age: 8% (boys) and 4% (girls)
- During adolescence: 1% to 3%

The etiology of enuresis is poorly understood, but there is a clear genetic link. Loci for enuresis are located on chromosomes 5, 12, 13, and 22. Risk factors include a familial link; when both parents have a history of enuresis as children, the child's incidence is 77% as compared to 44% with one parental history.[25,28] Sleep apnea, attention deficit disorder, autism, and obesity are also associated with pediatric enuresis.[25,26] Drug-induced causes of pediatric enuresis include lithium, clozapine, risperidone, valproic acid, selective serotonin reuptake inhibitors, and theophylline. In a minority of cases, psychological factors (eg, divorce of parents, school trauma, sexual abuse, or hospitalization) may contribute to secondary enuresis. Potentially treatable organic causes of enuresis are listed in Table 53–6.

Table 53–6

Major Potentially Treatable Organic Causes of Enuresis

Potentially Treatable by Surgery
- Ectopic ureter
- Lower UTI congenital anomalies
- Neurogenic bladder
- Bladder calculus (stone) or foreign body
- Obstructive sleep apnea

Potentially Treatable by Medications
- UTI
- Diabetes mellitus
- Diabetes insipidus
- Fecal impaction
- Constipation

UTI, urinary tract infection.

PATHOPHYSIOLOGY

LO 6

Microstructural abnormalities and maturational delays of neuronal circuits have been identified in the frontal cortex of children with enuresis.[25] Physiological factors associated with pediatric enuresis include reduced bladder function and/or capacity, altered arousal to a full bladder, detrusor over-activity at night, and/or nocturnal polyuria from lack of circadian rhythm of nocturnal ADH secretion.[25,28]

Definitions applicable to pediatric patients are helpful in discerning the etiology:

- Bladder capacity: (30 + [30 × age] mL)
- Nocturnal polyuria: urine production greater than 130% of expected bladder capacity for age
- Normal functional bladder capacity: maximum voided volume greater than 70% of expected bladder capacity for age

TREATMENT

Desired Outcomes

- Reduction in the number of enuresis episodes and restoration of continence[32]
- Partial response: a 50% to 89% reduction
- Response: 90% or more reduction
- Full response: 100% reduction or less than 1 symptom occurrence monthly
- Prevention of relapse (< 1 symptom recurrence monthly) and maintenance of treatment success[23]
- Continued success: No relapse in 6 months after the interruption of treatment
- Complete success: No relapse in 2 years after the interruption of treatment

Patient Encounter 2, Part 1

A 9-year-old boy is brought into your clinic. His mother seeks advice regarding her child's inability to stay dry for more than a few nights in a row. The child's father had a history of bedwetting until 11 years of age, when it resolved. The mother asks for an over-the-counter medication to help the child. The child is frustrated because he wants to attend a sleep-away camp and is concerned about being teased by his friends. The family recently moved across the country, are stressed, and the child already started classes at the new school.

What additional information do you need to know before creating a treatment plan for this child?

What risk factors does the child have for pediatric enuresis?

Clinical Presentation and Diagnosis: Pediatric Enuresis

Proper assessment of the child or adolescent with enuresis should explore every aspect of UI, including the genitourinary and nervous systems. The minimum assessment should include:[24,28,29]

- Interview of the child and parent(s), being sensitive to the emotional consequences of the enuresis.
- Direct physical examination, looking for enlarged adenoids/tonsils, bladder distention, fecal impaction, abnormal genitalia, spinal cord anomalies, and abnormal neurologic signs (look for an organic cause amenable to surgery or medications; see Table 53–6).
- Obtain urinalysis for glucose, protein, WBC, or leukocyte esterase; obtain urinalysis and urine culture if symptoms of UTI are present.
- A 7 or more day diary of wet and dry nights prior to intervention is useful to monitor the response to treatment.
- Nonmonosymptomatic enuresis may require a more extensive workup, including voiding cystourethrogram, renal and/or bladder ultrasound, urodynamics, and sleep studies.

- Prevention or minimization of disease complications (delay in childhood developmental milestones, adverse psychological effects on the child/caregivers)
- Minimization of adverse effects and costs related to treatment
- Improvement in the quality of life of the child and caregivers

Patient Encounter 2, Part 2

PMH: Unremarkable pregnancy/delivery. Developmental milestones WNL

Immunization: Up to date

FH, SH: Lives with both parents and two siblings, ages 3 and 6 years

Meds: None

ROS: (+) nocturnal incontinence 5 to 6 nights per week; no daytime incontinence; no UTIs, urgency, frequency, dysuria, lower abdominal fullness, or other lower urinary track symptoms; no signs of constipation or fecal impaction

PE:

VS: BP 100/70 mm Hg, P 82 beats/min, RR 16 breaths/min, T 37.0°C (98.6°F)

Resp: Clear breath sounds bilaterally

CV: Clear to auscultation, no murmurs

Abd: Soft, nontender, nondistended; (+) bowel sounds; bladder not palpable

Neuro: WNL (gross sensory, motor, reflexes)

GU, Rectal: Deferred

Labs: Urinalysis WNL

Given this additional information, what is your assessment of this child's enuresis?

Identify your treatment goals for this patient.

What nonpharmacologic and pharmacologic interventions are appropriate for this child?

General Approach to Treatment

Treatment is guided by the findings of the patient assessment. A referral to urologists is needed in cases of daytime wetting, abnormal voiding (eg, unusual posturing, discomfort, straining, poor stream), history of recurrent UTIs, and abnormalities of the genitalia. Psychotherapy is recommended in cases with a true psychological cause.

Guidelines for the evaluation and management of nocturnal enuresis have been developed.[24,28,29] Management of primary monosymptomatic nocturnal enuresis in children may involve one or a combination of interventions. The management of secondary nocturnal enuresis focuses on addressing the underlying contributing factor. However, most children with secondary enuresis are treated in the same manner as those with primary enuresis. The National Institute for Health Care and Excellence guideline algorithm (Figure 53–1) outlines useful treatments and distinguishes approaches based on the child's age, maturity, and abilities, and the frequency of enuresis.[29]

Initial management with education and motivational/behavioral therapy, called urotherapy, (Table 53–7) should be used for 3 to 6 months.[23,27] If this fails, an enuresis alarm or pharmacologic treatment may be chosen. KEY CONCEPT Enuresis alarms are the most effective and lasting first-line therapy. For a faster response or in unmotivated families, desmopressin is an effective and ideal agent for the short-term control of pediatric enuresis, especially for sleepovers or camp attendance. KEY CONCEPT Pharmacotherapy is indicated in patients who have difficulty adhering to nonpharmacologic therapy or if desired outcomes are not achieved with nonpharmacologic therapy. A general approach to therapy selection is:[30]

1. Child with nighttime normal urine output, normal bladder capacity: either alarm or desmopressin therapy
2. Child with reduced bladder capacity: Alarm therapy
3. Child with nocturnal polyuria, normal functional bladder capacity: Desmopressin
4. Child with excessive urine output and reduced nocturnal bladder capacity: Combination of alarm and desmopressin therapy

► *Nonpharmacologic Treatment*

Urotherapy The goal of urotherapy is to regulate bladder emptying and storage. Education about the condition, fluid/diet modification, journal keeping, and behavioral or motivational therapy represent the first steps in managing pediatric enuresis (see Table 53–7).[25,27,31] Motivational therapy allows about 25% of children to achieve 14 consecutive dry nights and 70% of them achieve at least a partial response. About 5% of children experience more than 2 wet nights in 2 weeks. If motivational therapy fails to lead to improvement after 3 to 6 months, active interventions, such as enuresis alarms (Table 53–8) or desmopressin, may be added.[32,33]

Alarm Therapy Enuresis alarms are indicated for motivated families and children with frequent enuresis of more than twice per week. They are the most effective ways of controlling

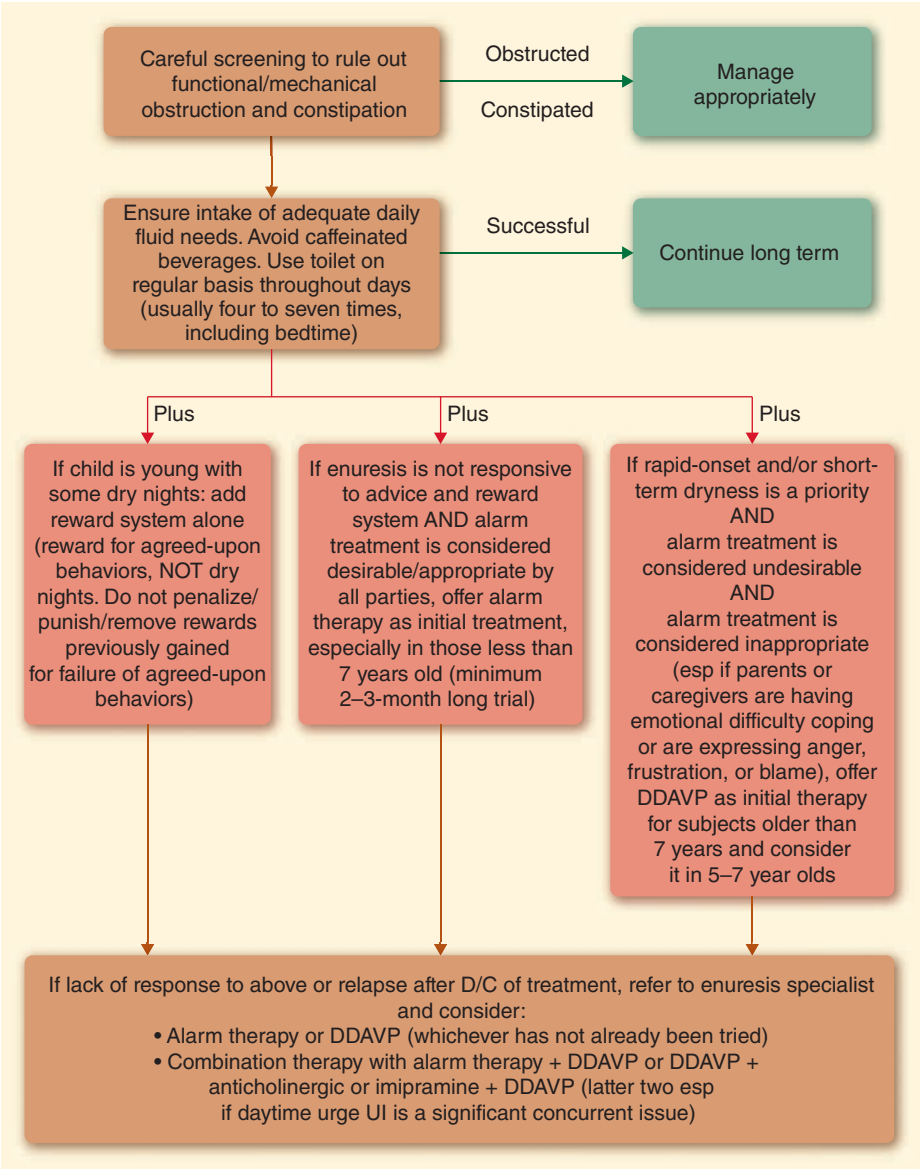

FIGURE 53–1. Enuresis treatment protocol. (D/C, discontinuation; DDAVP, desmopressin; UI, urinary incontinence.) (Modified from Nunes VD, O'Flynn N, Evans J, Sawyer L; Guideline Development Group. Management of bedwetting in children and young people: summary of NICE guidance. BMJ. 2010;341:c5399.)

Table 53–7

Initial Management of Pediatric Enuresis

Education and Advice to Children and Caregivers

- Enuresis is common; it occurs at least once per week in up to 25% of 5-year-old children; enuresis resolves on its own in the majority of children.
- Enuresis is the fault of neither the child nor the caregivers; children should not be punished for bedwetting.
- Reduce the impact of bedwetting by using bed protection and washable/disposable products.
- Keep a calendar of wet and dry nights to determine the effect of interventions.
- Encourage daily fluid intake in the morning and early afternoon. Restrict fluid and solute intake during the evening. A recommendation is to drink 66% of total daily fluid in the morning before the end of the school day and only 30% in the evening, after 5 PM.
- The child should attempt to void every 2–3 hours during the day and just before going to bed; wake the child at night to urinate or lift the sleeping child to the toilet and wake the child to urinate.
- Teach the child to delay urination in the daytime to increase bladder capacity.
- Avoid high-sugar and caffeine-based drinks, particularly in the evening hours.
- Discourage routine use of diapers and pull-ups, except when the child is sleeping away from home.

Motivational Therapy

- Motivational therapy is a good first-line therapy for nocturnal enuresis in younger children between the ages of 5 and 7 years who do not wet the bed every night.
- Motivate the child by keeping a record of progress and giving rewards for accomplished agreed-upon behavior, such as going to the toilet before bedtime. For example, a sticker on a calendar for each night using toilet at bedtime, a book for seven consecutive, etc. Do not use penalties (ie, removal of previously gained rewards).

Table 53–8

Behavioral Treatments for Enuresis

Lifting	Procedure wherein the caregiver takes the child to the toilet at regular intervals during the night to urinate without fully awakening him or her may work as a short-term measure
Night awakening	Procedure wherein the caregiver fully awakens the child to void at regular intervals or randomly, used on a short-term basis
Alarm	An alarm device and a moisture-sensitive sensor are used in combination, with the sensor being placed under the sheets, or more commonly, attached to the child's pajamas or underwear near the urethra. The arousal device is usually an auditory alarm and/or a vibrating belt or pager
Overlearning	This is started at a minimum of 2 weeks after the alarm has rendered the child dry; the child drinks 500 mL (about 16 oz) during the hour before going to bed; alarm use is continued until he or she is dry for 14 consecutive nights with the extra fluid intake; is used to reduce relapse rates seen with alarm use alone
Dry-bed training	This begins with an intensive first night of training that involves increased fluid consumption, hourly awakenings, praise when the bed is dry at hourly awakenings, and, when the alarm goes off, a mild reprimand and cleanliness training (child changes wet clothes and bed linens, remakes the bed, resets the alarm); before going to bed and after each wetting, the child engages in 20 practice trials of appropriate toileting (ie, positive practice): for each practice trial, the child lies in bed, counts to 50, arises and attempts to urinate in the toilet, then returns to bed; on subsequent nights, child is woken only once, usually about 3 hours after the child has gone to bed; after a dry night, the night awakening moves up 30 minutes earlier; it is discontinued when it is scheduled to occur 1 hour after bedtime; after 7 consecutive dry nights, the alarm is discontinued, but is reinstated if two episodes of wetting occur in a 1-week period

nocturnal enuresis and preventing relapses, and may be used in children younger than 7 years. They condition the child or caregiver to wake to the alarm sound or vibration and stop urinating until they go to the toilet. The alarm signals teach the child to wake enough to inhibit bladder contraction in response to the physiologic conditions present before wetting the bed completely. Enuresis alarms are curative in 60% to 80% of the patients, with long-lasting effects in 55% of children.[25,26] Alarm therapy is as effective as desmopressin and more effective than TCAs for pediatric enuresis.[27,31,33] Enuresis alarms can be combined with pharmacotherapy in patients who are partial- or nonresponders to drug therapy alone.[34,35]

The advantage of this therapy is providing a real cure without adverse effects. Because alarms modify conditioning, they are slow in onset and require patience and motivation. Other disadvantages include alarm failure, inability to wake the child, disruption of caregivers and family members, and cost since most are not covered by insurance policies.[27] Follow-up should be assessed 1 to 2 weeks after initiating alarm therapy; however, a full response is not expected to occur until a trial of 3 to 6 months.[27,29] A full response is defined as the achievement of a minimum of 14 consecutive dry nights. If no improvement is seen in 3 to 6 months, alternative interventions should be considered. Enuresis alarm can be reinitiated if a relapse occurs after discontinuation.[27]

Measures that have limited effectiveness in pediatric enuresis include:[25,36]

- Bladder stretching exercises
- Hypnotherapy
- Dietary changes
- Desensitization to allergens
- Acupuncture
- Chiropractic

▶ *Pharmacologic Treatment*

Desmopressin (DDAVP)[30,37] A synthetic analogue of vasopressin, desmopressin decreases urine production by enhancing water reabsorption in the collective tubules. It is indicated for nocturnal enuresis in children with ages 6 years or older who do not respond to initial management (see Figure 53–1), or as an alternative to alarm therapy. Desmopressin is most effective in a child with nocturnal polyuria and normal functional bladder capacity. It decreases the number of wet nights per week by about 1 night. About 30% of children become full responders while on the drug. However, 62% to 82% of them experience relapses.[25,31] Therapies for pediatric enuresis are listed in Table 53–9.

KEY CONCEPT Desmopressin is the drug of choice in pediatric enuresis. As of 2007, the intranasal formulation was no longer FDA-approved for the management of primary nocturnal enuresis due to postmarketing reports of seizures due to hyponatremia. Desmopressin is an alternative therapy to enuresis alarms. It works faster, which allows the child to attend camp or has sleepovers on short notice. Oral tablets may be started at 0.2 mg (one tablet) 1 hour before bedtime to reach peak effects. If response is not achieved in 10 to 14 days, the oral dose may be increased by 0.2 mg to a maximum dose of 0.6 mg. If the child cannot swallow the tablet, it may be crushed and consumed with soft foods. Sublingual tablets of 120 mcg are available outside the United States. They may be given 30 to 60 minutes before bedtime. If response is not achieved after 10 to 14 days, the dose may be increased to a maximum of 240 mcg.[24,31]

Treatment response should be assessed within 1 to 2 weeks. If effective, desmopressin can be continued for 3 to 6 months, administered either nightly, or as needed in special situations. When it is administered daily on a continuous basis, desmopressin should be withheld for 1 week every 3 months to determine whether continued use is necessary.[30] Lack of response to desmopressin may be due to reduced nocturnal bladder capacity, daytime wetting or suboptimal dosing. To minimize relapses, daily desmopressin should be tapered over a 2-week period. To do this, the daily dose may be reduced by one-half or the dose may be given every other day for 2 weeks before discontinuation.

The most serious complication of desmopressin therapy is water intoxication from dilutional hyponatremia and seizures. This occurs most frequently with the nasal formulation. Electrolyte monitoring in patients taking the oral formulation is recommended if comorbidities may exacerbate renal or electrolyte complications. To reduce the risk of water intoxication, children should drink no more than 8 oz (240 mL) of fluid from

Table 53–9

Therapies for Pediatric Enuresis

Therapy (FDA approval)	Dosage form	Dose (generic)	Advantages	Disadvantages	Adverse effects
Enuresis alarms	Sound and/or vibration		• Best response • Low relapse rates	• Requires motivation • Slow-acting	Sleep disruption
Desmopressin (> 6 years of age)	Oral, tablet 0.1 mg, 0.2 mg (generic)	0.2 mg, increased to 0.4 mg (Maximum 0.6 mg)	• Reduces urine volume at night • Faster acting than enuresis alarms	• Low response rate • High rate of relapse	Water intoxication, hyponatremia, seizures
Imipramine (> 6 years of age)	Oral, tablet 10 mg, 25 mg, 50 mg (generic)	10 mg to 25 mg (Maximum: 50 mg if < 12 years of age; 75 mg if > 12 years of age)	• Reduces bladder contractions • Equally effective to desmopressin	• High rate of relapse	Cardiac conduction disturbances; myocardial depression
Anticholinergics: oxybutynin (> 5 years of age)	Oral, tablet 5 mg; Syrup 5 mg/mL (generic)	5 mg once or twice a day	• Reduces bladder contractions • Effective in patients with low functional bladder capacity	Ineffective as monotherapy, use in combination therapy	Constipation, dry mouth
Anticholinergics: Tolterodine (not approved in children)	Oral, tablet 1 mg, 2 mg (generic)	1–2 mg per day	• Reduces bladder contractions • Effective in patients with low functional bladder capacity	Ineffective as monotherapy, use in combination therapy, limited data in children	Constipation, dry mouth

1 hour before to 8 hours after administration of desmopressin. Treatment should be interrupted during episodes of fluid and/or electrolyte imbalance (eg, diarrhea, vomiting, vigorous exercise, fever, or dehydration).[26]

Diuretics play a minor role in the treatment of enuresis for most patients and are not recommended by the enuresis guidelines. However, in cases of poor response to desmopressin or symptom deterioration after established positive response, oral furosemide 0.5 mg/kg in the early morning may be helpful. Furosemide works by reversing the abnormal circadian rhythm of renal tubular sodium handling, which is common in individuals with enuresis.[38]

Imipramine Imipramine was first used in the treatment of enuresis in the 1960s. It is FDA-approved for pediatric enuresis for ages 6 years and older, but is considered a second-line pharmacotherapy option for monosymptomatic enuresis. TCAs are as effective as desmopressin but are associated with more adverse reactions.[27,39] Their place in therapy is in a child who failed alarm and desmopressin therapies. Mechanisms of action of imipramine include anticholinergic and antispasmodic effects, as well as increasing plasma ADH concentrations, and/or lowering arousal threshold.[26,31] Although trials involving other TCAs have been performed, there is insufficient evidence to assess their relative efficacy compared with imipramine.

Response to imipramine, defined as one less wet night per week, is expected in 50% of children. However, relapse rates are up to 67%.[29] The usual initial dose is 10 to 25 mg at bedtime which may be increased if there is no response after 1 week. On average, the bedtime dose is 25 to 50 mg orally once a day. The dose should not exceed 50 mg in children between 6 and 12 years of age and 75 mg in children age 12 or older. After 1 month of successful response, the dose should be reduced to the lowest effective dose. As the patient continues the therapy, the medication is discontinued for a 2-week block every 3 months to reevaluate necessity of drug therapy.[31]

About 25% of children treated with TCAs experience gastrointestinal symptoms. Neurologic adverse effects including nervousness, personality change, or sleep disturbances are reported in approximately 5% of patients. Clinicians should monitor for the possibility of increased suicidality, particularly in children and young adults with preexisting depressive symptoms.[26]

The most serious adverse effects of TCAs are cardiac conduction disturbances, QT prolongation, and myocardial depression, particularly in cases of overdose. A history of sudden cardiac death in the family may preclude the use of TCAs unless cleared by a pediatric cardiologist. Therefore, safer options should be considered before starting any TCA for pediatric enuresis.[24]

Anticholinergics Since anticholinergic agents increase bladder capacity during sleep, they are the primary therapy for a child who has low bladder functional capacity. Monotherapy is ineffective so these agents are used in combination therapy only. Initial doses of IR oxybutynin are 5 mg and tolterodine 1 to 2 mg a day and are titrated upward based on clinical response. Maximal therapeutic effects can be seen within 2 months.[24,31] Children should be monitored for potential adverse events, such as urinary retention (may lead to UTIs), constipation (worsens urinary tract dysfunction), and decreased saliva secretion.

Combinations of Therapies In children who fail to respond to one therapy or who have frequent relapses, combinations of urotherapy, imipramine, oxybutynin, desmopressin, and/or alarm therapy can improve treatment response.[25,26] In a child with small bladder volumes and refractory enuresis, combination therapy with desmopressin and anticholinergic agents is more effective than desmopressin alone.

Other Drugs Various medications, such as indomethacin, phenmetrazine, amphetamine sulfate, ephedrine, atropine, furosemide, diclofenac, and chlorprothixene, have been tried in the treatment of nocturnal enuresis. Data suggest that

indomethacin, diclofenac, and diazepam are superior to placebo, but not better than desmopressin.[40] Current guidelines do not recommend any of these agents for pediatric enuresis.

▶ *Comparison of Therapies*

Multiple meta-analyses have been conducted to compare treatments for enuresis, although most trials enrolled a small number of subjects and were of poor methodological quality.[39,40] Overall, enuresis alarms are the most effective treatment method, from the standpoint of therapy effectiveness and reduced rate of relapse. The initial rate for success (< 1 wet night per month) is 66%, with 55% long-term success rate after discontinuation. Alarm therapy is at least as effective as desmopressin, but has significantly lower relapse rates (46% vs 60%–70% for desmopressin).[41] Combining enuresis alarms and other complex behavioral therapy further reduces relapse rates. There is inadequate data to compare the various commercial brands of alarms available to consumers.

▶ *Treatment of Relapse*

A relapse is defined by more than 1 wet night per month after a period of dryness.[23] When it occurs, consider reinitiation of the intervention which was previously effective (see Figure 53–1). For children with multiple recurrences after discontinuation of desmopressin, gradual dose tapering of desmopressin may be helpful. If relapse occurs following successful treatment with alarm therapy, the addition of desmopressin may be effective.[29] Management of therapy-resistant monosymptomatic nocturnal enuresis may include periodic new trials of the enuresis alarm with or without desmopressin, desmopressin alone, or a trial of imipramine, or a combination therapy that includes oxybutynin.[25]

Nonresponders experience less than 50% improvement in symptoms despite active interventions.[23] When motivated children and families do not respond to at least 3-month therapy of enuresis alarm and/or desmopressin, referral to a specialist (eg, developmental-behavioral pediatrician, pediatric urologist) may be warranted.[25]

Patient Encounter 2, Part 3

Based on the information available, develop a care plan for this patient's enuresis. Your plan should include:

(a) A statement about the drug-related needs and/or problems

(b) A patient-specific detailed therapeutic plan

(c) Monitoring parameters to assess efficacy and safety

OUTCOME EVALUATION

- Monitor the patient for symptom relief in 2 weeks, 1 month, and every 3 months until symptom resolution. Has the treatment plan achieved the desired outcomes jointly developed by the health care team, the patient, and parents/guardians? If so, to what degree? Evaluate the daily diary completed by the patient or parents/guardians since the last

Patient Care Process: Pediatric Enuresis

Collect Information:

- Identify urinary symptoms, exacerbating factors, and family issues.
- Review past medical history.
- Obtain a thorough medication history, including use of prescription, nonprescription, and complementary/alternative drug products.

Assess the Information:

- Determine whether the enuresis is due to secondary causes. Assess whether there are any exacerbating factors or enuresis-related complications.
- Are there any potentially treatable organic or drug-induced causes of enuresis (see Table 53–6)? Assess parental motivation when attempting nonpharmacologic approaches for the treatment of enuresis.
- Could patient's past medical/medication history contribute to enuresis (see Table 53–1)? Determine which, if any, treatments in the past had been helpful.

Develop a Care Plan:

- Establish realistic treatment goals with the involvement of the child and caregiver.
- If patient is already receiving nonpharmacological interventions and/or drug therapy, assess treatment choice, drug dosing, efficacy, adverse effects, adherence, etc.
- Have the child and caregiver given the current treatment plan an adequate duration of trial? How is the child responding to the current treatment plan?
- Patient-specific detailed therapeutic plan: See Table 53–9 for Therapies for pediatric enuresis.

Implement the Care Plan:

- Educate the patient and/or caregiver on pediatric enuresis, urotherapy, and motivational therapy (see Table 53–7). The patient and/or caregiver should be offered behavioral therapy and/or enuresis alarm with proper education using the "teach back" method (see Table 53–8).
- Provide the patient and/or caregiver with education regarding drug therapy (timing of drug administration, adverse effects, potential drug–drug interactions, etc).

Follow-up: Monitor and Evaluate:

- Evaluate the patient for adverse events, allergies, and interactions (drug–drug and drug–disease) and adherence.
- Evaluate treatment response in 1 to 2 weeks after therapy initiation. Adjust medication dosing if needed.
- Allow at least 3 months to assess efficacy of treatment.
- Identify expected adverse effects and educate regarding avoidance and management of these adverse effects.

clinic visit and quantitate the clinical response (the number of dry nights per week, the number of nights with two or more enuresis episodes, etc). If a diary has not been used, elicit from the patient and caregiver the clinical response since last visit. Consider dosage modification or alternative therapy depending on patient response and adverse effects of therapy.

- Elicit adverse events of therapy, including severity, using a nonleading manner. Ask the patient or parents/guardians what measures, if any, were used to alleviate adverse effects. Assess therapy adherence.
- The balance of clinical response, tolerability, and burden on the caregiver will determine the approach to management. As most nonpharmacologic approaches are "all or none" and drug titration is limited by the maximum recommended dose, clinicians may consider changing therapy if clinical results are inadequate over an appropriate trial period.
- Refer patients with refractory enuresis to a health care professional who specializes in the management of bedwetting.

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Abbreviations Introduced in This Chapter

ADH	Antidiuretic hormone
BPH	Benign prostatic hyperplasia
CYP	Cytochrome P450
DDAVP	Desmopressin
ER	Extended release
IR	Immediate release
MUI	Mixed urinary incontinence
OAB	Overactive bladder
OUI	Overflow urinary incontinence
PFMR	Pelvic floor muscle rehabilitation
PVR	Postvoid residual
SUI	Stress urinary incontinence
TCA	Tricyclic antidepressant
UI	Urinary incontinence
UTI	Urinary tract infection
UUI	Urge urinary incontinence

REFERENCES

1. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology of lower urinary tract function: report from the standardization sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:167–178.
2. Coyne Ks, Wein A, Nicholson S, et al. Economic burden of urgency urinary incontinence in the United States: a systematic review. J Manag Care Pharm. 2014;20:130–140.
3. Buckley BS, Lapitan MC; Epidemiology Committee of the Fourth International Consultation on Incontinence. Prevalence of urinary incontinence in men, women, and children-current evidence: findings of the Fourth International Consultation on Incontinence. Urology. 2010;76:265–270.
4. Gorina Y, Schappert S, Bercovitz A, Elgaddal N, Kramarow E. Prevalence of incontinence among older Americans. National Center for Health Statistics. Vital Health Stat 3. 2014(36):1–33.
5. Rovner ES, Wyman J, Lam S. Urinary incontinence. In: Dipiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York City: McGraw-Hill; 2017:1353–1372.
6. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (Non-neurogenic) in adults: AUA/SUFU guideline. American Urological Association. 2014.
7. Lucas MG, Bedretdinova D, Berghmans LC, et al. Guidelines on urinary incontinence. European Association of Urology. 2013.
8. Qaseem A, Dallas P, Forciea MA, et al. Clinical Guidelines Committee of the American College of Physicians. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2014;161:429–440.
9. Shamliyan T, Wyman J, Kane RL. Nonsurgical treatments for urinary incontinence in adult women. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
10. Culbertson S, Davis M. Nonsurgical management of urinary incontinence in women. JAMA. 2017;317:79–80.
11. Homma Y, Yoshida M, Seki N, et al. Symptom assessment tool for overactive bladder syndrome—overactive bladder symptom score. Urology. 2006;68:318–323.
12. Domoulin C, Hay-Smith EJ, Mac Habée-Séguin G. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2014;5:CD005654.
13. Hay-Smith EJ, Herderschee R, Dumoulin C, Herbison GP. Comparisons of approaches to pelvic floor muscle training for urinary incontinence in women. Cochrane Database Syst Rev. 2011;12:CD009508.
14. Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Benefits and harms of pharmacologic treatment for urinary incontinence in women: a systematic review. Ann Intern Med. 2012;156:861–874, W301–W310.
15. Rai BP, Cody JD, Alhasso A, Stewart L. Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults. Cochrane Database Syst Rev. 2012:CD003193.
16. Bridgeman MB, Friia NJ, Taft C, Shah M. Mirabegron: β_3-adrenergic receptor agonist for the treatment of overactive bladder. Ann Pharmacother. 2013;47:1029–1038.
17. Jacklin P, Duckett J, Renganathan A. Analytic model comparing the cost utility of TVT versus duloxetine in women with stress urinary incontinence. Int Urogynnecol J. 2010;21:977–984.
18. Rahn DD, Carberry C, Sanses TV, et al. Society of Gynecologic Surgeons Systematic Review Group. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. Obstet Gynecol. 2014;124:1147–1156.
19. Cody JD, Jacobs ML, Richardson K, et al. Oestrogen therapy for urinary incontinence in post-menopausal women. Cochrane Database Syst Rev. 2012;10:DC001405.
20. Guay DRP. Duloxetine. The first therapy licensed for stress urinary incontinence. Am J Geriatr Pharmacother. 2005;3:25–38.
21. Cornu JN, Merlet B, Ciofu C, et al. Duloxetine for mild to moderate postprostatectomy incontinence: preliminary results of a randomised, placebo-controlled trial. Eur Urol. 2011;59:148–154.
22. Serenity Pharmaceuticals. Noctiva® (desmopressin acetate) package insert. Milford, PA: Serenity Pharmaceuticals; 2017.
23. Nevéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society (ICCS). J Urol. 2006;176:314–324.

24. Neveus T, Eggert P, Evans J, et al. Evaluation and treatment for monosymptomatic enuresis: a standardization document from the International Children's Continence Society. J Urol. 2010;183:441–447.
25. Caldwell PHY, Deshpande AV, Von Gontard A. Management of nocturnal enuresis. BMJ. 2013;347:1–6.
26. Traisman ES. Enuresis: evaluation and treatment. Pediatr Ann. 2015;44:133–137.
27. Baird DC, Darnall CR, Seehusen DA, et al. Enuresis in children: a case-based approach. Am Fam Physician. 2014;90:560–568.
28. Paediatric Society New Zealand. Noctural enuresis "Bedwetting," 2005.
29. Nunes VD, O'Flynn N, Evans J, Sawyer L; Guideline Development Group. Management of bedwetting in children and young people: summary of NICE guidance. BMJ. 2010;341:c5399.
30. Walle JV, Rittig S, Bauer S, et al. Practical consensus guidelines for the management of enuresis. Eur J Pediatr. 2012;171:971–983.
31. Maternik M, Krzeminska K, Zurowska A. The management of childhood urinary incontinence. Pediatr Nephrol. 2015; 30:41–50.
32. Glazener CMA, Evans JHC, Peto RE. Alarm interventions for nocturnal enuresis in children. Cochrane Database Syst Rev. 2009:CD002911.
33. Perrin N, Sayer L, While A. The efficacy of alarm therapy versus desmopressin therapy in the treatment of primary mono-symptomatic nocturnal enuresis: a systematic review. Prim Health Care Res Dev. 2015;16:21–31.
34. Vogt M, Lehnert T, Till H, Rolle U. Evaluation of different modes of combined therapy in children with monosymptomatic nocturnal enuresis. BJU Intern. 2010;105:1456–1459.
35. Kwak KW, Park KH, Baek M. The efficacy of enuresis alarm treatment in pharmacotherapy-resistant nocturnal enuresis. Urology. 2011;77:200–204.
36. Huang T, Shu X, Huang YS, Cheuk DK. Complementary and miscellaneous interventions for nocturnal enuresis in children. Cochrane Database Syst Rev. 2011:CD005230.
37. Glazener CM, Evans JH. Desmopressin for nocturnal enuresis in children. Cochrane Database Syst Rev. 2009:CD002112.
38. DeGuchtenaere A, Vande Walle C, Van Sintjan P, et al. Desmopressin resistant nocturnal polyuria may benefit from furosemide therapy administered in the morning. J Urol. 2007;178:2635–2639.
39. Caldwell PHY, Sureshkhumar P, Wong WCF. Tricyclic and related drugs for nocturnal enuresis in children. Cochrane Database Syst Rev. 2016;(1):CD002117.
40. Deshpande AV, Caldwell PH, Sureshkumar P. Drugs for nocturnal enuresis in children (other than desmopressin and tricyclics). Cochrane Database Syst Rev. 2012;12:CD002238.
41. Kwak KW, Lee YS, Park KH, Baek M. Efficacy of desmopressin and enuresis alarm as first and second line treatment for primary monosymptomatic nocturnal enuresis: prospective randomized crossover study. J Urol. 2010;184:2521–2526.

54 Drug Hypersensitivity Reactions

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LEARNING OBJECTIVES

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

1. Describe the potential incidence of immunoglobulin-E (IgE)- and non-IgE-mediated (immune and nonimmune) drug hypersensitivity reactions and why it is difficult to obtain accurate estimates.
2. Describe the Gell and Coombs categories of reactions.
3. Identify the classes of drugs most commonly associated with IgE- and non-IgE-mediated drug hypersensitivity reactions.
4. Recommend specific treatment for a patient experiencing anaphylaxis.
5. Recommend an approach to drug selection in patients with multiple drug allergies.
6. Describe how drug desensitization procedures for selected drugs may be useful.

INTRODUCTION

Drug hypersensitivity reactions collectively encompass immunoglobulin E (IgE)- and non-IgE-mediated (immune and nonimmune, or pseudoallergic) drug hypersensitivity reactions. These reactions are rarely confirmed by testing and subject to both over-reporting and under-reporting, making statistical analysis imprecise. KEY CONCEPT Approximately 5% to 10% of adverse drug reactions occur on an allergic or immunologic basis. However, these represent a disproportionate 24% of reported adverse drug reactions in hospitalized patients and are costly, with accompanying morbidity and mortality.[1,2] Between 10% and 20% of hospital inpatients experience drug adverse events versus 7% in the general population, with about one-third possibly due to hypersensitivity; however, many such reactions may not be reported, especially in pediatrics.[1,3,4] Costs of inpatient drug hypersensitivity reactions are estimated to be $275 to $600 million annually.[5] This financial burden includes indirect costs: time and lost labor, use of more expensive alternative medications, and treatment failures, in addition to direct reaction treatment costs. Accurate data regarding outpatient reaction rates are even more difficult to collect. The term "drug allergy" in a patient record/electronic medical record (EMR) often conveys little medical meaning, as such information is self-reported, and may not delineate symptoms or incorporate provider assessment of probable causality (eg, adverse effect vs IgE-mediated). Potential clinical outcomes might therefore range from inappropriately excessive treatment to lack of recognition of anaphylaxis risk. Clearly, an understanding of mechanisms of drug hypersensitivity reactions and how these might be accurately identified, documented, managed, and ideally prevented is of vital importance.

PATHOPHYSIOLOGY

Drug hypersensitivity reactions are a result of diverse mechanisms of immune recognition and activation, resulting in a broad array of clinical findings. The fundamental Gell and Coombs classification, used for decades, remains a framework for considering mechanisms of immunologic drug reactions (Table 54–1).[6,7]

With advances in immunologic understanding, the underlying mechanisms for many drug hypersensitivity reactions have been found to be more complex and interrelated than suggested by the Gell and Coombs classification.[8] However, even with its shortcomings, this classification remains the most commonly used method to initially describe drug reactions resulting from hypersensitivity. KEY CONCEPT Immediate or Type I reactions are those allergic reactions mediated by IgE antibodies specific to the drug; Type II reactions are cytotoxic reactions mediated by drug-specific IgG or IgM antibodies; Type III reactions result from immune complexes circulating in the serum; and Type IV reactions are mediated by cellular mechanisms. Type IV reactions are further subdivided into Type IVa involving recruitment of monocytes, Type IVb with predominantly eosinophils, Type IVc composed of CD4+ or CD8+ T cells, and Type IVd showing neutrophils.[9]

Immune Mechanisms

The cellular immune mechanisms involved in drug hypersensitivity are quite complex.[10] The immune system must first recognize non-self material, or antigens. This recognition is predominantly controlled by T lymphocytes, which have specific surface receptors to accept signals from specialized antigen presenting cells (APCs). Two different signals are typically required for T-cell activation. The presentation of the foreign substance by APC to the T-cell constitutes the first signal. The APC must then concomitantly provide a second signal in addition to the antigen to fully activate the T-cell. If the second signal is not provided, the T-cell becomes nonresponsive or anergic. Thus, the second signal controls the type of immune response that will be initiated by the T-cell.

Depending on the exposure to antigens and the cytokines involved, naïve T-helper cells (CD4+ T-cells) can differentiate

Table 54–1

Reaction Classification, Clinical Symptoms, and Potential Causative Drugs[6,7]

Gell and Coombs Classification	Immune Response	Clinical Symptoms	Potential Causative Drugs[a]
Type I	IgE	Anaphylaxis, urticaria	β-Lactam antibiotics: penicillins (primarily), cephalosporins, carbapenems Non–β-lactam antibiotics: sulfonamides, vancomycin Others: insulins, heparin
Type II	IgG	Hemolytic anemia, thrombocytopenia	Quinidine, methyldopa, penicillins, heparin
Type III	IgG, IgM	Vasculitis, serum sickness, lupus	Penicillins, sulfonamides, radiocontrast agents, phenytoin, minocycline
Type IV			β-Lactam antibiotics, sulfonamides, phenytoin
IVa	Th1 cytokines	Tuberculin reaction eczema	See text for examples
IVb[b]	Th2 cytokines	Maculopapular and bullous exanthema	
IVc[b]	Cytotoxic T cells (CD4 and CD8)	Same as IVb, also eczema, pustular exanthema	
IVd	T-cells (IL-8)	Pustular exanthema	

[a]These drugs represent a list of causative agents. Many drugs can cause these reactions.

[b]IVb and IVc reactions may combine to produce erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necroylsis.

Ig, Immunoglobulin.

into one of a number of specialized effector T-helper cells, each appearing to have a unique regulatory element, pattern of cytokine production, and function. Type 1 effector T-helper cells, or Th1, are typically associated with activation of T-cells to induce B-cell IgG antibody production and to provide direct T-cell recruitment of cells to kill other cells infected with viruses or intracellular bacteria. Th1 responses are thought to cause certain delayed hypersensitivity reactions (Gell-Coombs Type IV). Th2 immune responses induce B cells to produce IgE, and increase tissue eosinophils, yielding potential immediate allergic reactions (Gell-Coombs Type I) or delayed hypersensitivity (Type IV), respectively. In the case of Type I reactions, specific IgE antibody produced in response to an antigen results in membrane-binding of that IgE to mast cells. Upon repeat exposure to the antigen, crosslinking of IgE on these mast cells occurs, accompanied by massive release of preformed mediators including histamine (H). Other T-helper-effector cell subtypes cause additional inflammatory patterns seen in drug hypersensitivity.

Drugs as Antigens

Many drugs are small molecules, which the immune system does not normally recognize as antigens. This fact has resulted in several hypotheses concerning how drugs can elicit an immune response.[10] The first widely accepted hypothesis was the haptenation hypothesis, which states that the drug becomes covalently bound to a normal "self" protein. The combination of the drug bound to the protein is then large enough to be recognized as foreign by the immune system, leading to an immune response.[10] Another hypothesis is the pro-hapten hypothesis, in which a nonreactive drug becomes chemically reactive during metabolism and then covalently binds to self-proteins. An example of this is sulfamethoxazole metabolism to sulfamethoxazole-nitroso, which is highly reactive. Another hypothesis is the pharmacologic interaction (p-i) hypothesis, which has the drug (or metabolite) directly binding to the T-cell receptor, initiating an immune response. In this case, T-cells are directly activated, despite not interacting with APCs, bypassing the usual signaling requirements.

As suggested by several of these hypotheses, the metabolism of the drug often plays a critical role. The fact that many drugs are primarily metabolized in the liver helps to explain why the liver is often involved in drug hypersensitivity reactions. It has also been recognized that skin **keratinocytes** are a site of drug metabolism. This discovery may help explain why the skin is involved in many forms of reactions elicited by different drugs.[11] Indeed some of the most common of the life-threatening drug reactions are predominately cutaneous, including **Stevens-Johnson syndrome** (SJS), **toxic epidermal necrolysis** (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS).[12]

Nonimmune (Pseudoallergic) Drug Reactions

KEY CONCEPT Reactions occur that clinically resemble IgE-mediated or immune drug reactions but lack an immune basis, sometimes called "pseudoallergic" reactions. These include the entire spectrum of clinical severity, but occur via other, unknown mechanisms.

Nonimmune drug hypersensitivity reactions are important in patient counseling and management considerations. They represent common biological occurrences such as direct histamine release by vancomycin or opiates, whereas immunologic (or IgE-mediated) reactions are based on the structure of the drug. Even a history of mild IgE-triggered symptoms may carry significant potential for anaphylaxis on readministration. In contrast, nonimmune drug reactions tend to remain constant, whether mild or severe, and are dose-related. Ionic radiocontrast media administration, as a classic example, can consistently cause **urticaria** in some, and life-threatening hypotension in others.

Nonimmune drug hypersensitivity reactions, then, are reactions where the components of the immune system are used similarly, but without the "learning" response by T-cells and

Clinical Presentation and Diagnosis of IgE-mediated and other Immune Drug Reactions

Reaction	Mediators Involved	Signs and Symptoms
Anaphylaxis	Ig-E-driven reaction resulting in mast cell degranulation and histamine release.	Skin (eg, pruritus, urticaria), respiratory tract (eg, dyspnea, wheezing), gastrointestinal tract (eg, nausea, cramping), and cardiovascular system (eg, hypotension, tachycardia)
Note: Onset is usually within 30 minutes, but can be 2 hours or more. Treatment must begin immediately. Anaphylaxis may recur 6 to 8 hours after initial exposure, warranting observation for up to 12 hours.		
Cytotoxic Reactions	Drug-specific IgG or IgM antibodies	Hemolytic anemia, thrombocytopenia, granulocytopenia, or agranulocytosis
Immune Complex Reactions	IgG, IgM deposition	Serum sickness-like syndrome (eg, arthralgias, fever, malaise, and urticaria) that typically develops 7 to 14 days after exposure to the causative antigen
Dermatologic Reactions	IgE or cellular mechanisms (See Table 54–1)	See below for dermatologic reaction types

- *Urticaria*: These are itchy, raised, swollen areas on the skin. Also known as hives.
- *Maculopapular rash*: A rash that contains both macules and papules. A macule is a flat, discolored area of the skin, and a papule is a small raised bump. A maculopapular rash is usually a large area that is red and has small bumps.
- *Erythema multiforme*: A rash characterized by papular (small raised bump) or vesicular (blister) lesions and reddening or discoloration of the skin, often in concentric zones about the lesion.
- *Stevens-Johnson syndrome*: A severe expression of erythema multiforme (known as erythema multiforme major). It typically involves the skin and the mucous membranes, with the potential for severe morbidity and even death.
- *Toxic epidermal necrolysis*: A life-threatening skin disorder characterized by blistering and peeling of the top layer of skin.

generally without the much greater danger that true immunologic sensitization implies. Nonimmune drug reactions may be considered as a subtype of idiopathic reactions, rather than an activation of the patient's immune system. The pathophysiology of these reactions is generally unknown, but indicators of immune activation are not seen when they occur. An example is a reaction seen with vancomycin infusion. It typically consists of pruritus, an erythematous rash that involves the face, neck, and upper torso and is usually associated with vancomycin infusions given over less than one hour. This reaction is commonly referred to as red man syndrome.[13]

PROBLEMATIC DRUG CLASSES AND TREATMENT OPTIONS

The first priority is to avoid doing serious harm by administering a drug the patient cannot tolerate. One can frequently establish the likelihood of a relationship between the suspected drug and observed reaction, and also whether it is likely to be an immune or idiopathic reaction, by examining the time course and specific signs and symptoms objectively. Evaluating the patient's physical findings and laboratory values if available (taking into account preexisting diseases) may further clarify the need to change treatments and add therapy for the reaction itself.

Reviewing the original indications for the treatment that caused the reaction is important. For example, in many respiratory illnesses a prescribed antibiotic might be unnecessary. If a particular disease persists and definitive indications for treatment are established, alternatives must be sought, either by adjusting dose or administration rate, finding an effective and unrelated alternative medication, or desensitizing the patient to the original drug.

When adverse drug reactions occur, the health care provider should carefully investigate all aspects of the reaction and assess the potential for it to recur. Many patients have frightening associations of the term "drug allergy" with anaphylaxis, an anxiety that is difficult to allay. In this manner, a label of drug allergy may hamper future medical care, with treatment refusals, nonadherence to therapy, or resultant use of more toxic or less effective alternative treatments. If the original reaction is clearly documented, health care providers can appropriately counsel patients about risk.

Anaphylaxis is a true medical emergency and must be treated immediately. Otherwise, managing allergic reactions begins with discontinuing the offending agent. Understanding the allergic reaction and potential for **cross-allergenicity** between similar drugs will assist in selecting an alternative medication. Desensitization is a management option for certain IgE-mediated drug allergies if there is a definitive indication and alternative therapies are not available. Although any agent may cause an allergic (IgE-mediated), immune or nonimmune (pseudoallergic) reaction, several drugs and drug classes are strongly associated with such reactions (Table 54–2). These classes will be discussed individually.

LO 3

Table 54–2

Problematic Drug Classes

β-Lactam antibiotics
Sulfonamide antibiotics
Aspirin and nonsteroidal anti-inflammatory drugs
Radiocontrast media
Opiates
Cancer chemotherapy
Insulin
Anticonvulsants

β-Lactam Antibiotics

Hypersensitivity reactions with β-lactam antibiotics, especially penicillin, may encompass any of the Types I through IV Gell-Coombs classifications. The most common reactions are maculopapular and urticarial eruptions.[14] Although rare (< 0.05%), anaphylactic reactions to penicillins cause the greatest concern, because they are responsible for the majority of all drug-induced anaphylaxis deaths in patients, accounting for 75% of all anaphylaxis cases in the United States.[6,15] The treatment of anaphylaxis is given in Table 54–3.[16]

LO 4

The health care professional is faced with a difficult task when approaching a patient who notes a history of penicillin allergy. Although as many as 12% of hospital patients report an allergy to penicillin, about 90% will have negative skin tests.[17] Table 54–4 shows the traditional protocol for penicillin skin testing.[18] This test only evaluates IgE-mediated reactions. A patient with a history of other serious reactions such as erythema multiforme, SJS, or TEN should not receive penicillin and should not be tested.

KEY CONCEPT Penicillins and cephalosporins both have a β-lactam ring joined to an S-containing ring structure (penicillins: a thiazolidine ring; cephalosporins: a dihydrothiazine ring). The extent of cross-allergenicity appears to be relatively low, with an estimate of approximately 4%.[19] *Cross-allergenicity is less likely with newer generation cephalosporins compared with the first-generation agents*. Anaphylactic reactions to cephalosporins are rare, with a predicted range of 0.0001% to 0.1%. Minor skin reactions including urticaria, exanthems, and pruritus are the most common allergic reactions with cephalosporins, showing severe reactions less often than with penicillins.[20]

For other β-lactam agents, the recommendations are fairly straightforward. Carbapenems should be considered potentially cross-reactive with penicillins and used with caution.[21] Monobactams (eg, aztreonam) do not cross-react with any β-lactam drugs except ceftazidime because they share an identical R-group side chain. Other cephalosporins sharing identical R-group specific side chains share cross-reactivity as well.

Table 54–3

Pharmacologic Management of Anaphylactic Reactions[16]

Immediate Intervention

Epinephrine 1:1000 (1 mg/mL)
- Adults: 0.2–0.5 mg IM, repeat every 5 minutes as needed
- Pediatrics: 0.01 mg/kg (maximum 0.3 mg) IM, repeat every 5 minutes as needed

Subsequent Interventions

Normal saline infusion
- Adults: 1–2 L at a rate of 5–10 mL/kg in the first 5 minutes, followed by slow infusion
- Pediatrics: up to 30 mL/kg in the first hour

Epinephrine infusion

If patient is NOT responding to epinephrine injections and volume resuscitation:
- Adults: epinephrine infusion (1 mg in 250 mL D_5W): 1–4 mcg/min, titrating based on clinical response or side effects
- Pediatrics: epinephrine infusion (0.6 × body weight [in kg] = number of mg diluted to a total of 100 mL normal saline: 1 mL/hour delivers 0.1 mcg/kg/min)

Other Considerations after Epinephrine and Fluids

Diphenhydramine
- Adults: 25–50 mg IV or IM
- Pediatrics: 1–1.25 mg/kg (maximum of 300 mg/24 hours)

Ranitidine
- Adults: 50 mg in D_5W 20 mL IV over 5 minutes
- Pediatrics: 1 mg/kg (up to 50 mg) in D_5W 20 mL IV over 5 minutes

Inhaled β-agonist (bronchospasm resistant to epinephrine)
- 2–5 mg in 3 mL of normal saline, nebulized, repeat as needed

Dopamine (hypotension refractory to fluids and epinephrine)
- 2–20 mcg/kg/min titrated to maintain systolic blood pressure > 90 mm Hg

Hydrocortisone (severe or prolonged anaphylaxis)
- Adults: 250 mg IV (prednisone 20 mg can be given orally in mild cases)
- Pediatrics: 2.5–10 mg/kg/24 hours

D_5W, dextrose 5% in water; IM, intramuscularly; IV, intravenous.

Adapted from Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010;126:477–480.

Table 54–4

Procedure for Performing Penicillin Skin Testing[18]

A. Percutaneous (Prick) Skin Testing

Materials	Volume
Pre-Pen 6 × 10^6 M	1 Drop
Penicillin G 10,000 Units/mL	1 Drop
β-Lactam drug 3 mg/mL	1 Drop
0.03% albumin-saline control	1 Drop
Histamine control (1 mg/mL)	1 Drop

1. Place a drop of each test material on the volar surface of the forearm.
2. Prick the skin with a sharp needle inserted through the drop at a 45° angle, gently tenting the skin in an upward motion.
3. Interpret skin responses after 15 minutes.
4. A wheal at least 2 × 2 mm with erythema is considered positive.
5. If the prick test is nonreactive, proceed to the intradermal test.
6. If the histamine control is nonreactive, the test is considered uninterpretable.

B. Intradermal Skin Testing

Materials	Volume
Pre-Pen 6 × 10^6 M	0.02 mL
Penicillin G 10,000 Units/mL	0.02 mL
β-Lactam drug 3 mg/mL	0.02 mL
0.03% albumin-saline control	0.02 mL
Histamine control (0.1 mg/mL)	0.02 mL

1. Inject 0.02–0.03 mL of each test material intradermally (amount sufficient to produce a small bleb).
2. Interpret skin responses after 15 minutes.
3. A wheal at least 6 × 6 mm with erythema and at least 3 mm greater than the negative control is considered positive.
4. If the histamine control is nonreactive, the test is considered uninterpretable.

Antihistamines may blunt the response and cause false-negative reactions.

Adapted from Sullivan TJ. Current Therapy in Allergy. St. Louis, MO: Mosby; 1985:57–61.

Sulfonamide Antibiotics

Sulfonamides are compounds that contain a sulfonamide moiety (ie, SO_2NH_2). This group includes sulfonamide antibiotics (sulfonylarylamines), and nonarylamine sulfonamides such as furosemide, thiazide diuretics, sulfonylureas, and celecoxib. The sulfonamide antibiotics contain an aromatic amine at the N4 position and a substituted ring at the N1 position.

Patient Encounter 1

A 21-year-old pregnant woman who is at the end of her first trimester has tested positive on prenatal screening for syphilis. She has a childhood history of penicillin allergy. Further history reveals that as a toddler she received amoxicillin and developed emesis, rash, difficulty breathing, and required emergency department treatment with administration of epinephrine. She has not received penicillin or any derivative since that time.

What is the probable mechanism of the prior amoxicillin reaction?

What should be noted on the patient's medication reaction history?

How might this patient be managed at present?

Allergists generally agree that most, but not all, patients allergic to antimicrobial sulfonamides will tolerate nonarylamine sulfonamides.[22] Predisposition to allergic reactions is a more likely reason for dual sensitivity than cross-reactivity between these differing molecules.[23] The term "sulfa allergy" should not be used as it can be confusing to patients and health care providers. The sulfonamide antibiotics are significant because they account for the largest percentage of antibiotic-induced TEN and SJS cases.[24]

KEY CONCEPT Reactions to sulfonamide antibiotics, ranging from mild (most common) to life-threatening (rare), occur in 2% to 4% of healthy patients, with rates as high as 65% in patients with acquired immunodeficiency syndrome (AIDS).[25] Anaphylaxis or nonimmune **anaphylactoid** reactions almost always occur within 30 minutes but may happen up to 90 minutes after exposure, most commonly after parenteral administration. Isolated **angioedema** or urticaria can occur within minutes to days. Serum sickness occurs within 1 to 2 weeks. Fixed drug eruptions (lesions) occur within 30 minutes to 8 hours. These lesions resolve within 2 to 3 weeks after drug removal. The more severe conditions of SJS and TEN tend to occur 1 to 2 weeks after initiation of therapy. Because trimethoprim-sulfamethoxazole is the drug of choice for patients with *Pneumocystis jiroveci* pneumonia, desensitization may be necessary. A history of SJS or TEN is an absolute contraindication for the desensitization procedure.

Patients with Multiple Antibiotic Allergies

LO 5

Dealing with those who report multiple antibiotic allergies can be challenging. Combining knowledge of cross-allergenicity with a careful assessment of patient history may be helpful in designing an antimicrobial regimen. Table 54–5 outlines a series of questions that can be useful in developing an effective treatment plan.[26] If available and indicated, skin testing may be useful to complete the puzzle. Often with careful assessment, an antibiotic of choice may be used when the patient's initial history would have ruled it out. Based on data gathered, the patient's record should reflect antibiotics safe to use if needed, antibiotics to be avoided, and antibiotics that can be used only after desensitization. Although Table 54–5 was designed with antibiotics in mind, it can be modified for multiple allergy situations.

Aspirin and Nonsteroidal Anti-Inflammatory Drugs

Aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs) can induce allergic and pseudoallergic reactions. Because these drugs are so widely used, with much over-the-counter use, the health care professional must have a basic understanding of the types of reactions that can occur and how to prevent them. Three types of reactions occur: bronchospasm with rhinoconjunctivitis, urticaria/angioedema, and anaphylaxis. Remember that patients with gastric discomfort or bruising from these agents may inappropriately describe themselves as being "allergic."

Two specific conditions—aspirin-exacerbated respiratory disease (AERD) and chronic idiopathic urticaria (CIU)—are important because they are commonly seen. AERD may include asthma, rhinitis with nasal polyps, and aspirin sensitivity.[27] Upon exposure to aspirin or an NSAID, patients with AERD experience rhinorrhea, nasal congestion, conjunctivitis, laryngospasm, and asthma. CIU exacerbations may also be seen with aspirin or NSAID-induced pseudoallergic reactions, as those with a history of CIU are likely to see a flare of urticaria if aspirin or a cyclooxygenase (COX)-1 inhibiting NSAID is given.[28] Cross-reactions between aspirin and older COX-1 inhibiting NSAIDs exist in patients with AERD and CIU. Even though product warning labels for COX-2 inhibitors state these agents should not be used in these two conditions, there are no reports of cross-reactivity in AERD and only rare reports in CIU.[29]

KEY CONCEPT IgE-mediated urticarial/angioedema reactions and anaphylaxis are associated with aspirin and NSAIDs. Urticaria is the most common form of an IgE-mediated reaction. However, most reactions are the result of metabolic idiosyncrasies, such as aspirin-induced respiratory disease, which may produce severe and even fatal bronchospasm. This class is second only to β-lactams in causing anaphylaxis. Most reactions in this class are

Table 54–5

Multiple Antibiotic Allergies: Obtaining Background Information

For **each** antibiotic to which the patient claims to be allergic, gather the following information:
- What type of infection was being treated?
- Have you ever received the drug without experiencing a reaction?
- How many times have you received the drug and experienced a reaction?
- What was the drug dose and route of administration with the last reaction?
- How many doses did you take before the onset of the last reaction?
- How many doses did you take after the last reaction?
- Can you describe the adverse reaction?
- What was the duration of the reaction?
- What treatment was given for the reaction?
- Was there any permanent damage?

For **each** antibiotic the patient has received and does not claim allergy, gather the following information:
- What was the last type of infection being treated?
- What was the drug dose and route of administration?
- Have you received this drug more than once without reactions?

Other information to be gathered:
- Have you had adverse reactions to any other drugs? If so, give dates and describe the reaction.
- Document any risk factors for allergic reactions such as chronic urticaria, liver or kidney disease, HIV (human immunodeficiency virus), or any other immune deficiencies.

Adapted from Macy E. Multiple antibiotic allergy syndrome. Immunol Allergy Clin North Am 2004;24:533–543.

due to a complex metabolic pattern, which causes increasingly recurrent and severe nasal polyps and often refractory asthma. The metabolic problem is constant once it emerges, accounting for the persistence and difficulty of these clinical problems. The metabolic problem is also capable of causing severe, sometimes fatal, acute reactions to aspirin or many if not all other NSAIDs. Rare reports of non–cross-reactive severe reactions suggest possible specific IgE-mediated reactions to individual NSAIDs, and there are some occurrences of urticaria related to NSAIDs as well. Because aspirin therapy is highly beneficial in primary and secondary prevention in coronary artery disease (CAD), aspirin desensitization should be considered in selected patients. Desensitization is contraindicated in patients who have experienced an aspirin-induced anaphylactoid reaction, hypotension, tachypnea, or altered consciousness. Alternate agents must be used. A comprehensive approach to aspirin-sensitive patients with CAD has been described.[30]

Radiocontrast Media

KEY CONCEPT Radiocontrast media may cause serious, immediate nonimmune hypersensitivity reactions such as urticaria/angioedema, bronchospasm, shock, and death. These reactions have been reduced with the introduction of nonionic, lower osmolality products. Because a small percentage of patients who have reacted previously to radiocontrast media will react if reexposed, several steps (listed below) should be taken to prevent reactions. These steps should also be followed in those with known risk factors: asthma, β-blocker use, and cardiovascular disease.[5] The steps are as follows:

- Determine whether the study is essential.
- Be sure the patient understands the risks.
- Ensure adequate hydration.
- Use nonionic, lower osmolar agents.
- Typical protocols include pretreatment with prednisone 50 mg orally 13, 7, and 1 hour(s) before the procedure and diphenhydramine 50 mg orally 1 hour before the procedure.

Delayed reactions with these agents occur in 1% to 3% of patients.[31] Although reactions are occasionally severe, most are mild and manifest as maculopapular rashes, fixed eruptions, erythema multiforme, and urticarial eruptions.

Patient Encounter 2

A 60-year-old woman with history of rheumatic fever and mitral regurgitation has developed a heart valve infection for which her physician has prescribed a regimen that includes vancomycin. The patient reports that she had an allergic reaction the last time she took vancomycin. Five minutes into the infusion she experienced significant flushing in her face and torso, making her feel very uncomfortable, without additional symptoms.

What kind of reaction did the patient experience previously with vancomycin?

Could vancomycin be used for treatment of this current infection? Discuss rationale.

Opiates

KEY CONCEPT Opiates (morphine, meperidine, codeine, hydrocodone, and others) stimulate mast cell mediator release directly, resulting in pruritus and urticaria with occasional mild wheezing. Though these reactions are not IgE-mediated, many patients state that they are "allergic" to one or more of the opiates. Pretreatment with an antihistamine may reduce these reactions which are rarely, if ever, life-threatening.[6] Avoiding other mast cell degranulating medications while patients require opiates also reduces the chances of frightening and uncomfortable reactions. Patients may also commonly state that they are "allergic" if they have experienced gastrointestinal upset or constipation with opiates. Obtaining a thorough history from the patient will prove useful. If a more serious reaction has occurred, a non-narcotic analgesic should be selected.

Cancer Chemotherapy

Hypersensitivity reactions have occurred with all chemotherapy agents. Reactions are most common with the taxanes, platinum compounds, asparaginases, and epipodophyllotoxins.[14] Reactions range from mild (flushing and rashes) to severe (dyspnea, bronchospasm, urticaria, and hypotension). IgE-mediated Type I reactions are the most common. To reduce the risk, patients are routinely premedicated with corticosteroids and H_1- and H_2-receptor antagonists. The platinum compounds have produced anemia, probably via a cytotoxic immunologic mechanism.

Insulin

Insulin is one of a very few medications that is itself a whole protein and can induce IgE sensitivity directly. This can result in anaphylaxis. Adverse reactions to insulin also include erythema, pruritus, and indurations, which are usually transient and may be injection site related.[32] For sensitivity reactions, treatment options include dexamethasone or desensitization. If the reaction is injection site related, a change in delivery system (ie, insulin pump or inhaled insulin) may be helpful.

Anticonvulsants

A wide range of hypersensitivity reactions, ranging from mild maculopapular skin eruptions to severe life-threatening reactions, can occur with anticonvulsants.[33] Aromatic anticonvulsants, primarily phenytoin, carbamazepine, phenobarbital, and primidone as well as some of the newer agents (lamotrigine, oxcarbazepine, felbamate, and zonisamide) can cause a life-threatening syndrome with symptoms including fever, a maculopapular rash, and evidence of systemic organ involvement. The rash may be mild at first but can progress to **exfoliative dermatitis**, erythema multiforme, SJS, or TEN. This syndrome is known as anticonvulsant hypersensitivity syndrome (AHS) or DRESS. The causative agent should be withdrawn immediately. Cross-sensitivity among aromatic anticonvulsant drugs ranges between 40% and 80%.[34] If a patient is hypersensitive to an aromatic anticonvulsant, a nonaromatic agent (ethosuximide, gabapentin, levetiracetam, topiramate, lacosamide, valproic acid) or the benzodiazepines may be useful.[34]

Drug Desensitization

Drug desensitization may be undertaken for some drugs in the absence of useful alternative medications. The risk of severe systemic reactions and anaphylaxis associated with desensitization must be compared with the risk of not treating the patient. A thorough evaluation should establish that the

drug probably caused the reaction by an allergic mechanism. Because of the dangers involved with drug desensitization, an expert review of the patient's indication for the drug should be conducted. Consider the possibility that the patient does not really need the drug.

KEY CONCEPT Desensitization is a potentially life-threatening procedure and requires continuous monitoring in a hospital setting, with suitable access to emergency treatment and intubation if required. It should only be undertaken under the direction of a physician with suitable training and experience. In such hands, desensitization may present less risk than treatment failure with a less effective alternative medication.

The possibility of readministering a suspected drug may be safely tested by gradual dose escalation in some cases, and there are certainly many more patients who are harmed by inappropriately withholding medications than there are those who suffer significant harm from testing and desensitization.[35]

Only Type I IgE-mediated allergy may be treated by classical desensitization. Desensitization may occur within hours to several weeks, unlike specific immunotherapy injections for inhalant allergy (ie, "allergy shots," which have effects over months to years). The mechanism of drug desensitization is poorly understood but produces temporary drug-specific tolerance of the offending drug. Any interruption of therapy of 24 hours or more requires full repeat desensitization, and abrupt significant increases of dosage have been reported to break through the tolerance with some drugs.

The desensitization process probably involves either: (a) cross-linking small subthreshold numbers of bound IgE molecules gradually depleting mast cells of their mediators, or (b) binding of the IgE by monomers or hapten-protein entities that cannot cross-link the antibody. The low doses used at the beginning of all protocols would provide small amounts of antigen, favoring these mechanisms. Both drug-specific IgE and IgG serum concentrations increase after successful desensitization, but skin test positivity generally decreases.[36]

Patient Encounter 3

A 57-year-old man at the end of a 10-day course of trimethoprim/sulfamethoxazole for resolving MRSA cutaneous infection develops fever of 103°F (39.4°C), a confluent, tender, nonpruritic erythematous rash on his trunk, and blisters along his lower lip. A few days later his truncal skin begins to slough. He is told to avoid "sulfa" antibiotics.

What type of reaction to sulfa antibiotic does this patient have?

What would be the management of this drug hypersensitivity in the future?

Would he be a candidate for drug desensitization?

Oral and intravenous (IV) protocols are available for most drugs in this category, with the oral route producing somewhat milder reactions, but the IV route providing more precision in dosing. IV administration can also be used in unresponsive patients for whom the oral route is not feasible. Protocols generally begin at about 1% of the therapeutic dose and increase in intervals defined by the patient's reaction and the distribution and metabolism of the drug itself. Half-$\log_{10}$ dose increases (about threefold) are often tolerated.

LO 6 Penicillin desensitization is the most common drug desensitization protocol. It is required for penicillin-allergic patients when penicillin is clearly the only treatment option.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review the medical history and physical assessment findings.
- Speak with patient or caregiver to gain their perspective on the reaction.

Assess the Information:

- Based on the medication history, physical examination, and review of systems, determine the likelihood of the reaction being a drug-related problem. See Clinical Presentation and Diagnosis of IgE-mediated and other Immune Drug Reactions. Tables 54–1 and 54–2 may also be helpful.
- Use questions given in Table 54–5 to establish the nature of the reaction and the likelihood it was caused by the suspected drug. For nonantibiotics, the first question regarding infection type is not needed.
- If appropriate, see Table 54–4 for procedures for performing penicillin skin testing.

Develop a Care Plan:

- Document the reaction, in detail, in the patient's medical record.
- Recommend an alternative choice if the prescribed drug is contraindicated, and develop a plan to assess safety and effectiveness.
- Consult with health care professionals trained in desensitization if the patient has a true allergy and no acceptable alternative medication is available.

Implement the Care Plan:

- If reaction is anaphylactic in nature, see Table 54–3.
- The offending drug should be discontinued.
- The treatment goal is relief of symptoms. For mild symptoms such as rash or itching, an antihistamine such as diphenhydramine may be used. For wheezing, bronchodilators such as albuterol may be helpful.
- Recommend an alternative option for the contraindicated drug, or if no alternative is available, consult with appropriate health care professional regarding desensitization.
- Educate patients about drug hypersensitivities so they are able to work with health care providers to avoid these reactions in the future.

Follow-up: Monitor and Evaluate:

- Follow-up daily or more often, if necessary, to assure resolution of the reaction and optimal response to alternate therapy.

LO 6

Protocols have been adopted for most antibiotics. Specific procedures for oral and IV penicillin desensitization have been developed.[37]

Aspirin desensitization is useful in diseases for which low-level antiplatelet action is needed and in the care of patients with aspirin sensitivity and intractable nasal polyps. Lysine aspirin availability in Europe allows desensitization by inhalation at greatly reduced risk. Procedures utilizing ketorolac as a nasal topical application have been proposed in the United States.[38] As with all desensitizations, constant daily administration is required once the desired dose is reached. Several aspirin desensitization protocols have been described in the literature.[39,40]

All desensitization procedures are expected to produce mild symptoms in the patient at some point, and the patient must be made to understand this before doses are started. Mild sensitivity to the drug still remains, and large dose increases as well as missing doses should be avoided. Late complications, such as urticaria, may occur with Type I desensitization, and serum sickness or hemolytic anemia may also occur with high-dose therapy in allergic, desensitized patients.

Some regimens are designed for outpatient administration over much longer time periods and have been used, for example, with allopurinol dermal reactions. Such late-onset morbilliform reactions, sometimes overlapping with erythema multiforme minor, are difficult to evaluate, because it is often unclear to what extent the patients were at risk for a recurrent reaction.

Severe life-threatening reactions not mediated by IgE, such as SJS and TEN, are absolute contraindications to testing, desensitization attempts, and readministration.

OUTCOME EVALUATION

To successfully treat a patient with IgE-mediated or non-IgE (immune or nonimmune) drug hypersensitivity, several goals must be accomplished:

- If a reaction occurs, it must be identified and managed quickly.
- The patient should be educated about the reaction.
- True drug contraindications should be avoided if possible.
- Patients should receive the medications they need or a suitable alternative. If this is not possible due to an IgE-mediated mechanism, desensitization should be considered.
- Patients should always be monitored for adverse drug reactions.

Abbreviations Introduced in This Chapter

AERD	Aspirin-exacerbated respiratory disease
AHS	Anticonvulsant hypersensitivity syndrome
AIDS	Acquired immunodeficiency syndrome
APC	Antigen presenting cell
CAD	Coronary artery disease
CIU	Chronic idiopathic urticaria
COX	Cyclooxygenase
D_5W	Dextrose 5% in water
DIHS	Drug-induced hypersensitivity syndrome
DRESS	Drug reaction with eosinophilia and systemic symptoms
EMR	Electronic medical record
H (H_1, H_2)	Histamine
HIV	Human immunodeficiency virus
Ig	Immunoglobulin (followed by the specific type of immunoglobulin: E, G, or M)
IM	Intramuscular
IV	Intravenous
NSAIDs	Nonsteroidal anti-inflammatory drugs
p-i	Pharmacologic interaction
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
Th	T-helper cell

REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. A meta-analysis of prospective studies. JAMA. 1998;269:1200–1205.
2. Allergy statistics: Drug allergy. American Academy of Allergy Asthma and Immunology. Available from: http://www.aaaai.org/about-the-aaaai/newsroom/allergy-statistics.aspx#Drug_Allergy. Accessed May 25, 2018.
3. Gomes ER, Demoly P. Epidemiology of hypersensitivity reactions. Curr Opin Allergy Clin Immunol. 2005;5(4):309–316.
4. Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in/out patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol. 2001;52:77–83.
5. Adkinson NF, Essayan D, Gruchalla R, et al. Task force report: future research needs for the prevention and management of immune-mediated drug hypersensitivity reactions. J Allergy Clin Immunol. 2002;109(3):S461–S478.
6. Solensky R, Khan D. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010;105:259–273.
7. Pichler WJ. Delayed drug hypersensitivity reactions. Ann Intern Med. 2003;139:683–690.
8. Uetrecht J, Naisbitt DJ. Idiosyncratuc adverse drug reactions: current concepts. Pharmacol Rev. 2013;65:779–808.
9. Khan DA, Solensky R. Drug allergy. In: 2010 Primer on allergic and immunologic diseases. J Allergy Clin Immunol. 2010;125:S126–S137.
10. Pilger WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011;127:S74–S81.
11. Paquet P, Delvenne P, Pierard GE. Drug interactions with normal and TEN epidermal keratinocytes. Curr Drug Saf. 2012;7:352–356.
12. Phillips EJ, Chung WH, Mockenhaupt M, et al. Drug hypersensitivity: pharmacogenetics and clinical syndromes. J Allergy Clin Immunol. 2011;127:S60–S66.
13. Davis RL, Smith AL, Koup JR. The "red man's syndrome" and slow infusion of vancomycin [letter]. Ann Intern Med. 1986;104:285–286.
14. Gruchalla RS. Allergic disorders. J Allergy Clin Immunol. 2003;111(2):S548–S559.
15. Neugut A, Ghatak A, Miller R. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med. 2001;161:15–21.
16. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. J Allergy Clin Immunol. 2010;126:477–480.
17. Thethi AK, Van Dellen RG. Dilemmas and controversies in penicillin allergy. Immunol Allergy Clin North Am. 2004;24:445–461.
18. Sullivan TJ. Current Therapy in Allergy. St. Louis, MO: Mosby; 1985:57–61.
19. Kelkar PS, Li JT. Cephalosporin allergy. N Engl J Med. 2001;345:804–809.

20. Madaan A, Li JT. Cephalosporin allergy. Immunol Allergy Clin North Am. 2004;24:463–476.
21. Kula B, Djordjevic G, Robinson JL. A systematic review: can one prescribe carbapenems to patients with IgE-mediated allergy to penicillins or cephalosporins. Clin Infectious Dis. 2014;59:1113–1122.
22. Dibbin DA, Montanaro A. Allergies to sulfonamide antibiotics and sulfur-containing drugs. Ann Allergy Asthma Immunol. 2008;100:91–100.
23. Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med. 2003;349(17):1628–1635.
24. Slatore CG, Tilles SA. Sulfonamide hypersensitivity. Immunol Allergy Clin North Am. 2004;24:477–490.
25. Greenberger PA. Drug allergy. J Allergy Clin Immunol. 2006; 117:S464–S470.
26. Macy E. Multiple antibiotic allergy syndrome. Immunol Allergy Clin North Am. 2004;24:533–543.
27. Sanchez-Borges M. NSAID hypersensitivity. Med Clin N Am. 2010;94:853–864.
28. Sanchez-Borges M, Caprilles-Hulett A, Caballero-Fonesca F. Cutaneous reactions to aspirin and NSAIDs. Clin Rev Allergy Immunol. 2003;24:125–135.
29. Stevenson DD. Aspirin and NSAID sensitivity. Immunol Allergy Clin North Am. 2004;24:491–505.
30. Ramanuja S, Breall JA, Kalaria VG. Approach to "Aspirin allergy" in cardiovascular patients. Circulation. 2004;110:e1–e4.
31. Christiansen C. X-ray contrast media—an overview. Toxicology. 2005;209:185–187.
32. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. Am J Clin Dermatol. 2003;4(10):661–667.
33. Behi E, Shorvon S. Antiepileptic drugs and the immune system. Epilepsia. 2011;52(suppl 3):40–44.
34. Bohan KH, Mansuri TF, Wilson NM. Anticonvulsant hypersensitivity syndrome: implications for pharmaceutical care. Pharmacotherapy. 2007;27(10):1425–1439.
35. Adkinson NF Jr. Drug allergy. In: Middleton's Allergy: Principles & Practice, 6th ed. Philadelphia, PA: Mosby; 2003:1690.
36. Schmitz-Schumann M, Juhl E, Costabel U. Analgesic asthma-provocation challenge with acetylsalicylic acid. Atemw Lungenkrkh Jahrgang. 1985;10:479–485.
37. Weiss ME, Adkinson NF. Diagnostic testing for drug hypersensitivity. Immunol Allerg Clin North Am. 1998;18: 731–734.
38. White A, Bigby T, Stevenson D. Intranasal ketorolac challenge for the diagnosis of aspirin exacerbated respiratory disease. Ann Allergy Asthma Immunol. 2006;97:190–195.
39. Melillo G, Balzano G, Bianco S, et al. Report of the INTERASMA Working Group on Standardization of Inhalation Provocation Tests in Aspirin-induced Asthma. Oral and inhalation provocation tests for the diagnosis of aspirin-induced asthma. Allergy. 2001;56(9):899–911.
40. Woessner K, White A. Evidence-based approach to aspirin desensitization in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2014;133:286–287.e1–e9.

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55 Solid Organ Transplantation

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LEARNING OBJECTIVES

LO

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

1. Describe the reasons for solid organ transplantation.
2. Differentiate between the functions of cell-mediated and humoral immunity and how they relate to organ transplant.
3. Describe the roles of antigen-presenting cells (APCs) in initiating the immune response.
4. Compare and contrast the types of rejection including hyperacute, acute, chronic, and humoral rejection.
5. Define the terms "host–graft adaptation" and "tolerance," paying close attention to their differences.
6. Discuss the desired therapeutic outcomes and appropriate pharmacotherapy utilized to avoid allograft rejection.
7. Compare and contrast currently available immunosuppressive agents in terms of mechanisms of action, adverse events, and drug–drug interactions (DDI).
8. Develop a therapeutic drug-monitoring plan to assess effectiveness of the immunosuppressive drugs.
9. Design an appropriate therapeutic regimen for the management of immunosuppressive drug complications based on patient-specific information.
10. Write appropriate patient education instructions and identify methods to improve medication adherence following transplantation.

INTRODUCTION

The earliest recorded attempts at organ transplant date back thousands of years.[1] More than a few apocryphal descriptions exist from ancient Egypt, China, India, and Rome describing experimentation with transplantation. However, it was not until the early 1900s that French surgeon, Alexis Carrel, pioneered the art of surgical techniques for transplantation.[1] Together with Charles Guthrie, Carrel experimented in artery and vein transplantation. Using revolutionary methods in **anastomosis** operations and suturing techniques, Carrel laid the groundwork for modern transplant surgery. He was one of the first to identify the dilemma of rejection, an issue that remained insurmountable for nearly half a century.[1]

Prior to the work of Alexis Carrel, malnourishment was the prevailing theory regarding the mechanism of **allograft** rejection.[1] However, in 1910, Carrel noted that tissue damage in the transplanted organ was likely caused by multiple, circulating biological factors. It was not until the late 1940s with the work of Peter Medawar that transplant immunology became better understood. Medawar defined the immunologic nature of rejection using skin allografts. In addition, George Snell observed that grafts shared between inbred animals were accepted but were rejected when transplanted between animals of different strains.[1]

The seminal work by early transplant researchers eventually led to the concept of histocompatibility.[1] Histocompatibility describes the process by which polymorphic genes encode cell membrane antigens that serve as targets for immune response, even within a species. Further research in transplant immunobiology led to more accurate understanding of the alloimmune response.[1]

Joseph Murray performed the first successful organ transplant in 1954, a kidney transplant between identical twins.[1] This was a success largely because no immunosuppression was necessary as donor and recipient were genetically identical. Murray's achievement laid the groundwork for modern-day transplantation. Organ transplants performed in the United States reached a record high of 34,770 in 2017, an almost 25% increase from 2012.

EPIDEMIOLOGY AND ETIOLOGY

Heart

Nearly 6 million Americans are afflicted with heart failure. Cardiac transplantation is the treatment of choice for patients with severe end-stage heart failure. Candidates for cardiac transplantation generally present with New York Heart Association (NYHA) class III or IV symptoms and have an **ejection fraction** of less than 20% (0.20). General indications for cardiac transplantation include rapidly declining cardiac function, requirement of intravenous (IV) inotropes, and a projected 1-year mortality rate of greater than 75%. Mechanical support with an implantable left ventricular assist device may be appropriate as bridge therapy while patients await a viable organ.[1] Most heart transplants are **orthotopic**; however, in certain situations, **heterotopic** cardiac transplants have been performed.

There were 3244 heart transplant procedures in the United States in 2017.[2] Indications for heart transplant include:

LO 1

- Cardiomyopathy (ie, dilated myopathy, hypertrophic cardiomyopathy, restrictive myopathy)
- Congenital heart disease
- Coronary artery disease
- Valvular heart disease

Intestine

An intestine transplant may involve the use of an entire intestine or shortened segment. Most intestine transplants completed in the United States involve the transplant of the full organ and are often performed in conjunction with liver transplantation. Although most intestine transplants involve organs harvested from a deceased donor, recent advances have made it possible for living donor intestinal segment transplants. There were 109 intestine transplants in the United States in 2017.[2] Reasons for intestine transplant include:

LO 1

- Functional bowel problems (ie, Hirschsprung disease, neuronal intestinal dysplasia, pseudoobstruction, protein-losing enteropathy, microvillous inclusion disease)
- Short gut syndrome (ie, intestinal atresia, necrotizing enterocolitis, intestinal volvulus, massive resection secondary to inflammatory bowel disease, tumors, mesenteric thrombosis)

Kidneys

More than 26 million Americans have chronic kidney disease (CKD), with an additional 20 million at increased risk for kidney disease. End-stage renal disease (ESRD) constitutes a small portion of CKD patients, with more than 640,000 diagnosed throughout the United States as of 2012. However, the ESRD population continues to increase. All patients with ESRD should be considered for renal transplantation if they are healthy enough to undergo surgery.

Most kidney transplants are heterotopic, where the kidney is implanted above the pelvic bone and attached to the patient's iliac artery and vein. The ureter of the transplant kidney is attached directly to the recipient's bladder or native ureter. The native kidneys are usually not removed, and data have shown that under most circumstances, removal of the native kidneys does not influence patient survival (ie, survival of the transplant patient, without regard to function or survival of the allograft) and allograft survival.[1] There were 19,849 (14,038 deceased donors and 5811 living donors) kidney transplants performed in the United States in 2017.[2] Reasons for kidney transplant include:

LO 1

- Congenital, familial, and metabolic disorders (ie, congenital obstructive uropathy, Fabry disease, medullary cystic disease, nephrolithiasis)
- Diabetes mellitus (DM)
- Glomerular diseases (ie, antiglomerular basement membrane disease, focal segmental glomerular sclerosis, IgA nephropathy, hemolytic uremic syndrome, systemic lupus erythematosus, Alport syndrome, amyloidosis, membranous nephropathy, Goodpasture syndrome)
- Hypertension
- Neoplasm (ie, renal cell carcinoma, Wilms tumor)
- Polycystic kidney disease
- Renovascular disease
- Tubular and interstitial diseases (ie, analgesic nephropathy, drug-induced nephritis, oxalate nephropathy, radiation nephritis, acute tubular necrosis, sarcoidosis)

Liver

A liver transplant may involve the use of the entire organ or a segment. The majority of cases involve utilizing the full organ. In recent years, segmental transplants have been conducted using living donors. This procedure requires donation of the left hepatic lobe, which accounts for nearly 60% of the overall liver mass. This type of procedure is possible because the liver can regenerate; therefore, both donor and recipient, in theory, will have normal liver function shortly after the transplant procedure. There were 8082 (7715 deceased donors and 367 partial lobe-living donors) liver transplants done in the United States in 2017.[2] Reasons for liver transplant include:

LO 1

- Acute hepatic necrosis (ie, chronic or acute hepatitis B or C)
- Biliary atresia
- Cholestatic liver disease/cirrhosis (ie, primary biliary cirrhosis)
- Metabolic disease (ie, Wilson disease, primary oxalosis)
- Neoplasms (ie, hepatoma, cholangiocarcinoma, hepatoblastoma, bile duct cancer)
- Noncholestatic cirrhosis (ie, alcoholic cirrhosis, postnecrotic cirrhosis, drug-induced cirrhosis)

Lungs

Lung transplants may involve deceased donation of two lungs or a single lung. More recently, lobar transplants from blood group–compatible living donors have been performed for a small segment of the population. Most have been performed on cystic fibrosis patients. On rare occasions, a simultaneous heart–lung transplant occurs. This type of procedure is reserved for patients with severe pulmonary and cardiac disease. There were 2449 (all deceased donors) lung transplants and 29 simultaneous heart–lung transplants in the United States in 2017.[2] Reasons for lung transplant include:

LO 1

- α-1-Antitrypsin deficiency
- Congenital disease (ie, Eisenmenger syndrome)
- Cystic fibrosis
- Emphysema/chronic obstructive pulmonary disease
- Idiopathic pulmonary fibrosis
- Primary pulmonary hypertension

Pancreas

The exact nationwide prevalence of all diseases of the pancreas has not been fully quantified; however, DM, both types 1 and 2, affects nearly 21 million people in the United States. Some people suffering from DM may also be afflicted with ESRD. A small percentage of these patients undergo a simultaneous pancreas-kidney (SPK) transplant, which may be accomplished using organs from deceased or living donors. Transplant of a pancreas may involve either the entire organ or a pancreas segment. Currently, whole-organ transplant is the most common procedure, with a portion of the duodenum often transplanted along with the pancreas. Living donors are often the source of segmental transplants. In recent years, isolation and transplantation of β-islet

cells alone have been completed. Islet transplantation is intended to treat organ dysfunction by replacing nonfunctioning islet cells with new ones. Islet transplants are still considered experimental, and long-term benefit and/or risk of this procedure needs to be studied extensively. Future success of islet cell transplantation is dependent on identifying a nontoxic immunosuppressive combination. There were 213 pancreas transplants and 789 SPK procedures in the United States in 2017.[2] Reasons for pancreas transplant include:

LO 1

- DM (ie, type 1 and 2, DM secondary to chronic pancreatitis or cystic fibrosis)
- Pancreatic cancer

PATHOPHYSIOLOGY

Major Histocompatibility Complex

The primary target of the immune response after organ transplant is the major histocompatibility complex (MHC).[1,3] The MHC is a region of highly polymorphic genes located on the short arm of chromosome 6. The human MHC is referred to as human leukocyte antigen (HLA). HLA is a set of glycoproteins expressed on the surface of most cells. These proteins are involved in immune recognition, which is the discrimination of self from nonself, but are also the principal antigenic determinants of allograft rejection.[1,3]

The HLA have been classified into two major groups, class I and II:

- Class I: expressed on the surfaces of all nucleated cells and recognized by $CD8^+$ cells (ie, cytotoxic T-cells); subclasses are HLA-A, HLA-B, and HLA-C.
- Class II: expressed solely on the surfaces of antigen-presenting cells (APCs). The APCs serve to stimulate $CD4^+$ cells (ie, helper T-cells); subclasses are HLA-DP, HLA-DQ, and HLA-DR.

T and B Lymphocytes

Lymphocytes are one of five kinds of white blood cells. Mature lymphocytes are astonishingly diverse in their functions. The most abundant of the lymphocytes are T lymphocytes (ie, T-cells) and B lymphocytes (ie, B-cells).

▶ *T Lymphocytes*

LO 2

KEY CONCEPT T-cells play a major role in the cell-mediated immune response. These cells are produced in the bone marrow, but mature in the thymus, hence the abbreviation "T." There are three recognized subclasses of T-cells:

- Cytotoxic T-cells ($CD8^+$) promote target cell destruction by activating cellular **apoptosis** or killing the target cell via the release of cytotoxic proteins.
- Helper T-cells ($CD4^+$) are the great communicators of the immune response. Once activated, they proliferate and secrete cytokines that regulate the function of **effector cells**. Some helper T-cells secrete cytokines that recruit cytotoxic T-cells, B-cells, or APCs, whereas others secrete cytokines that turn off the immune response.
- Regulatory T-cells, or suppressor T-cells suppress activation of an immune response.

▶ *B Lymphocytes*

LO 2

B-cells play a large role in the humoral immune response. In humans, B-cells are produced and mature in the bone marrow. The human body produces several types of B-cells. Each is unique, with a distinctive cell surface receptor protein that binds to only one particular antigen. Once B-cells encounter their antigen and receive a cytokine signal from helper T-cells, they can further differentiate into one of two cells, plasma cells or memory B-cells. Plasma cells secrete antibodies that induce the destruction of target antigens through complement recruitment and/or **opsonization**. Memory B-cells play an important role in long-term immunity, as they are capable of rapidly responding to subsequent exposures to their target antigen.

Antigen-Presenting Cells (APCs)

LO 3

KEY CONCEPT An APC is a cell that displays a foreign antigen complexed with MHC on its cell surface. Its major responsibility is to present these foreign antigens to T-cells, which can identify this complex using their T-cell receptors (TCRs). There are three main types of APCs: dendritic cells (DCs), macrophages, and activated B-cells. DCs are present in tissues that are in contact with the environment, such as skin and the lining of the nose, lungs, stomach, and intestines. They are responsible for **phagocytosis**, after which they express the foreign antigen on their cell surface and then migrate to lymphoid tissues to interact with T- and B-cells to initiate the immune response. Macrophages' main role is removal of pathogens and necrotic debris. However, like DCs, macrophages also phagocytize antigens. The first time an antigen is encountered, the DCs and macrophages act as the primary APCs. However, if the same antigen is encountered again, memory B-cells become the most important APC because they initiate the immune response quickly after antigen presentation. It appears that both DCs and macrophages have the most activity in terms of **allorecognition**.

Allorecognition

KEY CONCEPT Recognition of the antigens displayed by the transplanted organ (alloantigens) is the prime event that initiates the immune response against the allograft. There are currently two accepted pathways for allorecognition:

- Direct pathway: Donor APCs migrate out of the allograft into the recipient's lymph nodes and present donor MHC molecules to the recipient's T-cells.
- Indirect pathway: Recipient APCs migrate into the graft and phagocytize alloantigens. The recipient's APCs present donor MHC molecules to the recipient T-cells in lymph nodes.

T-Cell Activation

KEY CONCEPT Whether it is by direct or indirect pathways, for a T-cell to become activated against the allograft, two interactions or signals must take place between the APCs and the recipient's T-cells[1,3]:

- Signal 1 is the interaction of the TCR with the foreign antigens presented by APCs.
- Signal 2 is an interaction between one of several costimulatory receptors and paired ligands on the cell surfaces of the APCs and T cells, respectively. Both interactions must occur simultaneously as Signal 1 in the absence of Signal 2 induces T-cell **anergy**.
- Once activated, T-cells undergo **clonal expansion** under the influence of cytokines, specifically interleukin-2 (IL-2). These steps elicit an antidonor T-cell response that results in graft destruction.

Mechanisms of Acute Rejection

After activation, cytotoxic T-cells emerge from lymphoid organs to infiltrate the graft and trigger the immune response. These cells induce graft destruction via two mechanisms: (a) secretion of cytotoxic proteins (ie, perforin, granzyme) and (b) induction of cellular apoptosis through interaction. Besides the cytotoxic T-cells, several other cell lines may play a role in allograft destruction including B-cells, granulocytes, and natural killer (NK) cells.

Types of Rejection

▶ *Hyperacute Rejection*

LO 4

Hyperacute rejection is an immediate recipient immune response against the allograft due to the presence of preformed recipient antibodies directed against the donor's HLA. This type of reaction generally occurs within minutes of transplantation. The organ must be removed immediately to prevent severe systemic responses. In the case of cardiac or lung transplantation in which the organ cannot be promptly removed, short-term mechanical circulatory support is required until an alternative organ becomes available. Those at the highest risk for hyperacute rejection include any patients who have preformed HLA or ABO blood group antibodies, including those with a history of previous organ transplant or multiple blood transfusions, as well as women who have had children. Hyperacute rejection has been largely eliminated due to routine pretransplant surveillance testing.

▶ *Acute Rejection*

LO 4

Acute rejection is a cell-mediated process that generally occurs early posttransplant; however, it can occur at any time after transplant. This reaction is mediated through alloreactive T-cells. Table 55–1 presents organ-specific signs and symptoms of acute rejection.[1]

▶ *Antibody-Mediated Rejection*

LO 4

Antibody-mediated rejection (AMR) is the process of creating graft-specific antibodies.[4] This type of rejection occurs less frequently than cell-mediated acute rejection. Histologic findings are similar to those of hyperacute rejection, but the severity of rejection is usually less with AMR. AMR is generally characterized by deposition of immunoglobulins and complement in allograft tissues. However, AMR may be diagnosed without the presence of complement. Although rare, donor-specific antibodies (DSA) may be present or develop later following transplant. Presence of DSA is a strong predicator of AMR which might lead to allograft injury and failure following transplantation. Treatment for this type of rejection is not well defined; however, several reports have shown that plasmapheresis, immunoglobulin therapy, rituximab, bortezomib, or eculizumab may be effective.[4]

▶ *Chronic Rejection*

LO 4

Chronic rejection has traditionally been thought of as a slow, insidious form of acute rejection, resulting in worsening organ function over time. The exact immunologic processes of chronic rejection are poorly understood; however, many believe that both the cell-mediated and humoral immune systems and drug-induced toxicities play a vital role in its development. Currently, retransplantation is the only effective treatment option.[1,3]

▶ *Host–Graft Adaptation*

LO 5

"Host–graft adaptation" describes the decreased immune response against the allograft over time.[1,3] This phenomenon is evident by the reduced incidence of acute rejection episodes seen months after transplantation. In theory, host–graft adaptation is thought to be secondary to a weakened T-cell response to donor antigens while patients receive maintenance immunosuppression.[1,3]

Tolerance

LO 5

Tolerance is the process that allows organ-specific antigens to be accepted as self.[1] This means the immune system would cease to respond to the allograft, and immunosuppressive medications would not be required. Immune tolerance has been achieved in the lab, but has yet to be successfully accomplished in humans.[1]

Immunologic Barriers to Transplantation

One of the more common barriers to successful transplantation is the presence of preformed HLA antibodies or ABO blood group incompatibility.[4] In cases in which these antibodies exist, if they are not adequately removed prior to transplant, they are likely to result in AMR and poor graft survival. To improve outcomes, assessment of pretransplant immune risk factors plays

Table 55–1

Organ-Specific Signs and Symptoms of an Acute Rejection Episode[1]

Organ	Clinical Symptoms	Laboratory Signs
Heart	Lethargy, weakness, SOB, DOE, hypotension, tachycardia, atrial flutter, ventricular arrhythmias	Leukocytosis, biopsy positive for mononuclear infiltrates
Kidney	Weight gain, decreased urine output, malaise, hypertension, edema	Increased SCr, BUN, leukocytosis, biopsy positive for lymphocytic infiltration
Intestine	GI symptoms (ie, bloating, cramping, diarrhea, increased stomal output)	There are no reliable biochemical markers for intestine transplant rejection, but biopsies may be helpful
Liver	Graft tenderness and swelling, back pain, anorexia, ileus, tachycardia, jaundice, ascites, encephalopathy	Abnormal LFTs, increased bilirubin, alkaline phosphate, transaminases, biopsy positive for mononuclear cell infiltrate with evidence of tissue damage
Lung	Fever, impaired gas exchange, SOB, malaise, anxiety	Decreased FEV, infiltrate on CXR, biopsy positive for lymphocytic infiltration
Pancreas	Graft tenderness and swelling, polyuria, abdominal pain	Increased FBS, leukocytosis, decreased C-peptide and urinary amylase levels

BUN, blood urea nitrogen; CXR, chest x-ray; DOE, dyspnea on exertion; FBS, fasting blood sugar; FEV, forced expiratory volume; GI, gastrointestinal; LFTs, liver function tests; SCr, serum creatinine; SOB, shortness of breath.

an important role in prevention of immune-mediated allograft injuries. The introduction of pretransplant cross-matching and the use of ABO-compatible donors has largely eliminated hyperacute rejection episodes. However, these immunologic barriers are present in several potential recipients with willing organ donors, and patients are left to wait for a deceased donor or undergo pretransplant immunomodulation in an attempt to prevent these antibodies from affecting the allograft.[4]

▶ *ABO Incompatibility*

The expanding deceased donor waiting list encouraged some centers to evaluate the use of ABO desensitization protocols to transplant patients with ESRD that had willing but ABO-incompatible donors.[4] The desensitization protocol most commonly used in the United States involves reducing ABO antibody titers through plasmapheresis with IV immunoglobulin (IVIG). Use of plasma exchange to achieve an ABO antibody titer of less than 1:8 to 1:32 has resulted in long-term renal transplant results that are comparable to those of ABO-compatible transplants, despite an incidence of acute AMR that approaches 10% to 30%.[4]

TREATMENT

Desired Outcomes

LO 6 KEY CONCEPT The major focus of pharmacotherapy in transplantation is to achieve long-term patient and allograft survival while avoiding major adverse drug reactions.[1,3,5,6] Short-term outcomes (eg, acute rejection rates, 1-year graft survival) have improved significantly since the first successful transplant due to an improved understanding of the immune system and enhancements in surgical techniques, organ procurement, immunosuppression, and posttransplant care. However, the frequency of graft loss remains higher than desired in kidney and heart transplantation.[1,3,5,6]

It is imperative that transplant practitioners be aware of the specific advantages and disadvantages of available immunosuppressants, as well as adverse reactions and drug–drug interaction (DDI) profiles. There are generally three stages of medical immunosuppression: (a) induction therapy, (b) maintenance therapy, and (c) treatment of rejection. KEY CONCEPT

LO 6 Immunosuppressive regimens utilize multiple medications working on different targets of the immune system. Refer to Table 55–2 for a list of all available immunosuppressive agents.[1,5,6]

Table 55–2

Currently Available Immunosuppressive Agents[1,5,6]

Generic Name (Brand Name)	Common Dosage	Common Adverse Effects
Induction Therapy Agents		
Alemtuzumab (Campath)	20–30 mg × single doses	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Antithymocyte globulin equine (ATGAM)	15 mg/kg IV × 5–14 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Antithymocyte globulin rabbit (Thymoglobulin)	1.5 mg/kg IV × 3–7 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Basiliximab (Simulect)	20 mg IV × 2 doses	None reported compared to placebo
Maintenance Immunosuppressants		
Cyclosporine (Sandimmune, Neoral, Gengraf)	4–5 mg/kg/day by mouth twice a day	Neurotoxicity, gingival hyperplasia, hirsutism, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte abnormalities
Tacrolimus (Prograf, Astagraf XL, Envarsus XR)	0.05–0.075 mg/kg by mouth twice a day or once daily if using Astagraf XL or Envarsus XR	Neurotoxicity, alopecia, hypertension, hyperlipidemia, glucose intolerance, nephrotoxicity, electrolyte abnormalities
Azathioprine (Imuran)	1–2.5 mg/kg by mouth once a day	Myelosuppression, GI disturbances, pancreatitis
Mycophenolate mofetil (CellCept)	0.5–1.5 gm by mouth twice a day	Myelosuppression, GI disturbances
Enteric-coated MPA (Myfortic)	720 mg by mouth twice a day	Myelosuppression, GI disturbances
Sirolimus (Rapamune)	1–10 mg by mouth once a day	Hypertriglyceridemia, myelosuppression, mouth sores, hypercholesterolemia, GI disturbances, impaired wound healing, proteinuria, lymphocele, pneumonitis
Everolimus (Zortress)	0.75 mg by mouth twice daily	Hypertriglyceridemia, myelosuppression, mouth sores, hypercholesterolemia, GI disturbances, impaired wound healing, proteinuria, lymphocele, pneumonitis
Prednisone (Deltasone)	Maintenance: 2.5–20 mg by mouth once a day	Mood disturbances, psychosis, cataracts, hypertension, fluid retention, peptic ulcers, osteoporosis, muscle weakness, impaired wound healing, glucose intolerance, weight gain, hyperlipidemia
Belatacept (Nulojix)	10 mg/kg on postop days 1 and 4 10 mg/kg at the end of postop weeks 2, 4, 8, and 12 5 mg/kg at the end of postop week 16 and every 4 weeks thereafter	GI disturbances, electrolyte abnormalities, headache

GI, gastrointestinal; IV, intravenous; MPA, mycophenolic acid.

Induction Therapy

LO 6 KEY CONCEPT The goal of induction therapy is to provide a high level of immunosuppression in the early posttransplant period, when the risk of acute rejection is highest.[5] This stage of immunosuppression is initiated intraoperatively and concluded within the first 1 to 10 days after transplantation. Antibody induction therapy is not a mandatory stage of recipient immunosuppression and is typically predicated on immunologic risk. However, since acute rejection is a major concern in solid organ transplant (SOT) recipients and its impact on chronic rejection is undeniable, induction therapy is often considered essential in some organs to optimize outcomes.[5]

▶ *Goals of Induction Therapy*

LO 7 KEY CONCEPT Induction agents are highly immunosuppressive, allowing for significant reductions in acute rejection and improved 1-year graft survival.[5] Due to their unique pharmacologic effect, these agents are often considered essential in patients at high risk for poor short-term outcomes, such as patients with preformed antibodies, history of previous transplants, multiple HLA mismatches, or transplantation of organs with prolonged cold ischemic time, or from expanded-criteria donors. Specifically in renal transplantation, induction therapy plays an important role in preventing early-onset calcineurin inhibitor (CNI)–induced nephrotoxicity. With induction therapy, CNI initiation can be delayed until the graft regains some degree of function. Induction therapy is imperative when employing corticosteroid sparing or avoidance protocols.[5]

The improved short-term outcomes gained from induction therapy come with a degree of risk.[5] By using these highly immunosuppressive agents, particularly the antilymphocyte antibodies (ALA; the antithymocyte antibodies and alemtuzumab), the ability to mount a cell-mediated immune response is significantly reduced, which increases the risk of opportunistic infections and malignancy. Cytokine release syndrome is a common complication of T-cell depleting agents and may require premedications of diphenhydramine and acetaminophen before infusions.[5]

▶ *Currently Available Induction Therapies*

The objective of induction therapy is to prevent acute cellular rejection in the early posttransplant period and prolong allograft survival following transplantation. These agents are categorized as depleting and nondepleting. Depleting agents exert their pharmacological effects through the depletion of T and B lymphocytes (thymoglobulin, antithymocyte globulin equine [e-ATG], alemtuzumab, rituximab), while nondepleted agents exert their pharmacological effects through inhibition of T-cell activation (basiliximab).

LO 7 **Basiliximab** Basiliximab is a chimeric monoclonal antibody that acts as an IL-2 receptor antagonist.[5,7] These receptors are present on almost all activated T cells. Basiliximab inhibits IL-2–mediated activation of lymphocytes, which is an important step in T-cell clonal expansion. Basiliximab is not a T-cell depleting agent and can be given with premedications.

LO 7 The dose of basiliximab is 20 mg IV given 2 hours prior to transplant, followed by a second 20 mg dose on postoperative day 2–4.[5,7] This dosing schedule can be used for both children greater than or equal to 35 kg (77 lb) and adults. Two 10 mg doses with the same dosing schedule should be used for children less than 35 kg (77 lb). There are no specific dosage adjustments needed in renal or hepatic impairment.[5,7] Incidence of all adverse reactions with basiliximab was similar to placebo in trials, and there are no reported DDIs with basiliximab.[5,7]

LO 6 LO 7 **Antithymocyte Globulin Rabbit** Antithymocyte globulin rabbit (r-ATG) is a polyclonal antibody that induces T-cell clearance, but more importantly, it alters T-cell activation, homing, and cytotoxic activities.[7] It is also believed that r-ATG plays a role in inducing T-cell apoptosis. This agent is typically dosed at 1.5 mg/kg/day and is usually administered for 3 to 7 days after transplantation.[5] Many renal transplant centers aim to initiate the first dose intraoperatively to reduce organ reperfusion injury.[8]

Adverse reactions are common and may include fever (63.4%), chills (57.3%), headache (40.2%), nausea (36.6%), diarrhea (36.6%), malaise (13.4%), dizziness (8.5%), **leukopenia** (57.3%), **thrombocytopenia** (36.6%), and generalized pain (46.3%).[9-11] Incidence of infection is 36.6%, with **cytomegalovirus (CMV) disease** occurring in 13.4% of patients. There are no reported DDIs with the use of r-ATG at this time.[5,7]

LO 7 **Antithymocyte Globulin Equine** e-ATG is a polyclonal antibody that contains antibodies against several T-cell surface markers, similar to r-ATG. Compared to other antithymocyte preparations, e-ATG is associated with significant batch to batch variability and reduced efficacy. Most transplant centers prefer to use r-ATG (Thymoglobulin) over e-ATG (ATGAM).

e-ATG is associated with several adverse reactions.[5,7] The most common are fever (63%), chills (43.2%), headache (34.6%), back pain (43.2%), nausea (28.4%), diarrhea (32.1%), dizziness (24.7%), malaise (3.7%), leukopenia (29.6%), and thrombocytopenia (44.4%). Overall incidence of opportunistic infections is 27.2%, with CMV occurring in 11.1% of patients. There are currently no reported pharmacokinetic DDIs.[5,7]

Alemtuzumab Alemtuzumab is a recombinant DNA-derived monoclonal antibody that binds to CD52, which is present on most B and T lymphocytes, macrophages and NK cells, and a subpopulation of granulocytes.[5,7] After complexing with the CD52 cell surface marker, alemtuzumab induces an antibody-dependent cell lysis. This agent produces a rapid and extensive lymphocyte depletion that may take several months to years to return to pretransplant levels. Although it is not Food and Drug Administration (FDA) approved for use in organ transplantation, studies have demonstrated that a single dose of 30 mg IV at the time of transplant is effective in preventing acute rejection.[5]

LO 6 LO 7

Alemtuzumab is associated with serious adverse reactions including anemia (47%), neutropenia (70%), thrombocytopenia (52%), headache (24%), dysesthesias (15%), dizziness (12%), nausea (54%), vomiting (41%), diarrhea (22%), infusion-related reactions (15%–89%), and infection (37%; CMV viremia occurred in 15% of patients).[7] It is very important to premedicate with acetaminophen and diphenhydramine 30 minutes before infusion to reduce the incidence of infusion-related reactions.[5]

Comparative Efficacy There are a few studies that help to delineate the ideal induction therapy agent. Studies comparing r-ATG and e-ATG show that r-ATG is more effective in lowering acute rejection rates and improving 1-, 5- and 10-year allograft outcomes.[9,10,12] Conversely, a study evaluating the use of basiliximab versus r-ATG demonstrated similar short-term efficacy between both groups.[13] However, other analyses of these two agents demonstrated similar results for allograft and patient survival, but a benefit for r-ATG in lowering incidence of acute allograft rejection.[11,14] A more recent analysis showed that alemtuzumab improved transplant outcomes when compared with basiliximab

Patient Encounter Part 1

A 34-year-old man presents to your transplant center for a living-related renal transplant.

PMH:

- ESRD—secondary to focal segmental glomerulosclerosis (FSGS)
- One prior renal transplant from his mother 10 years ago, which failed 1 year ago from presumed nonadherence early after transplant resulting in multiple rejection episodes within the first few years posttransplant.
  - For the previous transplant the patient was maintained on tacrolimus and mycophenolate.
- Hypertension
- Insomnia
- Secondary hyperparathyroidism

FH: Father is alive and living with a history of cardiovascular disease and mother is alive and living with a history of basal cell carcinoma.

SH: The patient works as a mechanical engineer. He admits to social alcohol use (3 or 4 drinks per week) and denies any tobacco or IV drug use.

Admission Meds:

- Metoprolol succinate 50 mg by mouth once a day
- Amlodipine 10 mg by mouth once a day
- Furosemide 20 mg by mouth twice a day
- Zolpidem 10 mg by mouth once a day at bedtime
- Calcitriol 0.25 mg by mouth once a day
- Epo 4000 units intravenously every hemodialysis session

Allergies:

- NKDA

Misc:

- CMV Serostatus: Donor is CMV immunoglobulin G (IgG) positive
- CMV Serostatus: Recipient is CMV IgG negative
- EBV Serostatus: Donor is EBV IgG positive
- EBV Serostatus: Recipient is EBV IgG negative
- Patient has documented G6PD deficiency

Identify your treatment goals for this patient.

Create a plan for induction therapy (ie, would you recommend induction therapy, and if so, which agent?).

in patients with a low immunologic risk, and similar outcomes compared to r-ATG in patients with high immunologic risk.[15] When choosing an agent for induction therapy, one must weigh the risks versus benefits. Overall, the ALAs are considered to be most effective, but are associated with higher incidence of infectious disease and malignancy.[5]

Maintenance Immunosuppressive Therapy

LO 6 The goals of maintenance immunosuppression are to prevent rejection and optimize patient and graft survival.[6] Antirejection medications require careful selection and dose titration to balance the risks of rejection with those of toxicities.

KEY CONCEPT Common maintenance immunosuppressive agents are divided into five classes:

- Calcineurin inhibitors (CNI; cyclosporine and tacrolimus)
- Antiproliferatives (azathioprine and the mycophenolic acid [MPA] derivatives)
- Target of rapamycin (ToR) inhibitors (sirolimus and everolimus)
- Corticosteroids
- Costimulatory blockade (belatacept)

LO 7 Maintenance immunosuppression is generally achieved by combining two or more medications from the different classes, specifically targeting unique components of the immune response.[6] Refer to Figure 55–1 for a schematic representation of these different drug mechanisms and Figure 55–2 for an example protocol for administration of immunosuppressive medications posttransplant. This method of medication selection also minimizes toxicities by choosing agents with different adverse event profiles. Immunosuppressive regimens vary between organ types and transplant centers, but most often include a CNI with an adjuvant agent, plus or minus corticosteroids. Selection of an immunosuppressive regimen should be patient-specific, and one must take into account the patient's comorbidities, medication regimens, and preferences.[6]

▶ *Calcineurin Inhibitors*

KEY CONCEPT The CNIs, cyclosporine and tacrolimus, are considered the cornerstone of modern immunosuppressive protocols. LO 7 The CNIs work by complexing with cytoplasmic proteins (cyclosporine with cyclophilin and tacrolimus with FK binding protein-12).[6,7] These complexes inhibit calcineurin phosphatase, which results in reduced IL-2 gene transcription and a reduction in IL-2 synthesis. This diminishes T-cell activation.[6,7]

Cyclosporine Cyclosporine USP was first approved in 1983, but was associated with a variable oral absorption. The development of a newer formulation, cyclosporine microemulsion USP (ie, modified), introduced in 1994, allowed for more consistent drug exposure due to a more reliable pharmacokinetic profile.[1] Cyclosporine modified is the formulation of choice for most transplant centers utilizing cyclosporine. The two formulations are not interchangeable.[6]

LO 6 The usual oral adult dose of cyclosporine ranges from 3 to 7 mg/kg/day in two divided doses.[7] Appropriate selection of the starting dose depends on the organ type, the patient's comorbidities, and other concomitant immunosuppressive agents utilized. Cyclosporine modified is available as 25 mg and 100 mg capsules and an oral solution. An IV formulation of conventional cyclosporine is also available. When converting a patient from oral to IV, the dosage should be reduced to approximately one-third of the total daily oral dose.[7]

LO 8 Cyclosporine whole-blood trough concentrations (C_0) have traditionally been obtained to help monitor for efficacy and safety. Therapeutic C_0 may range from 50 to 400 ng/mL (mcg/L; 42–333 nmol/L). Target levels should be individualized for each

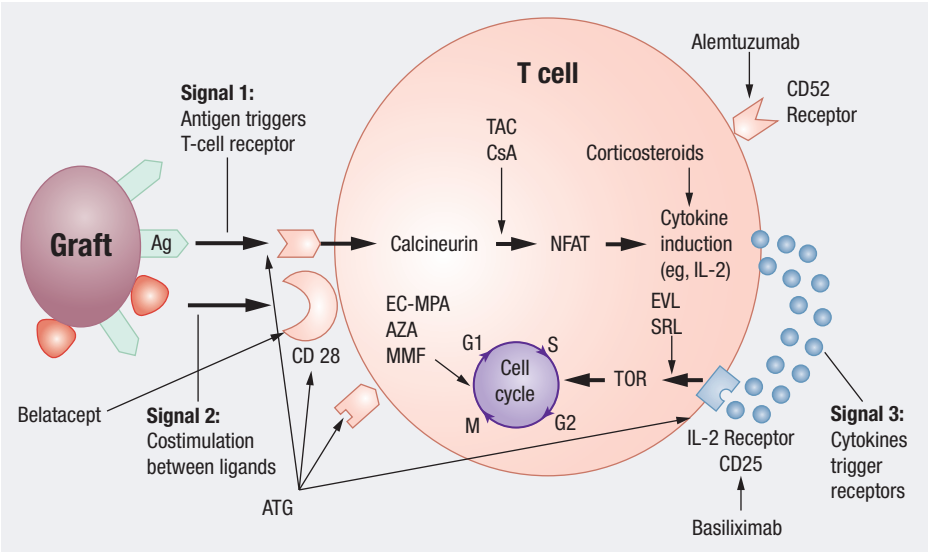

FIGURE 55–1. Identification of the sites of action of the various immunosuppressive medications. Allograft recognition through Signal 1 occurs when the antigen-major histocompatibility complex (MHC) molecule is recognized by the T-cell receptor (TCR). A costimulatory signal, Signal 2, initiates signal transduction with activation of second messengers, one of which is calcineurin. Together, Signal 1 and Signal 2 activate calcineurin phosphatase, which removes phosphates from the nuclear factors, allowing them to enter the nucleus with a subsequent increase in interleukin-2 (IL-2) gene transcription. Signal 3 occurs with the interaction of IL-2, with the IL-2 receptor on the cell membrane surface. This culminates in a signal that passes through the mammalian target of rapamycin (ToR) and induces cell proliferation and production of cytokines specific to the T-cell. (ATG, antithymocyte globulin; AZA, azathioprine; CsA, cyclosporine; EC-MPA, enteric-coated mycophenolic acid; EVL, everolimus; MMF, mycophenolate mofetil; NFAT, nuclear factors; SRL, sirolimus; TAC, tacrolimus.)

patient, usually depending on the organ transplanted, patient's condition, method of assay (liquid chromatography coupled to tandem mass spectrometry [LC-MS/MS], monoclonal, polyclonal), and time since transplantation.[6] Newer studies suggest that monitoring of concentrations at 2 hours postdose (C_2) correlates better with toxicity and efficacy when compared with C_0.[16]

LO 6 **Tacrolimus** Tacrolimus was approved in 1997. Oral starting doses range from 0.1 to 0.2 mg/kg/day in two divided doses. Tacrolimus is available in 0.5 mg, 1 mg, and 5 mg capsules and as an injectable.[7] Two once-daily tacrolimus formulations are also available. Once-daily formulations are not bioequivalent and should not be substituted in clinical practice; however, these differences in their compositions are unlikely to have any major therapeutic benefit. Tacrolimus C_0 should be monitored and maintained between 5 and 15 ng/mL (mcg/L; 6 and 19 nmol/L), again depending on the transplanted organ, patient's condition, and time since transplant.[6]

LO 8

The tacrolimus IV formulation is usually avoided due to the risk of anaphylaxis, because of its castor oil component, and nephrotoxicity.[6] Doses for IV administration are recommended to start at 0.01 mg/kg/day. In an effort to avoid IV tacrolimus, many transplant centers utilize sublingual (SL) tacrolimus in their patients unable to receive the medication by mouth.[6]

LO 7 **Adverse Drug Reactions** KEY CONCEPT One of the major disadvantages of the CNIs is their ability to cause nephrotoxicity. Acute nephrotoxicity has been correlated with high doses and is usually reversible.[7] Chronic CNI toxicity, however, is typically irreversible and linked to chronic drug exposure. Table 55–3 expands on the more common CNI–associated adverse events.[1,6]

Comparative Efficacy Even though cyclosporine and tacrolimus are both CNIs, there are several differences between the two. A meta-analysis comparing cyclosporine to tacrolimus in kidney transplantation showed tacrolimus was associated with significantly lower risk of allograft loss at 6 months and lower rates of acute rejection at 1 year.[17] Tacrolimus is the primary CNI in many transplant centers, due in large part to a more favorable adverse reaction profile.[6]

► *Antiproliferatives*

These agents are considered to be adjuvant to the CNIs or ToR inhibitors.[6]

Azathioprine Azathioprine was approved in 1968 as an adjunct immunosuppressant in renal transplant. Prior to the advent of cyclosporine, the combination of azathioprine and corticosteroids was the mainstay of immunosuppressive therapy. Use of azathioprine has declined markedly due to superiority of the MPA derivatives. KEY CONCEPT Azathioprine is a prodrug for 6-mercaptopurine (6-MP), a purine analog. 6-MP acts as an antimetabolite and inhibits DNA replication with a resultant reduction in T-cell proliferation.[6] It is available in oral and IV dosage forms.[7] The typical oral dose of azathioprine for organ transplantation is 1 to 3 mg/kg once a day.[7] Thiopurine methyltransferase (TPMT) is the main enzyme for inactivation of azathioprine. Approximately 10% of transplant recipients have reduced TPMT activity and are at risk for drug toxicity. Dose reductions due to drug accumulation are needed to avoid toxicities. In addition, the dose should be adjusted for renal function since 6-MP and its metabolites are renally eliminated.[7] Trough concentrations of 6-MP are not monitored; however, most clinicians often monitor for signs of myelosuppression. KEY CONCEPT Myelosuppression (mainly leukopenia and thrombocytopenia) is a frequent, dose-dependent and dose-limiting complication (> 50% of patients) that often prompts dose reductions.[7] Other common adverse events include hepatotoxicity (2%–10%) and adverse gastrointestinal (GI) events (10%–15%;

LO 6 LO 7

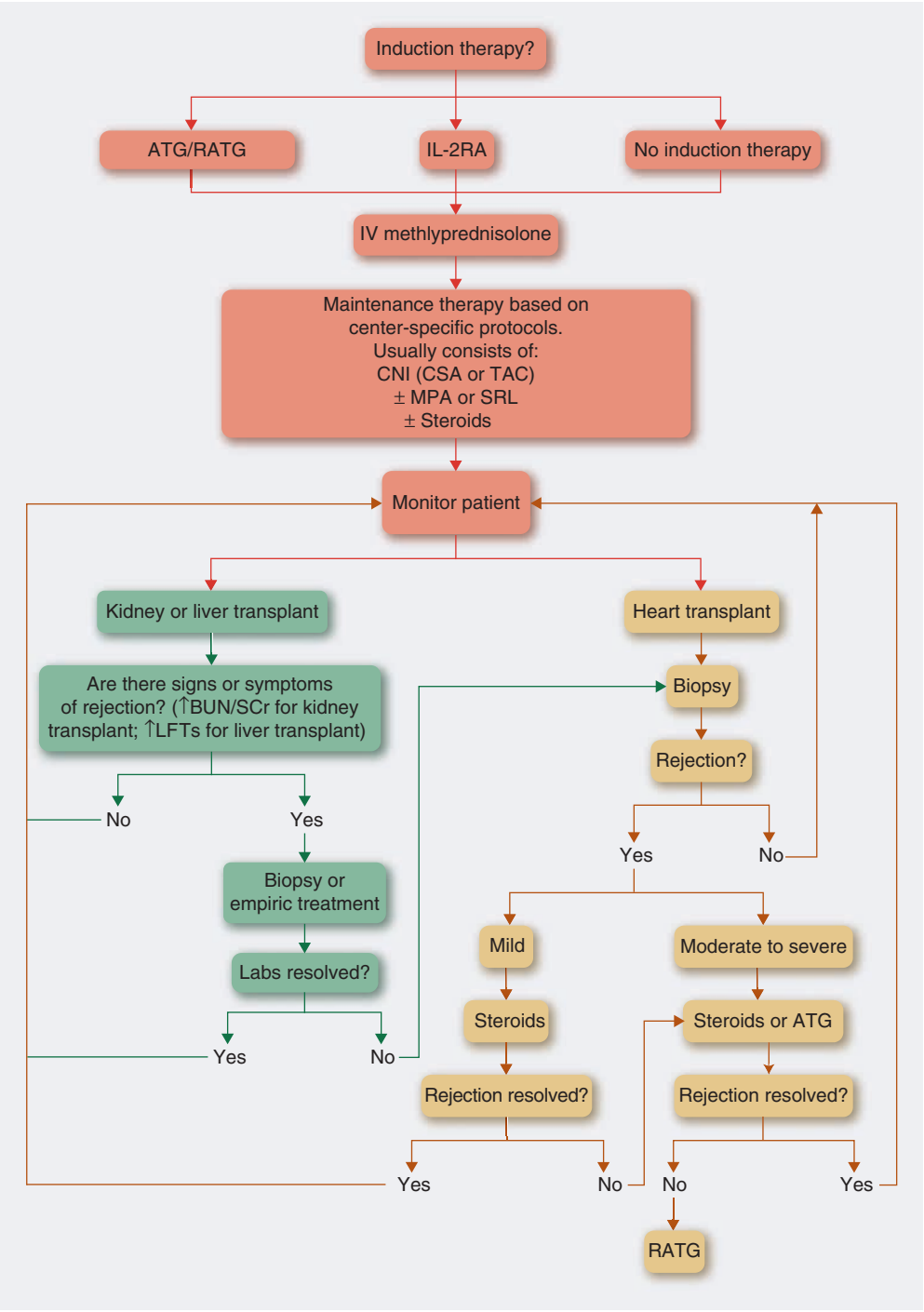

FIGURE 55–2. Example protocol of immunosuppressive medication use in organ transplantation. Center-specific protocols may use rabbit antithymocyte immunoglobulin (RATG), an interleukin-2 receptor antagonist (IL-2RA), or no induction therapy. In any situation, patients receive intravenous (IV) methylprednisone prior to, during, or immediately following the transplant operation. The patient then will begin the maintenance immunosuppressive regimen. The center-specific protocol will specify which calcineurin inhibitor (cyclosporine or tacrolimus) is used in combination with mycophenolate mofetil or sirolimus, with or without steroids. Patients then are monitored for signs and symptoms of rejection. If rejection is suspected, a biopsy can be done for definitive diagnosis, or the patient may be treated empirically for rejection. Empirical treatment generally involves administration of corticosteroids. If signs and symptoms of rejection are resolved with empirical therapy, the patient will continue to be monitored according to the center-specific protocol. If rejection is confirmed by biopsy, treatment may be based on the severity of rejection. High-dose corticosteroids are used most frequently for mild to moderate rejection. RATG can be used for moderate to severe rejections or steroid-resistant rejections. Protocols and algorithms may differ across transplant centers. (ATG, antithymocyte globulin; BUN, blood urea nitrogen; CNI, calcineurin inhibitor; CSA, cyclosporine; LFT, liver function test; MPA, mycophenolic acid; SCr, serum creatinine; SRL, sirolimus; TAC, tacrolimus.) (From Johnson HJ, Schonder KS. Solid Organ Transplantation. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017:1402.)

Table 55–3

Management of Common Adverse Effects of Calcineurin Inhibitors (CNIs)[1,6]

Adverse Event	Most Likely Offending CNI	Monitoring Parameters	Therapeutic Management Options
Nephrotoxicity	Either	• SCr • BUN • Urine output • Biopsy-proven CNI-induced nephrotoxicity	• Reduce CNI dose (if possible) • Use of CCB for hypertension control • Modify regimen (change to non-CNI containing regimen [ToR inhibitor or belatacept])[a]
Hypertension[b]	Cyclosporine	• Blood pressure • Heart rate	• Initiate patient-specific antihypertensive therapy • Reduce cyclosporine dose (if possible) • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]
Hyperlipidemia[b]	Cyclosporine	• Fasting lipid panel	• Initiate patient-specific cholesterol-lowering therapy • Reduce cyclosporine dose (if possible) • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]
Hyperglycemia[c]	Tacrolimus	• Blood glucose (fasting and nonfasting) • Hemoglobin A_{1c}	• Lifestyle modifications • Reduce tacrolimus dose (if possible) • Reduce steroids (if patient is taking them and if possible) • Initiate patient-specific glucose-lowering therapy (insulin or oral therapy) • Modify regimen (change to cyclosporine or non-CNI containing regimen)[a]
Neurotoxicities[c]	Tacrolimus	• Fine hand tremor • Headache • Mental status changes	• Reduce tacrolimus dose (if possible) • Modify regimen (change from tacrolimus to cyclosporine or non-CNI containing regimen)[a]
Hirsutism	Cyclosporine	• Patient complains of excessive hair growth or male-pattern hair growth	• Reduce cyclosporine dose (if possible) • Cosmetic hair removal • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]
Alopecia	Tacrolimus	• Patient complains of excessive hair loss	• Reduce tacrolimus dose (if possible) • Hair growth treatments (ie, minoxidil, finasteride in males only) • Consider use of multivitamin with thiamine and folic acid, and/or biotin 5000 mcg daily • Modify regimen (change to cyclosporine or non-CNI containing regimen)[a]
Gingival Hyperplasia	Cyclosporine	• Patient complains of excessive gum growth • Discuss options for therapy with the patient's dentist	• Reduce cyclosporine dose (if possible) • Oral surgery (gum resection) • Modify regimen (change to tacrolimus or non-CNI containing regimen)[a]

[a]Modifying the immunosuppressive regimen increases risk for rejection, even in stable patients. This option should be chosen cautiously and implemented with proper monitoring and follow-up.

[b]Tacrolimus is also associated with hypertension and hyperlipidemia, but to a much lower extent compared to cyclosporine.

[c]Cyclosporine is also associated with hyperglycemia and neurotoxicities, but to a much lower extent compared to tacrolimus.

BUN, blood urea nitrogen; CCB, calcium channel blocker; SCr, serum creatinine; ToR, target of rapamycin.

mostly nausea and vomiting). Importantly, pancreatitis and venoocclusive disease of the liver occur in less than 1% of patients following chronic azathioprine therapy.[7]

Mycophenolic Acid Derivatives Mycophenolate mofetil was approved in 1995 and enteric-coated MPA in 2004. Both agents are considered adjunctive immunosuppressants.[6] KEY CONCEPT Both mycophenolate mofetil and enteric-coated MPA are prodrugs for MPA. MPA acts by inhibiting inosine monophosphate dehydrogenase, a vital enzyme in the de novo pathway of purine synthesis. Inhibition of this enzyme prevents the proliferation of most cells that are dependent on the de novo pathway for purine synthesis, including T- and B-cells.[6] LO 7

Mycophenolate mofetil is available in 250 mg and 500 mg capsules, an oral suspension (100 mg/mL; in cherry syrup), and as an injectable.[7] The recommended starting dose of mycophenolate mofetil is 1000 to 1500 mg given twice daily. The conversion between oral and IV mycophenolate mofetil is 1:1. Enteric-coated MPA is available in 180 mg and 360 mg tablets. The appropriate equimolar conversion between mycophenolate mofetil and enteric-coated MPA is 1000 mg of mycophenolate mofetil to 720 mg of enteric-coated MPA.[6] The recommended starting dose of enteric-coated MPA is 720 mg given twice daily. Conversion of mycophenolate mofetil to enteric-coated MPA has been proven safe. MPA C_0 can be monitored; however, it is not routinely recommended.[6] LO 6 LO 6 LO 8

KEY CONCEPT The most common adverse events associated with these agents are GI (18%–54%; diarrhea, nausea, vomiting, and gastritis) and myelosuppression (20%–40%).[7] Despite LO 7

its enteric coating, enteric-coated MPA has the same degree of GI adverse events as mycophenolate mofetil.[6,18] However, recent data suggest that there is a benefit in converting patients with documented mycophenolate-induced GI disease from mycophenolate mofetil to enteric-coated MPA or to azathioprine.[19]

Comparative Efficacy The MPA derivatives have replaced azathioprine as the primary antiproliferative agent and are generally considered to provide a more specific immunosuppressive effect compared with azathioprine.[6] Mycophenolate mofetil and enteric-coated MPA have similar safety and efficacy data in renal transplant recipients.[18] The decision to choose one agent over another is a purely practitioner-dependent preference.

▶ *Target of Rapamycin Inhibitors*

LO 7 **Sirolimus** KEY CONCEPT Sirolimus inhibits T-cell activation and proliferation by binding to and inhibiting the activation of the mammalian ToR, which suppresses cellular response to IL-2 and other cytokines (ie, IL-4, IL-15).[6,7,20] Studies have shown that sirolimus may be used safely and effectively concomitantly with either cyclosporine or tacrolimus instead of an antiproliferative.[21] Sirolimus can also be used as an alternative agent for patients who do not tolerate CNIs due to nephrotoxicity or other adverse events.[6] At this time, the most exciting data for sirolimus point to its ability to prevent long-term allograft dysfunction when used as a substitute for the CNIs in renal transplant recipients.[20]

Sirolimus is available in 0.5 mg, 1 mg, and 2 mg tablets and a 1 mg/mL oral solution. Although some may elect not to do a loading dose, the package insert indicates that the current approved dosing regimen for sirolimus is a 6 mg loading dose followed by
LO 6 a 2 mg/day maintenance dose.[7] Use of a sirolimus loading dose of 5 to 15 mg/day for 1 to 3 days will allow for a more rapid achievement of adequate immunosuppression.[7] Maintenance doses of sirolimus usually range from 1 to 10 mg/day given once daily. Sirolimus blood C_0 should be maintained between
LO 8 3 and 10 ng/mL (mcg/L; 3 and 11 nmol/L), depending on the institution-specific protocols.[6] Of note, sirolimus has a half-life of approximately 62 hours, which means that it will not reach steady state after dosage changes for several days.[7]

LO 7 KEY CONCEPT The most common adverse events reported with sirolimus are leukopenia (20%), thrombocytopenia (13%–30%), and hyperlipidemia (38%–57%).[7] Other adverse effects include delayed wound healing, anemia, diarrhea, arthralgias, rash, proteinuria, pneumonitis, and mouth ulcers. One analysis suggests that use of sirolimus in kidney transplant recipients can reduce cardiovascular risk compared with CNI–based regimens.[22]
LO 7 Sirolimus has a black-box warning in newly transplanted liver and lung recipients due to severe and potentially life-threatening adverse events.[7] The long-term use of sirolimus in these populations may be appropriate, but not in the initial posttransplant period (ie, 3–6 months posttransplant).

Everolimus Everolimus is a derivative of sirolimus and has the
LO 6 same mechanism of action.[7,23] Everolimus is only indicated for prevention of rejection in low- to moderate-risk renal and liver transplant recipients. This agent is available in 0.25 mg, 0.5 mg, and 0.75 mg tablets. The recommended starting dose is 0.75 to
LO 8 1 mg twice daily without the need for a loading dose. Maintenance everolimus doses should be maximized to achieve a C_0 goal of 3 to 8 ng/mL (mcg/L; 3–8 nmol/L).[7,23] With a significantly shorter
LO 7 half-life compared with sirolimus, everolimus steady state can be reached within 4 to 6 days. The adverse event profile of everolimus is similar to that of sirolimus.[7,23]

▶ *Corticosteroids*

Traditional triple-therapy immunosuppressive regimens have consisted of a primary agent (ie, CNI, ToR inhibitor, belatacept), an antiproliferative, and corticosteroids.[6] In recent years, many renal transplant protocols have focused on corticosteroid sparing or avoidance. Avoidance or sparing of corticosteroids has been supported in the literature, although more studies are needed to help better characterize which patients should
LO 6 follow these protocols.[6,24] A typical taper includes a bolus of IV methylprednisolone 100 to 500 mg at the time of transplant, then tapered over days to months, depending on the type of organ, to a maintenance dose of prednisone 5 to 10 mg/day. Although most centers still use low-dose steroids for immunologically high-risk patients and nonrenal transplant patients, a number of renal transplant programs have developed an immunosuppression protocol that completely withdraws corticosteroids at some
LO 8 point posttransplantation.[6] Therapeutic drug monitoring of corticosteroids is not employed. Corticosteroids are associated
LO 7 with a variety of metabolic toxicities. The most common adverse events are summarized in Table 55–4.[1,6]

KEY CONCEPT Corticosteroids have various effects on immune and inflammatory responses, although their exact mechanism of immunosuppression is not fully understood. It is believed that high doses are directly lymphotoxic, and lower doses act by inhibiting the production of various cytokines that are necessary to amplify the immune response.[6,7]

The most commonly used corticosteroids are methylprednisolone (IV and oral) and prednisone (oral), although prednisolone and dexamethasone are also effective for organ

Table 55–4

Common Adverse Events Associated with Corticosteroids[1,6]

Body System	Adverse Event
Cardiovascular	Hyperlipidemia
	Hypertension
Central nervous system	Anxiety
	Insomnia
	Mood changes
	Psychosis
Dermatologic	Acne
	Diaphoresis
	Ecchymosis
	Hirsutism
	Impaired wound healing
	Petechiae
	Thin skin
Endocrine/metabolic	Cushing syndrome
	Hyperglycemia
	Sodium and water retention
Gastrointestinal	Gastritis
	Increased appetite
	Nausea, vomiting, diarrhea
	Peptic ulcers
Hematologic	Leukocytosis
Neuromuscular/skeletal	Arthralgia
	Impaired growth
	Osteoporosis
	Skeletal muscle weakness
Ocular	Cataracts
	Glaucoma
Respiratory	Epistaxis

transplantation. Corticosteroid doses vary by center-specific protocols, organ type, and patient characteristics.

▶ *Costimulatory Pathway Blocker*

Belatacept KEY CONCEPT Belatacept was approved in 2011 as the first IV biologic maintenance immunosuppressive agent in transplant.[25] Belatacept blocks CD80 and CD86 ligands, found on APCs.[7] The CD80 and CD86 proteins are responsible for stimulating CD28 on inactive T-cells, an essential costimulatory interaction (Signal 2). As detailed previously, Signal 1 without a complementary Signal 2 induces T-cell anergy.[25] Studies have shown that in combination with mycophenolate and corticosteroids, belatacept may be used in place of CNIs, demonstrating similar patient and allograft survival compared to a cyclosporine-based regimen.[26,27] Belatacept improved renal function; however, the incidence and intensity of acute rejection was significantly higher. Belatacept was also associated with improvements in blood pressure and lipid levels.[25]

LO 7

Belatacept is available in a 250 mg vial that requires reconstitution prior to administration.[7] The recommended dosing regimen is 10 mg/kg on the day of transplantation, followed by an additional dose 4 days later, and again at the end of weeks 2, 4, 8, and 12 posttransplant. Beginning at the end of week 16 posttransplant, belatacept is dosed at 5 mg/kg every 4 weeks thereafter.[7,25] Belatacept requires access to an infusion center/suite, or a home infusion service to ensure appropriate administration.

LO 6

The most common adverse effects associated with belatacept are infectious (urinary tract infection, 37%; upper respiratory infection, 15%), GI (diarrhea, 39%; constipation, 33%; nausea, 24%; vomiting, 22%), metabolic (hyperkalemia, 20%; hypokalemia 21%), and central nervous system (CNS; headache, 21%) complications.[7] Other adverse effects include peripheral edema, anemia, leukopenia, hypotension, arthralgia, and insomnia.[25] KEY CONCEPT Belatacept has a black-box warning for increased risk of posttransplant lymphoproliferative disorders (PTLD). Due to this risk, it is recommended that belatacept only be used in patients with a proven preexisting immunity to Epstein-Barr virus (EBV). An additional black-box warning advises against use of belatacept in liver transplant patients due to an increased risk of allograft loss and patient death.[7,25]

LO 7

Treatment of Acute Rejection Episodes

Acute rejection is generally treated with a course of high-dose methylprednisolone (250 to 1000 mg/day IV for 3 days), which is usually sufficient to ameliorate the episode. If the acute rejection episode is resistant to the initial course of steroids, a second course may be administered or the patient may begin therapy with r-ATG (1.5 mg/kg/day for 4 to 14 days).[28] Cellular rejection refractory to these treatments is rare and likely due to underlying causes such as an antibody-mediated component or other diagnosis. Treatments of refractory acute rejection may include alemtuzumab, IVIG, high-dose tacrolimus, or organ irradiation.

Managing Highly Sensitized Patients and Antibody-Mediated Rejection Episodes

The presence of preformed antibodies, high panel-reactive antibodies (PRA), and DSA are major barriers to successful transplantation.[4] This is true mainly because traditional immunosuppressants do not significantly affect the humoral immune system and are ineffective at management of AMR, which is a leading cause of allograft loss in kidney and heart transplant recipients. Without some form of intervention, antibody formation and rejection can significantly impact morbidity and mortality. Two major strategies are used for reduction of DSA pretransplant: (a) high-dose IVIG and (b) plasmapheresis plus low-dose IVIG. Each approach has advantages and disadvantages.[4]

In plasmapheresis or plasma exchange, patients' plasma is removed and replaced with albumin or fresh-frozen plasma.[4] Plasmapheresis produces a rapid reduction of preformed antibodies and allows transplantation to occur. The purpose of IVIG administration is to decrease anti-HLA alloantibody synthesis. The other mechanisms of IVIG are inhibition of complement-mediated injury, reduced B-cell proliferation and NK cells, and a decrease in phagocytosis. Most patients require four to five plasmapheresis sessions with IVIG to remove DSA. In patients at risk for bleeding, the use of albumin should be limited, and fresh-frozen plasma or a combination of both agents should be considered.[4]

In patients who develop AMR posttransplant, there are limited therapeutic options, none of which are FDA-approved. The potential options include plasmapheresis and IVIG, rituximab, bortezomib, and/or eculizumab.[4] All of these agents have an effect on humoral immunity, which may provide benefit to patients with AMR. The mechanisms of plasmapheresis and IVIG were discussed earlier.[4]

Rituximab is a chimeric monoclonal anti-CD20 antibody targeting B-cells.[4,7] This agent directly inhibits B-cell proliferation and induces cellular apoptosis through complement-mediated antibody-dependent cellular cytotoxicity. In an analysis of AMR treatment, the use of rituximab in conjunction with plasmapheresis/IVIG resulted in improved 3-year graft survival (92% vs 50%) and significantly reduced DSA at 3 months compared with high-dose IVIG alone.[29] Unfortunately, plasma cells lack CD20 and are unaffected by rituximab. However, rituximab may play an important role in reducing memory B-cell response. Overall, it appears that rituximab may provide beneficial effects in managing AMR and patients highly sensitized before transplant when used in combination with other therapies.[4]

Bortezomib is a proteasome inhibitor indicated for treatment of multiple myeloma.[4,7] It works by inducing cell-cycle arrest and apoptosis of plasma cells. Desensitization and treatment protocols using bortezomib have utilized doses of 1.3 mg/m^2 from one to four cycles. Acute hepatic dysfunction has rarely been reported; thus, bortezomib should be used cautiously in patients with moderate-to-severe hepatic impairment. Bortezomib has also been associated with significant myelosuppression and peripheral neuropathy. Bortezomib has been used in combination with plasmapheresis and IVIG or rituximab. The reported outcomes of these cases demonstrate graft survival rates of 85% to 100%. Anti-HLA antibodies are decreased by 50% within 2 weeks of therapy and remain suppressed for up to 5 months.[30,31] Bortezomib also seems effective in AMR refractory to plasmapheresis and IVIG.[4]

Eculizumab is a humanized monoclonal antibody directed against complement protein C5.[4,7] It inhibits the cleavage to C5a and C5b, thus preventing the generation of the membrane attack complex (MAC) and reducing antibody-dependent cell lysis. Eculizumab carries an FDA boxed warning of meningococcal infection. Meningococcal vaccination is recommended 14 days prior to eculizumab, but infections have been reported even in vaccinated patients. It is highly recommended to continue penicillin or alternative lifetime therapy in these patients. There are only a few case reports demonstrating eculizumab's efficacy for treating AMR, showing fast improvement of renal function observed within a week after eculizumab use.[4] Eculizumab is an important

agent for the prevention and treatment of atypical hemolytic uremic syndrome (aHUS) posttransplant.

Maintenance Immunosuppressive Therapies—Common Drug–Drug Interactions

KEY CONCEPT As the number of medications a patient takes increases, so does the potential for DDIs. Disease severity, patient age, and organ dysfunction are all risk factors for DDIs. In general, DDIs are either pharmacokinetic or pharmacodynamic interactions:

- Pharmacokinetic interactions result when one drug alters the absorption, distribution, metabolism, or elimination of another drug.
- Pharmacodynamic interactions include additive, synergistic, or antagonistic interactions that can affect efficacy or toxicity.

▶ *Pharmacokinetic Interactions*

Pharmacokinetic DDIs pose a major dilemma with the maintenance immunosuppressants. Pharmacokinetic interactions can either result in: (1) increased concentrations of one or more agents, with an increased risk for drug-induced toxicities, or (2) lowered (ie, subtherapeutic) drug concentrations, possibly leading to allograft rejection. These interactions can be seen during drug absorption, distribution, metabolism, and elimination.

Interactions of Absorption Gut metabolism, modifications in active transport, and changes in intestinal motility and chelation interactions alter absorption of the immunosuppressants. Active transporters (ie, P-glycoprotein [P-gp]) are present in the gut, brain, liver, and kidneys and play an important role in DDIs. P-gp provides a biological barrier, eliminating xenobiotics that may accumulate in these organ systems, thereby having a significant impact on the absorption and distribution of many medications. P-gp affects the absorption of the CNIs and ToR inhibitors. Medications that inhibit or induce the activity of P-gp have a significant impact on bioavailability of some of the immunosuppressive agents. For example, P-gp inhibitors, such as verapamil or quinidine, increase concentrations of cyclosporine, tacrolimus, sirolimus, and everolimus due to reduced P-gp-dependent drug elimination from the systemic circulation.[7]

There is a prominent interaction between the prokinetic agents and the CNIs seen through changes in intestinal motility. Metoclopramide increases the absorption of cyclosporine and tacrolimus by enhancing gastric motility and emptying, resulting in increased CNI concentrations.[7]

Most of the interactions with mycophenolate mofetil and enteric-coated MPA result in reductions in intestinal absorption. Proton pump inhibitors decrease the oral absorption of mycophenolate mofetil, but not enteric-coated MPA.[7] Divalent and trivalent cations (ie, aluminum, magnesium, calcium) decrease MPA absorption through chelation. These agents should be administered at least 1 hour before or 2 hours after MPA. Of note, iron does not appear to interact with the MPA preparations. The clinical implications of these DDIs are unknown, but reductions in MPA exposure can theoretically increase rejection risk.

Interactions of Distribution Interactions of distribution occur most often with highly protein-bound drugs.[7] MPA is the only highly protein bound (97%) maintenance immunosuppressant with an interaction of distribution. Concomitant administration of MPA with salicylates increases MPA-free concentrations. The adverse sequelae of this interaction are unknown. Drug interaction studies have not been conducted with MPA derivatives and other highly protein-bound drugs.

Interactions of Metabolism Oxidative metabolism by cytochrome P-450 (CYP) isozymes is the primary method of xenobiotic metabolism. The CNIs and ToR inhibitors are substrates of the CYP3A isozyme system. Most CYP-mediated metabolism takes place in the liver; however, CYP is also expressed in the intestine, lungs, kidneys, and brain. As CYP3A substrates, it is anticipated that cyclosporine, tacrolimus, sirolimus, and everolimus would experience similar DDIs with known substrates, inhibitors, and inducers of the CYP3A isozyme system.[6] Table 55–5 details clinically relevant DDIs that occur with the calcineurin and ToR inhibitors due to inhibition or induction of the CYP isozyme system.[7] LO 7

Given how extensive some immunosuppressant DDIs are, in some cases empiric dose changes are necessitated when coadministration with an interacting medication cannot be avoided. For example, it is recommended to reduce tacrolimus doses by one-third in patients initiating voriconazole. Some clinicians utilize interactions of metabolism to reduce the dose of an immunosuppressant, such as using diltiazem to treat hypertension, which also helps reduce tacrolimus doses and decrease pill burden.

Not all metabolic DDIs occur through the CYP system. Azathioprine has a considerable interaction with allopurinol and febuxostat that is mediated through the inhibition of xanthine oxidase, which is the enzyme responsible for metabolizing 6-MP to 6-thiouricate.[7] Combining these agents can result in 6-MP accumulation and severe myelosuppression. It is recommended that concomitant therapy with azathioprine and allopurinol or febuxostat be avoided, but if necessary, azathioprine doses must be empirically reduced by 75%.[7]

Interactions of Elimination Mycophenolate is metabolized to MPA-glucuronide (MPAG) via hepatic glucuronosyltransferase, and then excreted in bile for gut elimination.[7] Deconjugation of MPAG to MPA by intestinal flora results in continued MPA absorption several hours after its administration. Some medications (ie, cyclosporine, bile-acid sequestrants) interfere with the biliary excretion of MPAG, thereby eliminating MPA reabsorption in the intestines and lowering the MPA area under the curve (AUC).[7] In this type of interaction, separation of doses is ineffective; therefore, proper patient monitoring is warranted.

▶ *Pharmacodynamic Interactions*

Pharmacodynamic interactions are the backbone of modern immunosuppressive therapies that employ multiple medications with different mechanisms of action resulting in additive immunosuppression. Unfortunately, pharmacodynamic interactions can also be problematic, such as when medications with

Patient Encounter Part 2

Identify your treatment goals for the patient in terms of maintenance immunosuppressants.

Create a plan for maintenance therapy for the patient, making sure to compare and contrast the pros and cons of the different maintenance immunosuppressants.

Identify the need to continue the patient's pretransplant medications, and identify any potential DDIs that may exist with the addition of the maintenance immunosuppressants and the medications that he is currently taking.

Table 55–5

Potential Drug–Drug Interactions with the Calcineurin Inhibitors and Target of Rapamycin Inhibitors Mediated Through the Cytochrome P-450 (CYP) System 3A Isozyme[7]

Substrates[a]		Inducers[b]	Inhibitors[c]
Alfentanil	Loratadine	Carbamazepine	Boceprevir
Alprazolam	Lovastatin	Dexamethasone	Cimetidine
Amiodarone	Nevirapine	Etravirine	Clarithromycin
Amlodipine	Nicardipine	Ethosuximide	Clotrimazole
Atorvastatin	Nifedipine	Isoniazid	Delavirdine
Boceprevir	Omeprazole	Nevirapine	Diltiazem
Cilostazol	Paclitaxel	Phenobarbital	Erythromycin
Cisapride	Propafenone	Phenytoin	Fluconazole
Chlorpromazine	Progesterone	Prednisone	Fluoxetine
Clonazepam	Quetiapine	Rifabutin	Fluvoxamine
Cocaine	Quinidine	Rifampin	Grapefruit juice
Cortisol	Rilpivirine	Rilpivirine	Indinavir
Cyclophosphamide	Rivaroxaban	St. John's wort	Itraconazole
Dantrolene	Sertraline		Ketoconazole
Dapsone	Simvastatin		Miconazole
Diazepam	Tamoxifen		Nefazodone
Disopyramide	Testosterone		Nelfinavir
Enalapril	Tolvaptan		Posaconazole
Estradiol	Triazolam		Rilpivirine
Estrogen	Vandetanib		Ritonavir
Etoposide	Venlafaxine		Saquinavir
Everolimus	Vinblastine		Telapravir
Felodipine	Warfarin		Troleandomycin
Flutamide	Zolpidem		Verapamil
Lidocaine			Voriconazole
			Zafirlukast

[a]Substrates of the CYP3A4 isozyme will compete with cyclosporine, tacrolimus, and sirolimus for metabolism; therefore, concentrations of these medications will be increased (usually by ≤ 20%).

[b]Inducers of the CYP3A4 isozyme will enhance the metabolism of cyclosporine, tacrolimus, and sirolimus; therefore, concentrations of these medications will be decreased.

[c]Inhibitors of the CYP3A4 isozyme will decrease the metabolism of cyclosporine, tacrolimus, and sirolimus; therefore, concentrations of these medications will be increased.

LO 7

similar adverse events are used concomitantly. For example, nephrotoxic agents, such as amphotericin B, aminoglycosides, some HIV agents, and nonsteroidal anti-inflammatory drugs may potentiate the nephrotoxic effects of the calcineurin inhibitors.[7] The use of myelosuppressive agents, such as sulfamethoxazole-trimethoprim (SMZ-TMP) and valganciclovir, could enhance the myelosuppressive effects of induction therapy and the maintenance immunosuppressants.[7] In addition to reviewing prescription medications, it is essential to question patients about the use of nonprescription agents and dietary supplements, as these products also have the potential for significant interactions through methods discussed previously. Some examples are St. John's wort inducing metabolism of CNIs and ToR inhibitors, and willow bark having the potential to worsen CNI-induced nephrotoxicity.

Management of Immunosuppressive Drug Complications

▶ *Opportunistic Infections*

KEY CONCEPT Organ transplant recipients are at increased risk of infectious diseases, which are a chief cause of early morbidity and mortality.[32] The prevalence of posttransplant infection depends on many factors, including clinical risk factors, environmental exposures, and the degree of immunosuppression. Anti-infectives are universally prescribed in this population, and their use can be split into three different categories:

- Prophylaxis: antimicrobials given to prevent infection
- Empiric: preemptive therapy given based on clinical suspicion of an infection
- Treatment: antimicrobials given to manage a documented infection

Posttransplant infections generally occur in a standard pattern; therefore, prevention is a key management strategy.[32] The information in this section is designed to highlight prophylaxis options routinely used in organ transplant recipients. Refer to Table 55–6 for a list of agents used for the prevention of *Pneumocystis jiroveci* pneumonia and CMV disease.[33,34]

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***Pneumocystis jiroveci* Pneumonia** KEY CONCEPT Without prophylaxis, *P. jiroveci* pneumonia occurs in 5% to 15% of transplant recipients.[33] Antipneumocystis prophylaxis is enormously helpful and generally used in all organ transplant recipients. The duration of prophylaxis is usually 6 to 12 months after transplant, but may be prolonged in highly immunosuppressed patients (ie, active CMV disease, treatment for rejection) or liver or lung recipients. SMZ-TMP is the preferred agent for prophylaxis. One of its major advantages is its broad

Table 55–6

Prophylactic Options for *Pneumocystis jiroveci* Pneumonia and CMV[33,34]

Medication	Dosing	Common Adverse Events
Antipneumocystis Prophylaxis		
Sulfamethoxazole-trimethoprim (Bactrim, Septra, SMZ-TMP, cotrimoxazole)	One SS tablet by mouth once a day[a] One DS tablet by mouth once a day[a] One DS tablet by mouth every M/W/F[a]	Hyperkalemia Myelosuppression Nephrotoxicity Neutropenia Photosensitivity Rash
Pentamidine (NebuPent)	300 mg inhaled every 3–4 weeks	Bronchospasm Cough Hypoglycemia or hyperglycemia
Dapsone (Avlosulfon)	50–100 mg tablet by mouth once a day	Hepatotoxicity Myelosuppression Nephritis
Atovaquone (Mepron)	1500 mg suspension by mouth once a day	Elevated liver transaminases Nausea Rash
Antivirals		
Valganciclovir (Valcyte)	450–900 mg by mouth once a day[a]	Stomach upset Myelosuppression Headache
Ganciclovir (Cytovene)	5 mg/kg IV every day; or 1000 mg by mouth three times a day[a]	Stomach upset Myelosuppression Rash
Valacyclovir (Valtrex)	1–2 g by mouth four times a day[a]	Stomach upset Myelosuppression Headache
CMV hyperimmune globulin (CytoGam) and polyvalent IVIG	The maximum recommended total dosage per infusion is 150 mg/kg beginning within 72 hours of transplantation Follow-up doses and time intervals depend on the type of organ transplanted	Stomach upset Fevers and chills Flushing

[a]Dose adjustment required in renal insufficiency.

CMV, cytomegalovirus; DS, double-strength (800 mg SMZ, 160 mg TMP); IVIG, intravenous immunoglobulin; IV, intravenous; M/W/F, Monday, Wednesday, and Friday; SS, single-strength (400 mg SMZ, 80 mg TMP); SMZ, sulfamethoxazole; TMP, trimethoprim.

spectrum of activity. Not only is it effective against *Pneumocystis*, but it also has activity against *Toxoplasma* and other common bacterial infections. Patients who have sulfa allergies, glucose-6 phosphate dehydrogenase (G6PD) deficiency, or are intolerant of SMZ-TMP should be given one of the second-line treatments. Unfortunately, the second-line agents are antiparasitics and have no meaningful activity against common bacteria. These agents include dapsone, atovaquone, and pentamidine.[33]

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Cytomegalovirus CMV is a concerning opportunistic pathogen in transplantation due to its association with poor outcomes.[34] **CMV infection** is present in 30% to 97% of the general population, but CMV disease is typically restricted to immunocompromised hosts. The risk of CMV disease is highest among CMV-naive recipients who receive a CMV-positive organ (donor+/recipient–). Other factors that augment the risk of CMV disease include organ type (lung and pancreas recipients are highest risk) and immunosuppressive agents (ALA use increases risk). CMV disease characteristically occurs within the first 3 to 6 months posttransplantation, but delayed onset disease has been seen in patients receiving antiviral prophylaxis. Patients with CMV infection may present with flu-like symptoms, including fever, chills, aches, malaise, and fatigue. CMV infection may result in more profound symptoms in the immunosuppressed patient, including leukopenia, thrombocytopenia, and organ dysfunction.[34]

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KEY CONCEPT Several antivirals have proven effective in preventing and treating CMV.[34] Valacyclovir and valganciclovir, prodrugs of acyclovir and ganciclovir, respectively, have improved bioavailability compared with their parent compounds and offer the advantage of less frequent dosing. CMV prophylaxis is typically continued for the first 200 days, or longer, after transplantation. Although valganciclovir and IV ganciclovir are considered the prophylaxis agents of choice in most organ transplant recipients, national guidelines allow for consideration of prophylaxis with CMV hyperimmune globulin in heart and lung transplant populations. Both IV ganciclovir and oral valganciclovir may be used for preemptive therapy or for treatment of established CMV disease.[34] The adverse events are similar among these agents and include myelosuppression and GI effects.[7]

Fungal Infections Fungal infections are an important cause of morbidity and mortality in SOT recipients.[35] Immunologic (ie, immunosuppressants, CMV infection), anatomic (ie, tissue ischemia and damage), and surgical (ie, duration of surgery, transfusion requirements) factors contribute to the risk for invasive fungal infections. Mucocutaneous candidiasis (ie, oral thrush, esophagitis) is associated with corticosteroids and ALA.

LO 9

KEY CONCEPT Oral nystatin or clotrimazole troches are effective prophylactic options for the prevention of thrush. However, clotrimazole inhibits the CYP3A system in the gut and can

alter immunosuppressive levels.[7] The use of systemic antifungal prophylaxis, such as oral fluconazole, is controversial due to the potential for DDIs and risk of developing resistance. The American Society of Transplantation has recommended antifungal prophylaxis in liver, lung, intestine, and pancreas transplantation.[36,37] The choice of agents depends on the fungal risk in that particular population. For example, liver, intestine, and pancreas transplant recipients are at high risk for candidiasis; therefore, the use of medications that cover *Candida* spp. is crucial, such as the triazoles (ie, fluconazole, itraconazole) or echinocandins (ie, caspofungin, micafungin, anidulafungin). Lung transplant recipients are at high risk for aspergillosis; therefore, it is imperative to use antifungal prophylaxis that covers *Aspergillus* spp., such as the echinocandins, polyenes (ie, amphotericin B, lipid-based amphotericin B products) or new generation triazoles (ie, voriconazole, posaconazole).[36,37]

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Polyomavirus One infection complication seen only in renal transplant recipients is polyomavirus. In humans, there are two known pathologic polyoma strains, BK and JC. These viruses are rarely associated with disease in immunocompetent individuals. During periods of immunosuppression, the virus is reactivated and can be associated with significant morbidity.[38]

In renal transplant recipients, the major diseases caused by BK virus (BKV) are tubulointerstitial nephritis and ureteral stenosis.[38] Polyomavirus-associated nephropathy (PyVAN) presents with evidence of allograft dysfunction, resulting in either an asymptomatic acute or slowly progressive rise in serum creatinine (SCr) concentrations. Some studies have reported that PyVAN may affect up to 10% of renal transplant recipients, frequently resulting in permanent renal dysfunction or allograft loss.[38]

Patient Encounter Part 3

Identify your treatment goals for the patient in terms of antimicrobial prophylaxis.

Create a plan for the patient's antimicrobial prophylaxis, making sure to compare and contrast the pros and cons of the different agents in this patient.

LO 9

Currently, treatment options for BKV are limited, and management recommendations are generally focused on reductions in immunosuppression. There is a lack of a directed antiviral intervention; however, some centers have utilized IVIG, cidofovir, leflunomide, and the fluoroquinolone antibiotics to manage BKV infections. All of these agents have been reported to provide some benefit in managing BKV in anecdotal cases.[38]

LO 9

Vaccination Vaccination is one of the most effective means of preventing infection and related complications.[39] However, there is a valid concern that SOT recipients may mount an inadequate response to vaccination due to immunosuppression. Required vaccinations should be administered prior to transplantation so that an appropriate antibody response can develop (Table 55–7).[39] If this strategy is pursued, the earlier a vaccine is administered,

Table 55–7

Recommended Vaccinations Pre- and Posttransplant[39]

	Administration		
Vaccine	**Before SOT**	**After SOT**	**Additional Information**
Hepatitis A	X		Immunize as soon as possible during course of disease
Hepatitis B	X		Immunize as soon as possible during course of disease (before transplant, administer 40 mcg dose in a series of three to four doses)
Herpes Zoster	X		Live[a] virus, administer ≥ 14 days before immunosuppressant agents are initiated (experts advise 1 month before)
Human Papilloma Virus	X		Recommended for females aged 9–26, no recommendations for SOT
Influenza	X	X	Annual vaccination with inactivated intramuscular formulation recommended before and after SOT
Measles-Rubella	X		Live[a] virus, administer to patients who are seronegative, *before* transplant, or in women of childbearing age for prevention of congenital rubella syndrome
Pneumococcal	X	X	23-valent polysaccharide vaccine should be given once before transplant and boosters at 3 and 5 years after initial dose
Tetanus/Diptheria	X		TDaP booster indicated for < 65 years old (may be given ≤ 2 years after last TDaP booster in SOT patients)
Varicella	X		Live[a] virus, administer to patients who are seronegative, *before* transplant

[a]All live vaccines are contraindicated post solid organ transplant (SOT), as they can cause serious infection.

Live vaccines:

- Bacillus Calmette-Guerin
- Herpes zoster
- Live intranasal attenuated influenza
- Live oral typhoid
- Measles-rubella
- Vaccinia (smallpox)
- Varicella

TDaP, tetanus, diphtheria, and pertussis.

the more effective it may be, as end-stage organ failure can also contribute to a decreased immune response.[39]

In general, the weakest response to vaccine is within the first 6 months posttransplantation due to the intense level of immunosuppression during this period.[39] Vaccination within 6 months of transplant may be considered on a case-by-case basis in those patients who are at high risk of developing infection. Use of inactive vaccines is preferred in transplant recipients due to the relative risk of infection associated with live vaccines. Health care workers and family members who are in close contact with transplant recipients and have received a live vaccine should consider use of respiratory masks for at least 7 days after vaccination and adhere to strict oral and hand hygiene.[39]

▶ *Hypertension*

LO 9 KEY CONCEPT Cardiovascular disease has been identified as the leading cause of death in organ transplant recipients.[40] Posttransplant hypertension is associated with increased cardiac morbidity and patient mortality in transplant patients and is also an independent risk factor for allograft dysfunction. Based on all of the available posttransplant morbidity and mortality data, it is imperative that posttransplant hypertension be identified and managed appropriately.[40]

There are several mechanisms responsible for posttransplant hypertension including renal dysfunction, increased sensitivity to endothelin-1 and angiotensin, increased density of glucocorticoid receptors in the vascular smooth muscle, and decreased production of vasodilatory prostaglandins. However, one of the most easily recognized causes of posttransplant hypertension is the use of corticosteroids and CNIs. Corticosteroids cause sodium and water retention, thus increasing blood pressure, whereas CNIs reduce glomerular filtration rate (GFR) and renal blood flow, increase systemic and intrarenal vascular resistance, promote sodium retention, reduce concentrations of systemic vasodilators (ie, prostacyclin, nitric oxide), and increase concentrations of thromboxanes. Compared with cyclosporine, tacrolimus displays significantly less severe hypertension, and patients taking tacrolimus require fewer antihypertensive medications after transplant.[40]

LO 9 **Treatment** KEY CONCEPT Controlling hypertension after transplant is essential in preventing cardiac morbidity and mortality and prolonging graft survival. The target blood pressure in transplant recipients should be less than 130/80 mm Hg, consistent with national hypertension guidelines.[40]

Lifestyle Modifications To achieve a goal blood pressure, lifestyle modifications including diet, exercise, sodium restriction, and smoking cessation are recommended.[40] Unfortunately, lifestyle modifications alone are often inadequate in high-risk populations, and antihypertensive medications are usually initiated early after transplant.[40]

LO 9 **Immunosuppressive Regimen Modification** Because tacrolimus has shown the propensity to cause less severe hypertension compared to cyclosporine, conversion from cyclosporine-based immunosuppression to tacrolimus-based immunosuppression may be one way to reduce the severity of hypertension in transplant recipients. KEY CONCEPT Conversion to a ToR inhibitor or belatacept, which are not associated with hypertension, may also be an alternative to the CNIs in patients with difficult-to-treat hypertension. Corticosteroid taper or withdrawal are effective strategies for lowering blood pressure, but are not warranted in all clinical situations.[40]

LO 9 **Antihypertensive Agents** There is no single class of antihypertensive medications recognized as the ideal agent. Numerous factors must be considered when determining appropriate treatment, including the safety and efficacy data of available agents, patient-specific comorbidities, and medication cost.[40] A large majority of patients often require multiple medications to achieve goal blood pressure, and combination therapy is regarded as appropriate first-line therapy.[40]

The limited clinical studies support the use of calcium channel blockers (CCB) posttransplantation. Dihydropyridine calcium channel blockers have been associated with a higher GFR and lower incidence of allograft loss. The dihydropyridine calcium channel blockers have demonstrated an ability to reverse nephrotoxicity associated with cyclosporine and tacrolimus. The use of diltiazem and verapamil is discouraged for the treatment of hypertension because of potential drug interactions and lack of strong evidence in renal and liver transplant recipients. The addition of diltiazem to patients' regimens after cardiac transplant has also been shown to retard progression of cardiac allograft vasculopathy. β-Blockers and thiazide diuretics have proven benefits in reducing cardiovascular disease–associated morbidity and mortality in the general population.[40] Tolerability permitting, these agents are to be considered 2nd and 3rd therapies in most transplant recipients. The angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) have definite benefits in patients with nephropathy and are believed to have renoprotective effects in most patients. However, due to their ability to cause an initial increase in SCr, these agents should be used cautiously when combined with the CNIs. In general, antihypertensive therapy should focus on agents with proven benefits in reducing the progression of cardiovascular disease and must be tailored to a patient's needs.[40]

▶ *Hyperlipidemia*

LO 9 KEY CONCEPT Hyperlipidemia is seen in as high as 60% of transplant patients.[41] As a result of elevated cholesterol levels, transplant recipients are not only at increased risk of atherosclerotic events, but also allograft vasculopathy. Hyperlipidemia, along with other types of cardiovascular disease, is now one of the primary causes of morbidity and mortality in long-term transplant survivors.[41]

Elevated cholesterol levels in transplant patients are due to age, genetic disposition, renal dysfunction, DM, proteinuria, body weight, and immunosuppressive therapy. Many of the immunosuppressive agents can produce elevations in serum lipid levels.[41]

LO 9 **Treatment** KEY CONCEPT Lowering cholesterol has shown to significantly decrease severe rejection and transplant vasculopathy and improve 1-year survival in heart transplant recipients.[42] Although these results cannot be extrapolated to other transplant populations, they do demonstrate the potential benefits of aggressive cholesterol lowering in organ transplant recipients. Due to high prevalence of cardiovascular disease among organ transplant recipients, most practitioners consider these patients to be high risk for lipid lowering. Many guidelines state a target LO 9 calculated low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL (2.59 mmol/L) in high-risk patients.[41] Note: national guidelines for treating hyperlipidemia in the general population are often followed, despite their lack of transplant recommendations. Refer to Chapter 12, Dyslipidemias, for additional information.

LO 9 **Lifestyle Modifications** Generally, lowering cholesterol in patients begins with therapeutic lifestyle changes, including a reduction in saturated fat and cholesterol intake and an increase in moderate physical activity.[43] However, lifestyle modifications alone rarely allow a patient to achieve goal LDL-C level. Modification of the immunosuppressive regimen and use of cholesterol-lowering medications are often warranted.[41]

LO 9 **Immunosuppressive Regimen Modifications** Tacrolimus has shown the propensity to cause less severe hyperlipidemia when compared with cyclosporine. Conversion from cyclosporine-based immunosuppression to tacrolimus-based immunosuppression may be one way to counteract this disease in transplant recipients. Also, the ToR inhibitors have been associated with significant changes in lipids and triglycerides; therefore, conversion from a ToR inhibitor to a CNI or belatacept may be warranted in patients receiving ToR inhibitor therapy with resistant dyslipidemia.[41]

LO 9 **Cholesterol-Lowering Agents** 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, are considered first-line therapy for hyperlipidemia in the general population.[41] However, there is some uncertainty about the pathogenesis of cardiovascular disease in transplant recipients and whether statin therapy will have similar effectiveness in organ transplant recipients. Statins have shown definite advantages when used in heart transplantation, including a reduction in LDL-C and major adverse cardiac events (MACE), as well as an apparent cardioprotective effect. In renal transplant recipients, statins lower LDL-C levels and reduce the incidence of some cardiac events; however, the ability to lower MACE has not been seen in this population. Despite these mixed results, statins are still considered the primary therapeutic option for hyperlipidemia in organ transplant recipients.[41] When choosing a statin for management of hyperlipidemia in the transplant patient, a focus on potential DDIs is warranted. It is recommended that doses of atorvastatin not exceed 10 mg daily when taken with cyclosporine due to an increased risk of myopathy and rhabdomyolysis. Use of cyclosporine in conjunction with simvastatin is considered a contraindication due to the risk of skeletal muscle effects.[41]

LO 9 Fibric acid derivatives are an excellent choice for lowering triglycerides, but are not as effective as statins at lowering LDL-C.[41] These agents play a role in conjunction with statins in patients with both elevated cholesterol and triglycerides. Nicotinic acid is very effective at improving the lipid panel, with excellent results in lowering LDL-C, as well as increasing high-density lipoprotein cholesterol (HDL-C). However, patient tolerability is a concern with this agent. The bile acid sequestrants should be avoided in transplant recipients due to their high incidence of GI adverse events, as well as their propensity for pharmacokinetic DDIs with MPA. Ezetimibe has proven safe and effective in lowering LDL-C in renal transplant recipients. Future studies are needed to establish ideal regimens involving antihyperlipidemic and immunosuppressive medications to decrease morbidity and mortality and ultimately prevent cardiovascular events.[41]

▶ *New-Onset DM after Transplantation*

LO 9 KEY CONCEPT New-onset DM after transplantation (NODAT) is a serious complication that is often underestimated by transplant practitioners.[44] Kasiske and colleagues attempted to quantify the cumulative incidence of NODAT in renal transplant recipients and found that 8.3% of patients developed NODAT at 3 months posttransplant, 12.9% at 12 months, and 22.3% at 36 months.[45] Even more alarming is that recent studies have revealed an overwhelming prevalence of impaired glucose tolerance, which is also accepted as a risk factor for long-term morbidity and mortality. NODAT is associated with a 22% higher risk of mortality. Patients with NODAT are also more likely to suffer acute rejection episodes and infectious complications.[44]

LO 9 **Prevention** KEY CONCEPT NODAT prevention mainly consists of identifying patients at risk before transplant and controlling modifiable risk factors both before and after transplantation.[44] The major modifiable risk factors are choice of immunosuppressive therapy and body mass index (BMI). For example:

- Immunosuppressive medications: Steroid minimization and possibly withdrawal are effective strategies for preventing NODAT. Also, patients with worsening blood glucose who are receiving tacrolimus may benefit from conversion to cyclosporine or belatacept.[44]
- BMI: A reduction in body weight is recommended in obese patients prior to transplant to lower their NODAT risks.[44]

LO 9 **Treatment** KEY CONCEPT Lifestyle modifications are recommended in patients who have developed or those who are at increased risk of developing NODAT.[44] Insulin therapy and oral hypoglycemic agents are often utilized in those patients in whom lifestyle modifications alone have not controlled blood glucose. Refer to Chapter 43, Diabetes Mellitus, for proper instruction on choosing the appropriate treatment regimens in patients with DM.

▶ *Neoplasia*

Cancer Screening in Transplant Patients Transplant recipients are at increased risk for malignancies (Table 55–8).[46,47] The risk of developing Kaposi sarcoma following transplantation is over 200 times that in the general population. In addition, the risk of nonmelanocytic and melanocytic skin cancer is 10 to 20 times higher compared with the nontransplanted population. Transplant recipients are at greatest risk for the types of cancers associated with viral infections, such as PTLD, cervical, and vulvovaginal cancers. Solid organ tumors like colorectal and lung cancers are two to three times higher in transplant recipients when compared with the general population. The American Cancer Society and American Transplant Society recommend cancer screening for most adults who have undergone transplantation

Table 55–8

Overall Risk of Different Types of Cancer in Transplant Patients[46,48]

Cancer	Cumulative Incidence (per 100,000)	Male	Female
Kaposi sarcoma	140	17.4	62
Kidney/ureter	1010	14.1	14.6
Lymphoma	80	6.9	29.1
Bladder	126	1.6	3.6
Esophagus	70	2.4	2.8
Cervix	180	–	5.7
Liver	220	4.2	4.5
Melanoma	320	6.9	5.2
Lung/bronchus/trachea	690	2.3	3.6
Colorectal	510	1.6	2.8
Breast	1050	4	1.1
Prostate	1740	1.6	–

Table 55–9

Cancer Screening Recommendations in Transplant Patients[46,48]

Cancer Type	General Populations	Transplant Populations
Breast	Mammography every 1–2 years for all women ≥ 50 years old Clinical breast examination every 3 years in women 20–39 years old, yearly after age 40 Monthly self-examination	Mammography every 1–2 years for all women ≥ 50 years old May undergo screening between 40 and 49 years old but no evidence for or against screening in this age group
Cervical	Annual Pap smear and pelvic examination once sexually active; after three or more tests with normal results, may decrease frequency of examinations	Annual Pap smear and pelvic examination once sexually active
Colorectal	Annual FOBT plus flexible sigmoidoscopy every 5 years for all patients ≥ 50 years old or colonoscopy and DRE every 10 years	Annual FOBT plus flexible sigmoidoscopy every 5 years for all transplant patients ≥ 50 years old
Prostate	Annual DRE and PSA for men ≥ 50 years old with 10-year life expectancy or younger men at high risk	Annual DRE and PSA measurement in all males ≥ 50 years old
Hepatocellular	Not recommended for average-risk individuals α-Fetoprotein and ultrasound every 6 months in high-risk patients (no firm supporting data)	α-Fetoprotein and ultrasound every 6 months in high-risk patients (no firm supporting data)
Skin	Skin examination every 3 years between ages 20 and 40, annually thereafter	Monthly self-examination Total body skin examination every 6–12 months by dermatologists
Renal	Insufficient evidence to support routine screening	No firm recommendations Regular ultrasound of native kidneys
Lung	Insufficient evidence to support routine screening	No firm recommendations
Ovarian	Insufficient evidence to support routine screening	No firm recommendations
Testicular	Insufficient evidence to support routine screening	No firm recommendations
Endometrial	Insufficient evidence to support routine screening	No firm recommendations

DRE, digital rectal examination; FOBT, fecal occult blood test; PSA, prostate-specific antigen.

(Table 55–9).[46,47] Although clinical research has not yet proven that potential benefits of testing outweigh the harms of testing in transplant recipients, most believe that transplant recipients should be tested and screened very closely.[46]

LO 9

Skin Cancer Skin cancer remains the most common malignancy after transplantation. The incidence of these types of cancers increases with time posttransplant, with one study showing a prevalence rate of 35% among patients within 10 years after transplant. Also, skin cancers in transplant recipients tend to grow more rapidly and are more likely to metastasize.[46]

The most common risk factors for skin cancer development after transplant include increased age; excessive ultraviolet (UV) light exposure; high degree of immunosuppression; Fitzpatrick skin types I, II, and III; history of skin cancers; and infection by human papillomavirus.[46] KEY CONCEPT Many believe that ToR inhibitors in place of CNIs in transplant recipients can reduce the risk of nonmelanoma skin carcinomas.[48]

Transplant practitioners must be vigilant about educating their patients about excessive exposure to the sun.[46] Patients should be warned about the risk of skin cancer and be advised on simple methods to limit risk:

- Wear protective clothing (ie, long-sleeved shirts, pants, dark-colored clothing)
- Use of sunscreen, sun protection factor (SPF) 30 or higher, daily to all sun-exposed skin

► *Posttransplant Lymphoproliferative Disorders*

KEY CONCEPT PTLDs are a major complication following organ transplantation.[46] Large series of case reports have demonstrated that the incidence of PTLD is 1% for renal patients, 1.8% for cardiac patients, 2.2% for liver patients, and 9.4% for heart–lung patients. The risk of developing non-Hodgkin lymphoma is nearly 50-fold higher in organ transplant recipients compared with the general population. Another risk factor is the presence of EBV. Lymphomas are the most common form of PTLD.[46,47]

Disease incidence depends on certain factors including the type of organ transplanted, age of the transplant recipient, type and degree of immunosuppression, and exposure to EBV. The mortality rate in these patients is 50%, with most dying shortly after diagnosis. It has also been demonstrated that risk of developing PTLD is greater in EBV seronegative patients.[46,47] Belatacept has a black box warning outlining an increased risk of PTLD, especially of the CNS. Patients who are EBV seronegative or have an unknown immunity to EBV should not receive belatacept. Also, immunosuppressive regimens utilizing the ALAs have been proven to increase the risk of PTLD.[46,47]

LO 9

Treatment KEY CONCEPT Treatment for PTLD is still controversial; however, the most common treatment options include reduction of immunosuppression, chemotherapy, and anti–B-cell monoclonal antibodies.[46,47] PTLD continues to be a long-term complication of prolonged immunosuppression. Current treatment options are all associated with certain risks. Prevention is the most effective treatment for PTLD. A better understanding of the disease process and risk factors involved will aid in prophylaxis and treatment of this disorder.[46,47]

► *Pregnancy*

Females of childbearing age who do not wish to become pregnant after transplantation require adequate education on preferred forms of birth control.[49] The optimal method of birth control in this patient population is the barrier method (eg, condom, diaphragm). Use of intrauterine devices and progestin-based oral contraceptives is controversial, and associated risks must

be considered prior to initiating therapy. Intrauterine devices may be less effective in the setting of immunosuppression and predispose patients to an increased risk of infection. Progestin-based contraceptives are considered a less effective form of birth control, but may be a safe option in those patients without hypertension.[49]

LO 9

Female patients considering pregnancy after transplantation should be educated extensively regarding the potential impact of pregnancy on renal function and the risks that transplantation and medical immunosuppression may present to a fetus.[49] Risks to the infant include premature birth (50%) and intrauterine growth restriction (20%), which may result in death or long-term complications, including cerebral palsy, blindness, deafness, and learning deficiencies. Patients hoping to become pregnant should wait at least 1 year after transplantation to ensure reconstitution of gonadal function posttransplant, as well as demonstrate a 1-year freedom from acute rejection.[49]

Understanding the associated risk of immunosuppressives while pregnant is paramount considering their ability to cross the placenta as well as enter breast milk.[49] Tacrolimus and cyclosporine, both pregnancy category C, are the backbone of immunosuppressive therapy and have been used safely and effectively in pregnancy posttransplant for decades. Side effects associated with CNIs such as hypertension, diabetes, and nephrotoxicity should be monitored closely in the pregnant population. The ToR inhibitors are also pregnancy category C and have not been associated with fetal malformation but should be used cautiously in pregnant patients. Corticosteroids, pregnancy category B, are recognized to be relatively safe and have been used extensively in pregnancy after transplantation. However, they carry a risk of premature membrane rupture and newborn adrenal insufficiency. More common side effects associated with corticosteroids that may cause complications in pregnancy include hypertension, diabetes, weight gain, and poor wound healing. Due to teratogenic effects in animal studies, azathioprine is considered pregnancy category D; however, it has been used extensively as an antimetabolite in pregnant transplant patients without extensive evidence of harm to the fetus. 6-Mercaptopurine has not been shown to cross the placental barrier.[49]

Currently, the MPA derivatives, both pregnancy category D, are not considered optimal immunosuppressive agents for patients who become pregnant, and alternative therapies should be pursued.[49] These agents have a FDA-approved risk evaluation and minimization strategy to help minimize fetal exposure to MPA, prevent unplanned pregnancies in patients using MPA, collect data on MPA use in pregnancy via the Mycophenolate Pregnancy Registry, and educate patients about the risks associated with the use of this medication. A less teratogenic antimetabolite, azathioprine, should be substituted for mycophenolate mofetil or enteric-coated MPA in patients who plan on becoming pregnant. The safety of ALAs and rituximab in transplantation has yet to be fully determined; however, IVIG has been widely used without any documented adverse events. Newly available immunosuppressives, belatacept and everolimus, are pregnancy category C but are not recommended for use in pregnant patients due to inadequate human data.[49]

▶ *Immunosuppressant Therapy Adherence*

Transplant recipients require strict adherence to their medication regimens to ensure optimal outcomes. Nonadherence in this population can be attributed to the complexity of the regimens coupled with the variability in drug dosing, need for therapeutic drug monitoring, avoidance of potential DDIs, infectious risks, and drug toxicities. The incidence of nonadherence to immunosuppressant therapy in the first year posttransplant has been estimated to be as high as 23%.[50] This is especially alarming when one considers that 35% of all graft failures can be directly attributed to nonadherence. Risk factors associated with immunosuppressant therapy nonadherence include a history of substance abuse, personality disorders, and lack of social support. The role of the pharmacist in educating patients on the importance of their medication regimens and stressing the need for adherence is paramount in optimizing both patient and allograft survival after transplantation. Previous reports have suggested that intervention by a pharmacist posttransplant improves adherence.[50]

LO 10

Patient Encounter Part 4

The patient continues to have his posttransplant care at your renal transplant ambulatory care clinic. He returns to your clinic 1 month after the transplant.

Labs:

Na: 142 mEq/L (mmol/L)

K: 4.9 mEq/L (mmol/L)

Cl: 197 mEq/L (mmol/L)

CO_2: 19 mEq/L (mmol/L)

BUN: 24 mg/dL (8.6 mmol/L)

SCr: 0.9 mg/dL (80 µmol/L)

Glucose: 86 mg/dL (4.8 mmol/L)

Lipid panel: total cholesterol = 341 mg/dL (8.82 mmol/L); LDL-C = 179 mg/dL (4.63 mmol/L); HDL-C = 47 mg/dL (1.22 mmol/L); triglycerides = 575 mg/dL (6.50 mmol/L)

Uric Acid: 8.6 mg/dL (512 µmol/L)

Tacrolimus: 10.9 ng/mL (mcg/L; 13.5 nmol/L)

Vitals: BP = 164/95 mm Hg (162/88 mm Hg repeated); HR = 87

Medications:

- Tacrolimus 6 mg by mouth twice a day
- Mycophenolate mofetil 1000 mg by mouth twice a day
- Prednisone 10 mg by mouth once a day
- Atovaquone 1500 mg by mouth once a day
- Valganciclovir 900 mg by mouth once a day
- Metoprolol XL 100 mg by mouth once a day
- Amlodipine 10 mg by mouth once a day
- Zolpidem 10 mg by mouth once a day at bedtime

Identify why the patient is taking each agent listed.

What are some treatment options for the patient's elevated blood pressure?

What are some treatment options for the patient's elevated cholesterol?

What are some treatment options for the patient's elevated uric acid?

Design a monitoring plan for the patient's therapy.

OUTCOME EVALUATION

- Successful outcomes in solid-organ transplantation are generally measured in terms of several separate end points: (a) preventing rejection, (b) preventing immunosuppressive drug complications, and (c) improving long-term survival.
- Short-term goals revolve around reducing the incidence of acute rejection episodes and attaining a high graft survival rate. By accomplishing these goals, transplant clinicians hope to attain good allograft function to allow for an improved quality of life. These goals can be achieved through the appropriate use of medical immunosuppression and scrutinizing over the therapeutic and toxic monitoring parameters associated with each medication employed. In addition, transplant recipients should be monitored for adverse drug reactions, DDIs, and adherence with their therapeutic regimen.
- Long-term goals after organ transplant are to maximize the functionality of the allograft and prevent the complications of immunosuppression, which lead to improved patient survival. Clinicians must play multiple roles in the long-term care of transplant recipients, as not only must the patient be followed from an immunologic perspective, but practitioners must be focused on identifying and treating the adverse sequelae associated with lifelong immunosuppression including cardiovascular disease, malignancy, infection, and osteoporosis, among others. Again, limiting drug misadventures and ensuring adherence with the therapeutic regimen are important and should be stressed.

Patient Care Process

Collect Information:

- Perform a pretransplant evaluation, including taking a medication history for use of prescription, nonprescription, and complementary and alternative medications. Identify allergies to medications and other substances.
- Review all available diagnostic and laboratory data, and patient history and comorbidities to evaluate patient for transplant.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Document current medications that should be addressed prior to a surgical procedure (eg, anticoagulation, antiplatelet therapies).
- Identify comorbidities and how they may impact patient and allograft survival, and medication adherence.
- Review relevant laboratory tests (eg, DSA, PRA, infectious serologies of the recipient and donor [if known]).
- Evaluate current medications that will be continued posttransplant such as drugs to treat concomitant disease states (eg, hypertension, DM, dyslipidemia).
- For medications likely to be continued posttransplant, assess efficacy, safety, adherence, and any significant drug interactions with potential immunosuppressants or other medications following transplant. Are there any financial issues surrounding medications or access?
- Determine whether patient is taking any substance that could adversely affect transplant outcomes.
- Based on allergy history, determine whether the patient has compelling reasons to avoid center-specific immunosuppressants (eg, macrolide antibiotic allergy and tacrolimus) or antimicrobial prophylaxis (eg, sulfa allergy and SMZ-TMP).

Develop a Care Plan:

- Develop patient-specific short-term and long-term therapeutic goals.
- Propose an immunosuppressive regimen following transplantation, including:
  - Induction therapy (see Table 55–2):
    - Determine if the patient requires induction therapy based on type of organ being transplanted, recipient's history, and donor characteristics.
    - If induction therapy is warranted, assess for appropriate drug choice, dose, and duration of therapy.
  - Maintenance immunosuppressive agents (see Tables 55–2, 55–3, 55–4, and 55–5, and Figure 55–2):
    - Assess for appropriate choice, dose, and duration of therapy.
    - Assess for eligibility to utilize a steroid withdrawal regimen, or a CNI-sparing regimen.
    - Assess the need for therapeutic drug monitoring.
  - Antimicrobial prophylaxis (see Table 55–6):
    - Assess suitability of chosen prophylactic agents (eg, drug allergies, CMV donor and recipient serostatus, need for antifungal prophylaxis).
  - Medications used for comorbidities:
    - Assess appropriate selection of medications for pharmacokinetic and pharmacodynamic DDIs, need, efficacy, and side effects.
    - Determine if patient has insurance coverage and what agents are on formulary.

Implement the Care Plan:

- Educate the patient about the organ transplant, complications associated with transplantation, need for lifestyle modifications to reduce risk of complications (eg, wear sunscreen, low-sodium diet), drug therapy (including importance of adherence to therapeutic regimen and insurance/payer information), changes in drug therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address patient concerns about management of comorbidities, including medication adherence and lifestyle modifications.

(*Continued*)

Patient Care Process (*Continued*)

- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary.

Follow-up: Monitor and Evaluate:

- General therapeutic monitoring parameters based on organ transplanted and toxic monitoring parameters for medications prescribed.
- Continually evaluate the patient for presence of adverse drug reactions, drug allergies, or DDIs.
- In outpatient transplant clinic:
  - Monitor therapeutic parameters based on organ transplanted.
  - Obtain a thorough history of prescription, nonprescription, and complementary and alternative medication use.
  - Monitor the patient's maintenance immunosuppression, including adherence.
  - Assess for appropriate dose, duration of therapy, and toxic monitoring parameters for all prescribed medications.
  - Assess for new or worsening comorbid disease.
  - Antimicrobial prophylaxis:
    - Does the patient need continued prophylaxis therapy?
    - When do you stop prophylaxis?
  - Medications used for comorbidities:
    - Assess appropriate selection of medications for pharmacokinetic and pharmacodynamic DDIs, need, and efficacy.
    - Assess whether new medications are needed for existing comorbidities or new diagnoses.
  - Reassess patient-specific short-term and long-term therapeutic goals.
  - Continue with patient education regarding complications associated with transplantation, need for lifestyle modifications to reduce risk of complications (eg, wear sunscreen, low-sodium diet), and drug therapy.
  - Reemphasize the importance of adherence with therapeutic regimen.
  - Assess improvement in quality-of-life measures such as physical, psychological, and social functioning, and well-being.
  - Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status or organ function.

Abbreviations Introduced in This Chapter

6-MP	6-Mercaptopurine
ACE	Angiotensin-converting enzyme
aHUS	Atypical hemolytic uremic syndrome
ALA	Antilymphocyte antibodies
AMR	Antibody-mediated rejection
APC	Antigen-presenting cell
ARB	Angiotensin receptor blocker
ATG	Antithymocyte globulin
AUC	Area under the curve
BKV	BK virus
BMI	Body mass index
BUN	Blood urea nitrogen
C_0	Trough concentration
C_2	Drug concentration 2 hours postdose
CCB	Calcium channel blocker
$CD4^+$	Helper T-cells
$CD8^+$	Cytotoxic T-cells
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CNS	Central nervous system
CXR	Chest x-ray
CYP	Cytochrome P-450
DC	Dendritic cell
DDI	Drug–drug interaction
DM	Diabetes mellitus
DOE	Dyspnea on exertion
DRE	Digital rectal examination
DS	Double strength
DSA	Donor-specific antibody
e-ATG	Antithymocyte globulin equine
EBV	Epstein-Barr virus
ESRD	End-stage renal disease
FBS	Fasting blood sugar
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FOBT	Fecal occult blood test
FSGS	Focal segmental glomerulosclerosis
G6PD	Glucose-6-phosphate-dehydrogenase
GFR	Glomerular filtration rate
GI	Gastrointestinal
HDL-C	High-density lipoprotein cholesterol
HLA	Human leukocyte antigen
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
IgG	Immunoglobulin G
IL-2	Interleukin-2
IV	Intravenous
IVIG	Intravenous immunoglobulin
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
MAC	Membrane attack complex
MACE	Major adverse cardiac events
MHC	Major histocompatibility complex
MPA	Mycophenolic acid
MPAG	MPA-glucurinide
NK	Natural killer
NODAT	New-onset diabetes mellitus after transplantation
NYHA	New York Heart Association
P-gp	P-glycoprotein
PRA	Panel-reactive antibodies
PSA	prostate-specific antigen
PTLD	Posttransplant lymphoproliferative disorders
PyVAN	Polyomavirus-associated nephropathy

r-ATG (RATG)	Antithymocyte globulin rabbit
SCr	Serum creatinine
SL	Sublingual
SMZ-TMP	Sulfamethoxazole-trimethoprim
SOB	Shortness of breath
SOT	Solid organ transplant
SPF	Sun protection factor
SPK	Simultaneous pancreas-kidney
SS	Single strength
TCR	T-cell receptor
TDaP	Tetanus, diphtheria, and pertussis
ToR	Target of rapamycin
TPMT	Thiopurine methyltransferase
UV	Ultraviolet

REFERENCES

1. Danovitch G. Handbook of Kidney Transplantation, 5th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2009.
2. The Organ Procurement and Transplantation Network (OPTN). Available from: http://optn.transplant.hrsa.gov/data/. Updated March 2018. Accessed March 27, 2018.
3. Halloran PF. Immunosuppressive drugs for kidney transplantation. N Engl J Med. 2004;351:2715–2729.
4. Kim M, Martin ST, Townsend KR, Gabardi S. Antibody-mediated rejection in kidney transplantation: a review of pathophysiology, diagnosis, and treatment options. Pharmacotherapy. 2014;34: 733–744.
5. Gabardi S, Martin ST, Roberts KL, Grafals M. Induction immunosuppressive therapies in renal transplantation. Am J Health Syst Pharm. 2011;68:211–218.
6. Lee RA, Gabardi S. Current trends in immunosuppressive therapies for renal transplant recipients. Am J Health Syst Pharm. 2012;69:1961–1975.
7. Micromedex® Healthcare Series, (electronic version). Greenwood Village, Colorado, USA: Thomson Healthcare, Inc.; 2017.
8. Goggins WC, Pascual MA, Powelson JA, et al. A prospective, randomized, clinical trial of intraoperative versus postoperative Thymoglobulin in adult cadaveric renal transplant recipients. Transplantation. 2003;76:798–802.
9. Brennan DC, Flavin K, Lowell JA, et al. A randomized, double-blinded comparison of Thymoglobulin versus Atgam for induction immunosuppressive therapy in adult renal transplant recipients. Transplantation. 1999;67:1011–1018.
10. Hardinger KL, Schnitzler MA, Miller B, et al. Five-year follow up of thymoglobulin versus ATGAM induction in adult renal transplantation. Transplantation. 2004;78:136–141.
11. Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med. 2006;355:1967–1977.
12. Hardinger KL, Rhee S, Buchanan P, et al. A prospective, randomized, double-blinded comparison of thymoglobulin versus Atgam for induction immunosuppressive therapy: 10-year results. Transplantation. 2008;86:947–952.
13. Lebranchu Y, Bridoux F, Buchler M, et al. Immunoprophylaxis with basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. Am J Transplant. 2002;2:48–56.
14. Martin ST, Roberts KL, Malek SK, et al. Induction treatment with rabbit antithymocyte globulin versus basiliximab in renal transplant recipients with planned early steroid withdrawal. Pharmacotherapy. 2011;31:566–573.
15. Hanaway MJ, Woodle ES, Mulgaonkar S, et al. Alemtuzumab induction in renal transplantation. N Engl J Med. 2011;364: 1909–1919.
16. Citterio F, Scata MC, Romagnoli J, Nanni G, Castagneto M. Results of a three-year prospective study of C2 monitoring in long-term renal transplant recipients receiving cyclosporine microemulsion. Transplantation. 2005;79:802–806.
17. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ. 2005;331:810.
18. Gabardi S, Tran JL, Clarkson MR. Enteric-coated mycophenolate sodium. Ann Pharmacother. 2003;37:1685–1693.
19. Reinke P, Budde K, Hugo C, et al. Reduction of gastrointestinal complications in renal graft recipients after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium. Transplant Proc. 2011;43:1641–1646.
20. Ponticelli C. The pros and the cons of mTOR inhibitors in kidney transplantation. Expert Rev Clin Immunol. 2014;10(2):295–305.
21. MacDonald AS. A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation. 2001;71:271–280.
22. Karpe KM, Talaulikar GS, Walters GD. Calcineurin inhibitor withdrawal or tapering for kidney transplant recipients. Cochrane Database Syst Rev. 2017;7:CD006750.
23. Gabardi S, Baroletti SA. Everolimus: a proliferation signal inhibitor with clinical applications in organ transplantation, oncology, and cardiology. Pharmacotherapy. 2010;30:1044–1056.
24. Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg. 2008;248:564–577.
25. Martin ST, Tichy EM, Gabardi S. Belatacept: a novel biologic for maintenance immunosuppression after renal transplantation. Pharmacotherapy. 2011;31:394–407.
26. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10:535–546.
27. Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010;10:547–557.
28. Safa K, Magee CN, Azzi J. A critical review of biomarkers in kidney transplantation. Curr Opin Nephrol Hypertens. 2017;8:28–35.
29. Stegall MD, Gloor J, Winters JL, Moore SB, Degoey S. A comparison of plasmapheresis versus high-dose IVIG desensitization in renal allograft recipients with high levels of donor specific alloantibody. Am J Transplant. 2006;6:346–351.
30. Everly MJ, Everly JJ, Susskind B, et al. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. Transplantation. 2008;86:1754–1761.
31. Walsh RC, Brailey P, Girnita A, et al. Early and late acute antibody-mediated rejection differ immunologically and in response to proteasome inhibition. Transplantation. 2011;91:1218–1226.
32. Personett HA, Laub MR. Review of infectious disease prophylaxis in solid organ transplantation. Crit Care Nurs Q. 2017 Oct/Dec;40(4):383–398.
33. Martin SI, Fishman JA. Pneumocystis pneumonia in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):272–279.
34. Razonable RR, Humar A. Cytomegalovirus in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):93–106.
35. Gabardi S, Kubiak DW, Chandraker AK, Tullius SG. Invasive fungal infections and antifungal therapies in solid organ transplant recipients. Transpl Int. 2007;20:993–1015.

36. Silveira FP, Kusne S. Candida infections in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):220–227.
37. Singh N, Husain S. Aspergillosis in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):228–241.
38. Hirsch HH, Randhawa P. BK polyomavirus in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):179–188.
39. Danziger-Isakov L, Kumar D. Vaccination in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):311–317.
40. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension. 2018;71(6):1269–1324.
41. Riella LV, Gabardi S, Chandraker A. Dyslipidemia and its therapeutic challenges in renal transplantation. Am J Transplant. 2012;12:1975–1982.
42. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med. 1995; 333:621–627.
43. Riella LV, Safa K, Yagan J, et al. Long-term outcomes of kidney transplantation across a positive complement-dependent cytotoxicity crossmatch. Transplantation. 2014;97:1247–1252.
44. Rakel A, Karelis AD. New-onset diabetes after transplantation: risk factors and clinical impact. Diabetes Metab. 2011;37:1–14.
45. Liu FC, Lin HT, Lin JR, Yu HP. Impact of immunosuppressant therapy on new-onset diabetes in liver transplant recipients. Ther Clin Risk Manag. 2017:18;13:1043–1051.
46. Asch WS, Bia MJ. Oncologic issues and kidney transplantation: a review of frequency, mortality, and screening. Adv Chronic Kidney Dis. 2014;21:106–113.
47. Gottschalk S, Rooney CM, Heslop HE. Post-transplant lymphoproliferative disorders. Annu Rev Med. 2005;56:29–44.
48. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation. 2009;87:233–242.
49. Josephson MA, McKay DB. Women and transplantation: fertility, sexuality, pregnancy, contraception. Adv Chronic Kidney Dis. 2013;20:433–440.
50. Leven EA, Annunziato R, Helcer J, et al. Medication adherence and rejection rates in older vs younger adult liver transplant recipients. Clin Transplant. 2017;31:1–7.

56 Osteoporosis

Beth Bryles Phillips and Elizabeth A. Price

LEARNING OBJECTIVES

LO

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

1. Explain the association between osteoporosis and morbidity and mortality.
2. Identify risk factors that predispose patients to osteoporosis.
3. Describe the pathogenesis of fractures in patients with osteoporosis.
4. List the criteria for diagnosis of osteoporosis.
5. Recommend appropriate lifestyle modifications to prevent bone loss.
6. Compare and contrast the effect of available treatment options on reduction of fracture risk.
7. Recommend an appropriate treatment regimen for a patient with osteoporosis and develop a monitoring plan for the selected regimen.
8. Educate patients on osteoporosis and drug treatment, including appropriate use, administration, and adverse effects.

INTRODUCTION

Osteoporosis is a common and often silent disorder causing significant morbidity and mortality and reduced quality of life. It is characterized by low bone density and loss of strength in bone tissue resulting in an increased risk and rate of bone fracture. Osteoporosis is responsible for more than 2 million fractures in the United States annually. Approximately 10 million Americans have osteoporosis, and an additional 43 million are classified as having low bone density.[1,2] The cost of care is expected to rise to $25.3 billion by 2025. It is estimated that postmenopausal white women have a 50% lifetime chance of developing an osteoporosis-related fracture, whereas men have a 20% lifetime chance.[1] Common sites of fracture include the spine, hip, and wrist, although almost all sites can be affected.

The fractures associated with osteoporosis have an enormous impact on individual patients, not only causing initial pain, but also chronic pain, loss of mobility, depression, nursing home placement, and death. Patients with vertebral fractures may also experience height loss, **kyphosis**, and decreased mobility due to limitations in bending and reaching. These patients are also at greater risk of having a future vertebral fracture. Multiple vertebral fractures may lead to restrictive lung disease and altered abdominal anatomy, while patients with hip fractures have added risks associated with surgical intervention to repair the fracture. More than 50% of patients never fully recover or regain preinjury independence, and death may occur in up to 20% of patients within 2 years after fracture.[2]

EPIDEMIOLOGY AND ETIOLOGY

Osteoporosis is the most common skeletal disorder, but only a fraction of patients are evaluated and diagnosed, and less than one in four receives treatment after a fracture.[2,3] Osteoporosis can be classified as either primary (no known cause) or secondary (caused by drugs or other diseases). Primary osteoporosis is most often found in postmenopausal women and aging men, but it can occur in other age groups as well.[1,2]

The prevalence of osteoporosis varies by age, gender, and race/ethnicity and increases exponentially after age 50.[4] As a group, African Americans have the highest BMD, while Asian Americans have the lowest.[4] Most hip fractures occur in postmenopausal white women, who also have the highest incidence of fracture when adjusted for age. The frequency of fracture in African American and Hispanic women trail far behind that of Caucasians, although hip fracture-related mortality may be higher.[5] Although both men and women lose bone as they age, postmenopausal women have accelerated bone loss due to loss of estrogen. Men have some protection from osteoporosis due to their larger initial bone mass and size and lack of accelerated bone loss associated with menopause.[6] Secondary causes of osteoporosis, such as **hypogonadism**, are found more commonly in men with **fragility fractures**.[6]

PATHOPHYSIOLOGY

The human skeleton contains both cortical and trabecular bone. Cortical bone comprises approximately 80% of the skeleton, and its density and compactness account for much of bone strength. It is generally found on the surfaces of long and flat bones. Trabecular (or cancellous) bone has a sponge-like appearance and is found along the inner surfaces of long bones and throughout the vertebrae, pelvis, and ribs. This type of bone is more susceptible to osteoporotic fractures.

Under normal circumstances, the skeleton undergoes a dynamic and constant process of bone remodeling, responding to stress and injury through continuous replacement and repair. This process is completed by the basic multicellular unit, including both osteoblasts and osteoclasts. Osteoclasts are involved with resorption or breakdown of bone and continuously create microscopic cavities in bone tissue. Osteoblasts are involved in bone formation and continuously mineralize new bone in the

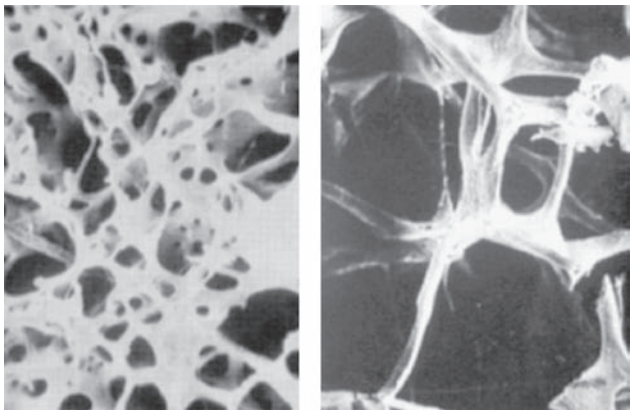

FIGURE 56–1. Normal trabecular bone (*left*) compared with trabecular bone from a patient with osteoporosis (*right*). The loss of mass in osteoporosis leaves bones more susceptible to breakage. (From Barrett KE, Barman SM, Boitano S. Brooks H. Ganong's Review of Medical Physiology, 25th ed. New York: McGraw-Hill; 2016: Figure 21–11; with permission. http://www.accesspharmacy.com.)

cavities created by osteoclasts. Until peak bone mass is achieved between the ages of 25 and 35, bone formation exceeds bone resorption for an overall increase in bone mass. Figure 56–1 illustrates the difference between normal and osteoporotic bone.

In osteoporosis, an imbalance in bone remodeling occurs. Most commonly, osteoclastic activity is enhanced, resulting in overall bone loss. However, a reduction in osteoblastic activity and bone formation also occurs in certain types of osteoporosis. Due to a decrease in endogenous estrogen, bone remodeling accelerates during menopause, and a substantial amount of bone is lost during the first 5 years after menopause. After this initial decline, bone loss continues to occur at a slower rate. The resultant bone loss and change in bone quality predispose patients to low-impact or fragility fractures.

CLINICAL PRESENTATION AND DIAGNOSIS

See accompanying text box for the clinical presentation of osteoporosis.

KEY CONCEPT The National Osteoporosis Foundation (NOF) recommends evaluating all postmenopausal women and men older than 50 years for osteoporosis risk and need for further diagnostic assessment. Many risk factors for osteoporosis and osteoporotic fractures are predictors of low bone mineral density (BMD) (Table 56–1). The risk for osteoporosis generally increases as the number of risk factors increases, and the risk of fractures increases as BMD decreases. Because osteoporosis is commonly caused by secondary factors (Table 56–2), medical history, medication history, and laboratory values should be evaluated to determine if further workup is needed.

Clinical Presentation of Osteoporosis

General

Many patients with osteoporosis are asymptomatic unless they experience a fragility fracture.

Symptoms of Fragility Fracture

Pain at the site of the fracture or immobility.

Signs

Height loss (> 2 cm), spinal kyphosis ("dowager's hump"), fragility fracture especially of the hip or spine.

Table 56–1

Risk Factors for Osteoporosis and Osteoporotic Fractures[1,2]

Risk Factors for Osteoporosis	Risk Factors for Falling and Fractures
Low bone mineral density[a]	Poor health/frailty
Female sex[a]	Impaired gait or balance
Age over 65[a]	Recent falls
Race/ethnicity[a]	Cognitive impairment
History of previous low trauma (fragility) fracture as an adult[a]	Impaired vision
Osteoporotic fracture in a first-degree relative (especially parental hip fracture)[a]	Environmental factors (eg, stairs, throw rugs, pets, poor lighting)
Low BMI or body weight (under 57.6 kg)[a]	Medications (eg, opioids, psychotropics, anticonvulsants)
Premature menopause (before 45 years old)[b]	
Secondary osteoporosis[b] (especially rheumatoid arthritis)[a]	
Oral glucocorticoid therapy[a]	
Current cigarette smoking[a]	
Alcohol intake (three or more drinks daily)[a]	
Low calcium intake	
Low physical activity	
Minimal sun exposure	

[a]Major risk factors used in the World Health Organization (WHO) fracture risk model.

[b]Secondary causes in the FRAX tool: type 1 diabetes, adult osteogenesis imperfecta, longstanding untreated hyperthyroidism, hypogonadism, premature menopause (before age 45), chronic malnutrition, malabsorption, and chronic liver disease.

BMI, body mass index.

Adapted from O'Connell M, Borhert JS. Osteoporosis and Osteomalacia In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017: Table 92–1; with permission..

Diagnostic Assessment

The diagnostic assessment for osteoporosis may include an assessment of BMD, vertebral imaging, laboratory workup, and other factors for secondary causes of osteoporosis, and biochemical markers of bone turnover. KEY CONCEPT Osteoporosis may be diagnosed by low bone density as determined by BMD or established history of low-trauma hip or vertebral fracture in adulthood.[1]

▶ *Measurement of Bone Mineral Density*

Osteoporosis is characterized by weakened bone tissue, and BMD is the best measure of bone strength, predicting approximately 70% of bone strength.[7] Low BMD is associated with an increased risk of fractures. BMD can be measured at various sites throughout the skeletal system and by various methods. Dual-energy x-ray absorptiometry (DXA) can be used to measure

Table 56–2[1,2]

Medical Conditions and Drugs Associated with Osteoporosis or Low Bone Mass

Medical Conditions	Drugs
Alcoholism	Anticoagulants (heparin, warfarin)
Chronic kidney disease	Anticonvulsants (phenytoin, phenobarbital)
Chronic obstructive pulmonary disease	Aromatase inhibitors (anastrozole, exemestane, letrozole)
Cushing syndrome	Cytotoxic drugs (eg, methotrexate, cisplatin)
Cystic fibrosis	Glucocorticoids (5 mg or more of prednisone daily or equivalent for at least 3 months)
Diabetes mellitus	Gonadotropin-releasing hormone analogs (leuprolide acetate, nafarelin, goserelin)
Eating disorders	Immunosuppressants (eg, tacrolimus)
GI disorders (eg, gastrectomy, malabsorption syndromes)	Lithium
Hematologic disorders (eg, hemophilia)	Medroxyprogesterone acetate
Hyperparathyroidism	Proton pump inhibitors
Hyperthyroidism	Selective serotonin reuptake inhibitors
Hypogonadal states	Thiazolidinediones
Organ transplantation	Thyroid supplements (due to over-replacement)
Skeletal cancer (eg, myeloma)	Total parenteral nutrition
Vitamin D deficiency	

central (hip and/or spine) and peripheral (heel, forearm, or hand) sites. Quantitative ultrasound, peripheral quantitative computed tomography, radiographic absorptiometry, and single-energy x-ray absorptiometry are used to measure peripheral sites.

The World Health Organization (WHO) recommends a standardized approach to measuring BMD for diagnosis of osteoporosis using central measurement of BMD by DXA.[2] Preferred sites for central measurement include the total hip, femoral neck, and lumbar spine. Some instruments used for peripheral bone densitometry are portable, allowing bone density to be measured in pharmacies and health-fair screening booths. In addition to accessibility, peripheral measurement of BMD is generally less expensive than central DXA, making it an attractive option for many patients. Peripheral BMD testing is useful in identifying patients who are candidates for central DXA and who are at increased risk of fracture, but it should not be used for diagnosis.

Once the BMD report is available, *T*-scores and *Z*-scores are used to interpret the data. The *T*-score is the number of standard deviations from the mean BMD in healthy, young, white women. Osteoporosis is defined as a *T*-score more than –2.5 standard deviations below the mean BMD in young adults (Table 56–3). Osteopenia, or low bone mass that may eventually lead to osteoporosis, is defined as a *T*-score between –2.5 and –1.0. The *Z*-score, defined as the number of standard deviations from the mean BMD of age- and sex-matched controls, is similar to the *T*-score but is corrected for both age and sex of the patient. *Z*-scores may be more clinically relevant in evaluating BMD in premenopausal women, men younger than the age of 50, and patients who may have secondary causes for low BMD.

▶ *Screening and Risk Factor Assessment*

The NOF recommends BMD measurements in the following groups: women age 65 and older, men age 70 and older, perimenopausal women and men age 50 to 69 with risk factors,

Table 56–3

World Health Organization (WHO) Definition of Osteoporosis

Classification	*T*-Score[a]
Normal	–1 or greater
Osteopenia	Between –1 to –2.5
Osteoporosis	Less than –2.5

[a]*T*-score is the number of standard deviations above or below the mean bone mineral density in young adults.

anyone with a fracture after age 50, and adults with a secondary cause for osteoporosis.[1]

FRAX (see *www.shef.ac.uk/FRAX*) is an additional tool developed by the WHO to evaluate an individual's 10-year probability of developing hip and major osteoporotic fractures based on femoral neck BMD *T*-score, age, and other risk factors.[1] The intended use is for men and women older than 40 years. The FRAX tool has not been validated for patients with previous or current use of pharmacotherapy to treat osteoporosis. Although the *T*-score is helpful in calculating risk of fracture with FRAX, fracture risk may be calculated without it.

▶ *Vertebral Imaging*

Vertebral fractures cause significant morbidity and mortality among patients with osteoporosis. They are often clinically silent, widespread, frequently recur, and commonly go undiagnosed. For these reasons, vertebral imaging is recommended in high-risk patients: (a) central *T*-score less than –1.0 in women age 70 and older and men age 80 and older; (b) central *T*-score less than –1.5 in women age 65 to 69 or men age 70 to 79; and (c) postmenopausal women and men age 50 and older who have had a fragility fracture in adulthood, reported decrease in height of 4 or more centimeters, documented reduction in height of 2 or more centimeters, or long-term glucocorticoid therapy.[1] Patients may receive vertebral imaging through traditional x-ray or lateral vertebral fracture assessment (VFA) available on some DXA machines.

▶ *Laboratory Evaluation*

Laboratory assessment has little value in diagnosing osteoporosis but can be beneficial in identifying or excluding secondary causes of bone loss, or for monitoring drug therapy. Screening laboratory tests for the most common causes of secondary osteoporosis include complete blood cell count, serum chemistries (electrolytes with calcium, phosphorus, and liver enzymes), vitamin D, and urinalysis. Bone turnover markers (BTMs), such as serum C-terminal telopeptide (S-CTX) and serum carboxy-terminal propeptide of type I collagen (PINP), measure skeletal activity and may play a role in monitoring efficacy of drug therapy. For example, a decrease in S-CTX suggests fracture risk reduction and effective treatment with antiresorptive therapy. Due to high assay variability, measuring BTMs for drug absorption, adherence, or efficacy should only be considered for patients in whom treatment decisions may be dependent on response to therapy or identifying nonresponders to therapy.[2]

TREATMENT

Desired Outcomes

KEY CONCEPT Treatment goals for osteoporosis include: (a) preventing fractures; (b) maintaining or increasing BMD; (c) preventing secondary causes of bone loss; and (d) reducing morbidity and

Patient Encounter Part 1: Patient History

HPI: A 76-year-old white woman presents to the clinic with her daughter for follow-up on her bone mineral density test results. She takes no prescription medication to prevent osteoporotic fracture. She takes calcium carbonate (Tums) approximately once a week for heartburn, in addition to omeprazole daily. Milk upsets her stomach, so she usually drinks tea, diet soda, or occasionally fruit juice. She is unable to eat much cheese or dairy products. She reports occasional gardening for exercise. Her diabetes has been well controlled with diet and metformin. She is motivated to keep her diabetes under control because she states she would be unable to self-administer daily insulin injections. She has thought about quitting smoking but is not ready to do so at this time. She reports tolerating her medications well and reports no problems. She lives alone in her own home in a rural community. She no longer drives and is dependent on her daughter who lives 2 hours away to take her to medical appointments. She does not like coming to the doctor because her daughter has difficulty getting time off work to take her to appointments. Her daughter comes to visit approximately once a month.

PMH: DM type 2, HTN, hyperlipidemia, GERD, lactose intolerance, osteoarthritis.

FH: Father died at age 76 with Alzheimer disease; mother died at age 92 with history of breast cancer and osteoporotic fracture of the hip; sister alive and well at age 69.

SH: Homemaker; smoked two packs a day for 40 years, now smokes 1/2 pack daily; denies alcohol use.

Meds: Acetaminophen 1000 mg TID as needed for joint pain, metformin 500 mg twice daily; lisinopril 10 mg daily; atorvastatin 40 mg daily, omeprazole 20 mg daily; calcium carbonate (Tums) 500 mg as needed.

Do any symptoms suggest the presence of osteoporosis?

What risk factors for osteoporosis does this patient have as defined by the World Health Organization?

What diseases or medications could contribute to osteoporosis in this patient?

What are her recommended daily intakes for calcium and vitamin D?

How could she incorporate more calcium into her diet?

mortality associated with osteoporosis. Strategies to prevent fractures include maximizing peak bone mass, reducing bone loss, and using precautions to prevent falls leading to fragility fractures.

Nonpharmacologic Therapy

▶ *Modification of Risk Factors*

Some osteoporosis risk factors (see Tables 56–1 and 56–2) are nonmodifiable, including family history, age, ethnicity, gender, and concomitant disease states. Other risk factors for bone loss may be minimized by early intervention, including smoking, low calcium intake, poor nutrition, inactivity, heavy alcohol use, and vitamin D deficiency. To avoid certain risk factors and maximize peak bone mass, efforts must be directed toward osteoporosis prevention at an early age.

▶ *Nutrition*

A healthy diet is essential to ensure sufficient nutrient intake and appropriate weight maintenance. Dietary calcium intake is important for achieving peak bone mass and maintaining bone density. Good dietary sources of calcium include dairy products, fortified juice, cruciferous vegetables (eg, broccoli, kale), salmon, and sardines (Table 56–4). Dietary intake generally provides 600 to 700 mg/day of calcium for men and women 50 and older. Supplementation to achieve recommended intake not attained by diet alone is important for primary prevention, as well as for those with a diagnosis of osteoporosis.

Adequate dietary intake of vitamin D is essential for calcium absorption. The most common source of vitamin D comes from exposure to sunlight. Ultraviolet rays from the sun promote synthesis of vitamin D_3 (cholecalciferol) in the skin, generally occurring within 15 minutes of direct sunlight exposure to bare skin without sunscreen. However, during the winter months, patients living in northern latitudes are not able to obtain the type of exposure that results in vitamin D synthesis.[2] It is recommended that individuals receive twice weekly sun exposure to ensure optimal synthesis. Vitamin D may also be found in some dietary sources, including fortified milk, egg yolks, salt-water fish, and liver.

▶ *Exercise*

Exercise can help prevent fragility fractures. Weight-bearing exercise such as walking, jogging, dancing, and climbing stairs can help build and maintain bone strength. Muscle-strengthening or resistance exercises can help improve and maintain strength, agility, and balance, which can reduce falls.[1] It is important to develop and maintain a lifelong routine of weight-bearing and resistance exercise, because the benefits on bone can be lost after cessation of the exercise program.[1]

Table 56–4

Foods Containing Approximately 300 mg of Elemental Calcium

1 cup[a] skim milk
1 cup soy milk (calcium-fortified)
1 cup yogurt
1½ oz[b] cheddar cheese
1½ oz jack cheese
1½ oz Swiss cheese
1½ oz part-skim mozzarella
4 tablespoonfuls[c] grated Parmesan cheese
8 oz tofu
1 cup greens (collards, kale)
2 cups broccoli
4 oz almonds
2 cups low-fat cottage cheese
3 oz sardines with bones
5 oz canned salmon
1 cup orange juice (calcium-fortified)

[a]One cup = 240 mL.

[b]One ounce (1 oz) = 28 g.

[c]One tablespoon ≈ 15 mL.

▶ *Falls Prevention*

The threshold at which individual patients develop a fracture varies, and other factors, such as fall risk, may play a role in fracture susceptibility. For this reason, fall history and evaluation of risk factors for falling should also be included in the initial evaluation. Patients with frailty, poor vision, hearing loss, or those taking medications affecting balance are at higher risk for falling and subsequent fragility fractures.[1,2]

A number of medications have been associated with an increased risk of falling, including drugs affecting mental status such as antipsychotics, benzodiazepines, tricyclic antidepressants, sedative/hypnotics, anticholinergics, and corticosteroids. Some cardiovascular and antihypertensive drugs can also contribute to falls, especially those causing orthostatic hypotension.[1] Efforts to decrease the risk of falling include balance training, muscle strengthening, removal of hazards in the home, installation of fall reduction measures such as handrails, and discontinuation of predisposing medications.[1,2] Patients with underlying physical and functional deficits may also benefit from physical and occupational therapy intervention to augment fall prevention strategies.[1,2]

Pharmacologic Treatment (Figure 56–2)

KEY CONCEPT The NOF recommends that all men and women older than 50 years be considered for pharmacologic treatment if they meet **any** of the following criteria: (a) history of hip or vertebral fracture, (b) *T*-score –2.5 or less at femoral neck or spine, or (c) osteopenia and at least a 3% 10-year probability of hip fracture or at least a 20% 10-year probability of major osteoporosis-related fracture as determined by FRAX.[1]

▶ *Calcium and Vitamin D*

KEY CONCEPT Calcium and vitamin D supplements to meet requirements should be added to all drug therapy regimens for osteoporosis to increase BMD and decrease the risk of hip and vertebral fractures.

Calcium plays an important role in maximizing peak bone mass and decreasing bone turnover, thereby slowing bone loss. When the calcium supply is insufficient, calcium is taken from bone stores to maintain the serum calcium level. Adequate calcium consumption is essential to prevent this from occurring and may also correct secondary hyperparathyroidism in elderly patients.

The NOF recommends a daily calcium intake of 1000 mg for men between the ages of 51 to 70 and a higher intake of 1200 mg for women older than 51 and men older than 71.[1] When these requirements cannot be achieved by diet alone, appropriate calcium supplementation is recommended. Intakes over 1200 to 1500 mg/day may increase the risk of developing kidney stones,[1] and supplementation greater than 2500 mg/day may lead to hypercalciuria and hypercalcemia. Additionally, excessive calcium supplementation may be associated with an increased risk of cardiovascular events.[8,9]

Calcium supplements are available in a variety of calcium salts and dosage forms. Daily calcium requirements are reported as elemental calcium. However, many product labels list calcium content in the salt form, so the percentage of elemental calcium must be known to calculate the elemental calcium content per tablet. A number of factors, including a single large intake of calcium, can limit calcium absorption, and special consideration must be given to calcium dosing to maximize absorption. Supplement doses should be limited to 500 to 600 mg of elemental calcium per dose, and absorption parameters, elemental calcium content, and adherence should be considered when choosing an appropriate supplement. Similar to other over-the-counter (OTC) products, various formulations may be included under the same general brand name (eg, Tums®), so product labeling is very important in determining the amount of calcium contained in the product. Table 56–5 lists several common OTC products with their calcium and vitamin D content.

Calcium carbonate should be taken with food to maximize absorption. Elderly patients or patients receiving proton pump inhibitors or H_2-receptor antagonists may have difficulty absorbing calcium supplements due to reduced stomach acidity. Calcium citrate may be better absorbed in these situations because an acid environment is not needed for absorption; it may be taken with or without food.

Common adverse effects include constipation, bloating, cramps, and flatulence, especially with calcium carbonate. Changing to a different salt form may alleviate symptoms for some patients. Calcium salts may reduce the absorption of iron and some antibiotics, such as tetracycline and fluoroquinolones. To mitigate absorption issues, calcium supplements should be administered 2 hours prior to or four hours after antibiotic or iron therapy.

Vitamin D is crucial for bone health. It is needed for calcium absorption and may aid in balance and reduce fall risk, enhance bisphosphonate efficacy, improve BMD, and reduce fracture risk.[2] The NOF recommends a daily vitamin D intake of 800 to 1000 IU daily for all adults age 50 and older.[1]

Vitamin D is available as a single entity, in combination with varying amounts of calcium salts, and in many multivitamin preparations. To avoid hypercalciuria and hypercalcemia, the maximum recommended dose for chronic use in most patients is 4000 IU/day.[10] High-dose ergocalciferol (vitamin D_2), 50,000 IU, is available by prescription only and is generally reserved for patients with vitamin D deficiency, whereas cholecalciferol (vitamin D_3) is available over-the-counter.

Patients at risk for vitamin D deficiency include elderly patients with malabsorption syndromes, chronic renal insufficiency, other chronic diseases, and those with limited sun exposure.[1] Frail, older patients in particular are at increased risk of deficiency due to decreased exposure to sunlight and subsequent decreased vitamin D synthesis in the skin, decreased GI absorption of vitamin D, and reduction in vitamin D_3 synthesis.

Many adults have low vitamin D levels, and vitamin D deficiency is an important secondary cause of osteoporosis.[2] Although vitamin levels should only be drawn in patients at risk for deficiency, patients with osteoporosis meet this criterion.[11] Laboratory determination of 25-hydroxyvitamin D levels should occur prior to the start of pharmacotherapy to determine whether supplementation is adequate or whether treatment of deficiency is needed. The Endocrine Society Vitamin D Deficiency clinical practice guideline recommends treatment with ergocalciferol 50,000 IU once weekly (or cholecalciferol equivalent of 6000 IU daily) for 8 to 12 weeks.[11] After 25-hydroxyvitamin D levels have risen above 30 ng/mL (75 nmol/L), cholecalciferol doses of 1500 to 2000 IU or more may be needed to maintain 25-hydroxyvitamin D levels between 30 and 60 ng/mL (75 and 150 nmol/L).[2,11]

▶ *Bisphosphonates*

KEY CONCEPT Bisphosphonates are first-line therapy for osteoporosis in both men and women due to established efficacy in preventing hip and vertebral fractures. They decrease bone resorption by rapidly binding to the bone matrix and inhibiting osteoclast activity. Once attached to bone tissue, bisphosphonates are released very slowly over several years. Alendronate, risedronate, and zoledronic acid are approved for use in men and women, whereas ibandronate is only approved for postmenopausal

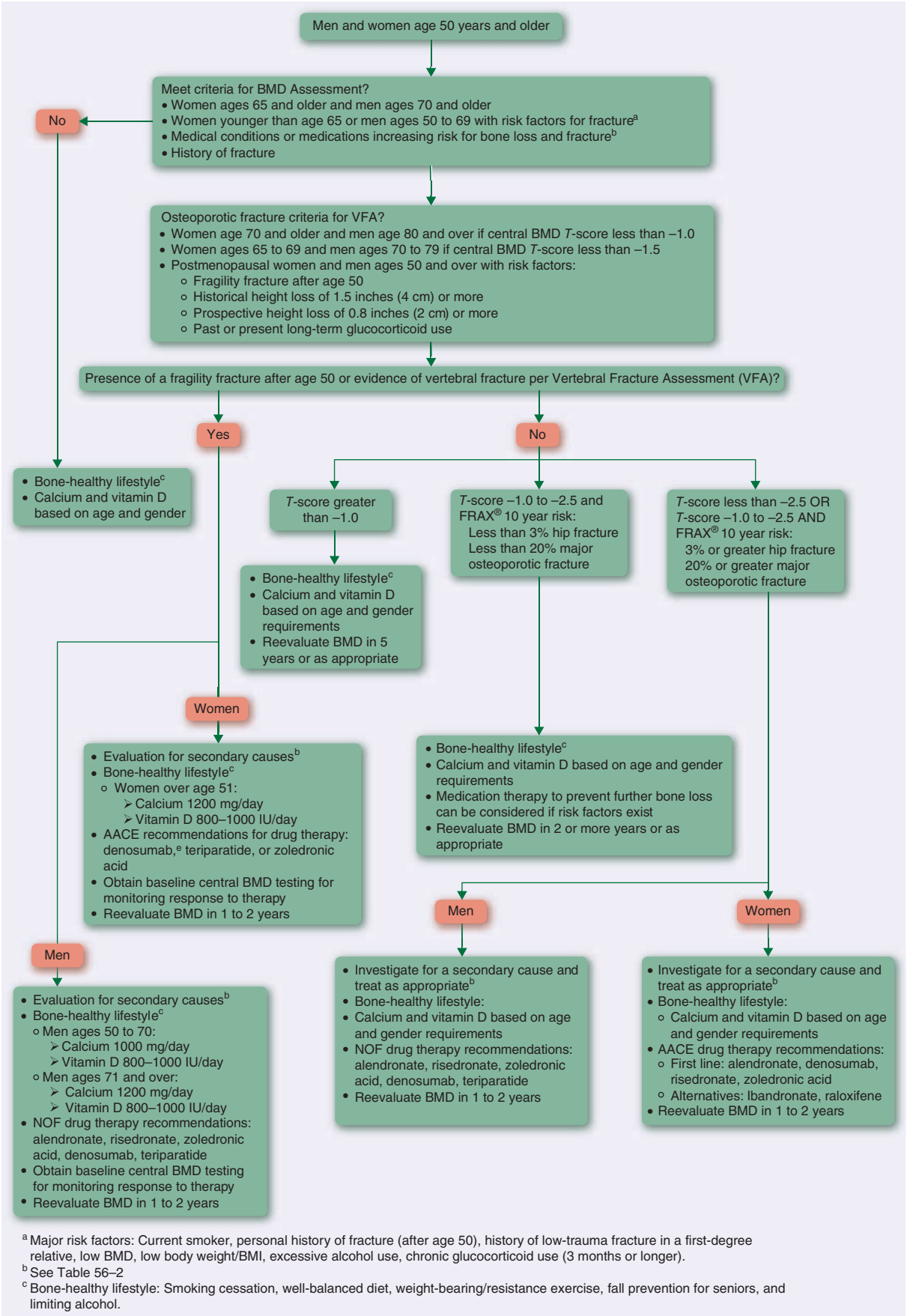

FIGURE 56–2. Algorithm for the management of osteoporosis in postmenopausal women and men ages 50 and older. (Adapted from O'Connell M, Borhert JS. Osteoporosis and Osteomalacia In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2017: Figure 92–3; with permission.)

Table 56–5

Calcium and Vitamin D Content of Common Supplements

Product (% Elemental Calcium)	Elemental Calcium per Tablet (mg)	Vitamin D per Tablet (IU)
Calcium Carbonate (40%)		
Tums 500 mg	200	—
Tums E-X 750 mg	300	—
Tums ULTRA 1000 mg	400	—
Os-Cal 500	500	—
Os-Cal 500 + D	500	200
Os-Cal Ultra	600	200
Caltrate 600	600	—
Caltrate 600 + D	600	200
Caltrate 600 + Soy	600	200
One-A-Day Women's Multivitamin	450	400
Rolaids 550 mg	220	—
Viactiv	500	100
Calcium Citrate (24%)		
Citracal	200	—
Citracal 250 mg + D	250	62.5
Citracal + D	315	200
Calcium Phosphate, Tribasic (39%)		
Posture – D	600	125
Calcium Lactate (13%)	85	—
Calcium Gluconate (9%)	60	—

osteoporosis. Ibandronate is generally considered a second-line bisphosphonate due to lack of documented efficacy in nonvertebral fractures in prospective trials.[2,12] Table 56–6 contains comparative dosing for the bisphosphonates. Although some bisphosphonates were approved for prevention doses at the time of initial data submission to the Food and Drug Administration (FDA) for approval, patients who meet criteria for drug treatment of osteoporosis should be given treatment doses.

Bisphosphonates can increase BMD by up to 5% to 8% in the lumbar spine and up to 3% to 6% in the hip.[13,14] BMD continues to increase with long-term bisphosphonate therapy of 7 to 10 years.[15,16] Although increases in BMD have been reported at other sites, most of the clinically significant increases occur in the hip or spine and are an important marker of treatment effects. Bisphosphonate therapy can also prevent vertebral and nonvertebral fractures, decreasing the vertebral fracture risk by as much as 40% to 50% with oral bisphosphonates and up to 70% with zoledronic acid.[1,17] IV zoledronic acid has also shown a 28% decrease in mortality associated with hip fracture.[18] Upon discontinuation of therapy, clinical trials with alendronate and zoledronic acid have shown sustained benefits in fracture risk reduction up to 5 years after therapy is stopped.[2] Long-term administration of bisphosphonates is considered beneficial in patients at high risk for fracture. However, for women who must discontinue bisphosphonate therapy due to intolerance or adverse events, improvements in BMD may be sustained.[16]

Patients may experience bone, muscle, or joint pain that resolves upon bisphosphonate discontinuation. Upper GI adverse effects occur in up to 20% of patients receiving oral bisphosphonates and are often related to inappropriate administration. These adverse effects range from relatively mild nausea, vomiting, and diarrhea to more severe esophageal irritation and esophagitis. Other common adverse reactions include dyspepsia, abdominal pain, nausea, and esophageal reflux. Esophageal ulceration, erosions with bleeding, perforation, stricture, and esophagitis may also occur. Advanced age, previous upper GI tract disease, and use of nonsteroidal anti-inflammatory drugs also increase the risk for GI adverse events, whereas once-weekly administration of oral bisphosphonates may decrease the risk.

IV zoledronic acid is associated with acute-phase reactions (flu-like symptoms) that can last for days, such as headache, arthralgia, myalgia, and fever.[1,2,18] Pretreatment with acetaminophen may prevent these symptoms.[2] Patients with moderate to severe renal impairment, severe dehydration, or taking concomitant diuretics or nephrotoxic drugs may be at higher risk of developing acute renal failure with zoledronic acid. Laboratory monitoring, including serum creatinine, alkaline phosphatase, phosphate, magnesium, and calcium, is recommended prior to administration of each zoledronic acid dose.

Serious but rare adverse events associated with long-term bisphosphonate use include **osteonecrosis** of the jaw (ONJ),[19,20] **subtrochanteric** fractures,[19] and nonvertebral atraumatic fractures.[20] These events may be related to oversuppression of bone turnover causing weakening of bone structure related to inhibition of osteoclastic activity.[21,22] ONJ is less common in patients receiving bisphosphonates for osteoporosis than other indications. Patients should complete major dental work prior to initiation of bisphosphonate therapy.[23,24] The rate of subtrochanteric fractures also increases with more than 5 years of use, and the risk appears to decline upon discontinuation of therapy.[23,25,26] Patients may experience thigh or groin pain prior to the fracture. The American Association of Clinical Endocrinologists (AACE) recommends a drug holiday after 5 years of oral bisphosphonate use and 3 to 6 years of IV bisphosphonate use for lower risk patients.[2] Esophageal cancer has also been reported with long-term therapy, but data are currently inconclusive.[2]

Oral bisphosphonates are poorly absorbed, and administration with food or calcium supplementation further reduces absorption. Proper drug administration is important for optimal absorption and prevention of adverse effects. See Table 56–6 for recommended administration.

Contraindications to bisphosphonates include hypersensitivity, hypocalcemia, pregnancy and renal impairment (creatinine clearance < 30 to 35 mL/min [0.50–0.58 mL/s]), or failure. Patients with esophageal abnormalities delaying swallowing (eg, **achalasia**, **stricture**), GI malabsorption (eg, celiac disease, Crohn disease, or gastric bypass), or who cannot remain upright for 30 minutes should avoid oral bisphosphonates; consider IV bisphosphonates for these patients.

▶ *Denosumab*

Denosumab is the first human monoclonal antibody FDA approved for treatment of postmenopausal osteoporosis. It is first-line therapy for women and men, and it can also be considered in patients unable to tolerate bisphosphonates due to GI contraindications or side effects and for patients with malabsorption or adherence issues.[2] Denosumab reduces nuclear factor-kappa B ligand (RANKL) action, which leads to selective inhibition of osteoclast formation, function, and survival. In contrast to bisphosphonates, the antiresorptive effects of denosumab are reversible, and beneficial effects on BMD may be lost within 2 years of discontinuation of therapy.[2]

Denosumab has been shown to increase BMD in the hip and spine by up to 6% and 9%, respectively; and decrease hip, vertebral, and nonvertebral fracture risk by up to 40%, 68%, and 20%, respectively.[27] Use of denosumab for up to 8 years has been associated with continued increases in BMD of up to 16.5% in

Table 56–6

Prescription Drug Therapy for Osteoporosis

Drug	Product Size	Indication/Usual Dose	Administration
Bisphosphonates			
Alendronate (Fosamax)	5-, 10-, 35-, 70-mg tablets; 70-mg with cholecalciferol 2800 IU; 70-mg with cholecalciferol 5600 IU; 70-mg oral solution	Prevention of PM osteoporosis: 5 mg orally daily or 35 mg orally once weekly Osteoporosis (men and women): 10 mg orally once daily or 70 mg orally once weekly Glucocorticoid-induced osteoporosis: 10 mg once daily Avoid when CrCl < 35 mL/min (0.58 mL/s)	Take after an overnight fast with 6–8 oz (180–240 mL) plain water while sitting or standing upright at least 30 minutes prior to morning meal. Do not lie down for 30 minutes after administration. Do not take with other medications or fluids. Do not crush, chew, or suck on the tablet.
Ibandronate (Boniva)	150-mg tablets; 3-mg/3 mL injection	PM osteoporosis: 150 mg orally once monthly; 3 mg IV push over 15–30 seconds every 3 months Avoid when CrCl < 30 mL/min (0.5 mL/s)	Same as alendronate except administer at least 1 hour prior to morning meal and refrain from lying down for 1 hour after administration.
Risedronate (Actonel, Atelvia)	5-, 30-, 35-, 75-, 150-mg tablets; 35-mg delayed release tablets	PM osteoporosis: 5 mg orally daily, 35 mg orally once weekly, 75 mg on 2 consecutive days each month, or 150 mg once monthly Male osteoporosis: 35 mg orally weekly or 150 mg orally monthly Glucocorticoid-induced osteoporosis: 5 mg orally daily Avoid when CrCl < 30 mL/min (0.50 mL/s)	Same as alendronate. Delayed release tablets may be taken with food.
Zoledronic acid (Reclast)	5 mg/100 mL IV infusion	Prevention of PM osteoporosis: 5 mg infused IV over 15 minutes or longer every 24 months Treatment of osteoporosis (men and women), glucocorticoid-induced osteoporosis: 5 mg infused IV over 15 minutes or longer every 12 months Avoid when CrCl < 35 mL/min (0.58 mL/s)	Infuse over at least 15 minutes. May premedicate with acetaminophen.
Monoclonal Antibody			
Denosumab (Prolia)	60 mg/mL SC prefilled syringe	PM or male osteoporosis, glucocorticoid-induced osteoporosis: 60 mg SC every 6 months	Inject in the upper arm, upper thigh, or abdomen. Keep refrigerated.
Osteoanabolic Agents			
Abaloparatide (Tymlos)	3120 mcg/1.56 mL pen injector (30 doses)	PM osteoporosis: 80 mcg SC daily	Inject into abdomen. Keep refrigerated.
Teriparatide (Forteo)	250 mcg/mL, 2.4-mL prefilled pen	Osteoporosis (men and women), glucocorticoid-induced osteoporosis: 20 mcg SC daily	Inject into thigh or abdominal wall. Keep pen refrigerated.
Estrogen Agonists/Antagonists			
Raloxifene (Evista)	60-mg tablets	PM osteoporosis: 60 mg daily	May be taken with or without food.
Bazedoxifene/ conjugated estrogens (Duavee)	20 mg/0.45 mg	PM osteoporosis + menopausal symptoms: one tablet daily	Only for short duration.
Calcitonin			
Calcitonin salmon (Miacalcin)	200 IU/0.9 mL, 3.7-mL nasal spray	PM osteoporosis: Nasal spray: 200 IU daily	Nasal spray: Alternate nostrils on a daily basis.

CrCl, creatinine clearance; PM, postmenopausal; SC, subcutaneously.

the lumbar spine and 6.8% in the hip without additional safety concerns.[28] Sustained reductions in fracture risk have also been shown with 6 years of use.[29]

Common adverse effects include back pain, arthralgias, fatigue, headache, dermatologic reactions, diarrhea, and nausea. Serious adverse reactions, including hypophosphatemia, hypocalcemia, dyspnea, and skin and other infections, can also occur. Patients should seek medical attention if they experience any symptoms of infection. Denosumab can worsen hypocalcemia in predisposed patients, such as those with severe kidney disease, and preexisting hypocalcemia should be corrected before initiating therapy. Suppression of bone turnover has been associated with denosumab therapy, and ONJ has also been reported.[2] Drug holidays are not recommended for denosumab therapy because, unlike the bisphosphonates, the beneficial effects on bone and fracture risk are lost once the drug is discontinued.[2]

Denosumab has a Risk Evaluation and Mitigation Strategy (REMS) program, in which the manufacturer is required by

Patient Encounter Part 2: Physical Examination and Diagnostic Tests

ROS: 4-cm height loss since middle age; (+) back and knee pain; weight decrease of 7 lbs in last 6 months with unintended weight loss

PE:

Gen: Well-developed white female in no acute distress

VS: BP 134/76 mm Hg, P 76 beats/min, RR 18 breaths/min, T 36.3°C (97.3°F), Wt 55 kg (121 lb), Ht 64 in (163 cm), BMI 20.8 kg/m^2

Chest: No crackles or rhonchi

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Spine: Mild kyphosis present, nontender

Abd: Soft, nontender, nondistended; normal bowel sounds, no hepatosplenomegaly

Ext: No clubbing, cyanosis, or edema

Labs: Na 139 mEq/L (mmol/L); K 4.0 mEq/L (mmol/L); SCr 0.9 mg/dL (80 µmol/L); A1C 6.3% (0.063; 45 mmol/mol hemoglobin); 25(OH)D 21 ng/mL (52 nmol/L)

Bone Densitometry by DXA

- BMD of femoral neck: *T*-score = –1.8
- BMD of lumbar spine: *T*-score = –2.4

Vertebral Fracture Assessment: L1 wedge compression fracture present

What additional risk factors and signs of osteoporosis are present in this patient?

What are the goals of pharmacologic and nonpharmacologic therapy?

List at least three nonpharmacologic interventions important in her treatment plan.

What factors support pharmacotherapy for osteoporosis in this patient?

What type of supplement(s) would you recommend for this patient to meet her calcium and vitamin D requirements? Why?

the FDA to inform patients and health care providers of the risks associated with its use.[30] Denosumab is administered as a subcutaneous injection once every 6 months by a health care provider and should be stored in the refrigerator until administration. Once at room temperature, the vial or prefilled syringe must be used within 14 days.

▶ *Osteoanabolic Therapy*

Abaloparatide and teriparatide are osteoanabolic therapies that exert beneficial effects on bone through stimulation of the parathyroid hormone (PTH) type 1 receptor. Activation of this receptor promotes osteoblastic activity and bone formation but may also enhance bone resorption.[31] The overall net effect is an increase in BMD. These drugs should be reserved for patients with a high fracture risk or those in whom other therapies have been ineffective.[2,32] Both agents are available for self-injection as prefilled pens and administered as daily subcutaneous injections.

Teriparatide, recombinant human PTH (1–34), is FDA-approved for treatment of postmenopausal and male osteoporosis. Teriparatide increases BMD in the spine and hip by 9% and 3%, respectively; and reduces vertebral and nonvertebral fracture risk by 65% and 53%, respectively.[33]

Abaloparatide, a synthetic analog of PTH-related protein (PTHrP), was approved in 2017 for treatment of postmenopausal women at high risk of fracture based on the results of clinical trials in this population.[34] Abaloparatide increases BMD in the femoral neck and lumbar spine by up to 3.6% and 11.2%, respectively; it reduces vertebral and nonvertebral fractures by 86% and 43%, respectively, in high-risk women.[34,35]

Common adverse effects of both drugs include nausea, headache, leg cramps, dizziness, orthostatic hypotension, injection site discomfort, hypercalciuria, and hypercalcemia.[2,32] Abaloparatide may also be associated with palpitations.[35] Neither drug should be used in patients with preexisting hypercalcemia. Observations of osteosarcoma in animal studies led to the inclusion of a "black box warning" in product labeling for both drugs, but the risk has not been confirmed in humans.[2]

Patient-related concerns include cost of therapy and need for daily subcutaneous injections. Treatment is not recommended beyond 2 years, and BMD declines once treatment is stopped although sustained benefits in fracture reduction may be seen for 1 to 2 years after discontinuation.[2] The AACE recommends initiating treatment with alendronate or another bisphosphonate following osteoanabolic therapy (known as sequential therapy) to prevent these losses and maintain or provide further reduction in fracture risk.[2]

▶ *Estrogen Agonists/Antagonists*

Raloxifene has estrogen-like activity on bones and cholesterol metabolism, and estrogen antagonist activity in breast and endometrium. It reduces bone resorption and decreases overall bone turnover. It is recommended as alternative therapy after bisphosphonates, denosumab, or osteoanabolic therapies.[2]

Raloxifene has been shown to increase BMD in the vertebrae (2%–3%) and hips (1%–2%), and reduce vertebral fracture rates by as much as 55%.[36] Significant decreases in nonvertebral fractures have not been demonstrated.[2] Raloxifene has been shown to decrease the incidence of breast cancer in high-risk women. It also decreases total and low-density lipoprotein (LDL) cholesterol, which generated initial enthusiasm for additional cardiovascular benefits. However, mixed results have been seen on cardiovascular disease, stroke, and noncardiovascular mortality.[37,38]

Adverse effects of raloxifene include hot flushes, leg cramps, and increased risk of venous thromboembolism.[37] A previous history of venous thromboembolism is a contraindication to therapy. Hot flushes are very common and may be intolerable in postmenopausal women who are already predisposed to experiencing them.

Bazedoxifene, a third-generation estrogen agonist/antagonist, has similar effects to raloxifene. It is currently available only as a combination product with conjugated estrogens (Duavee) for treatment of moderate to severe vasomotor symptoms associated with menopause and for prevention of postmenopausal osteoporosis.[1] Other therapies should be considered for women who meet criteria for osteoporosis treatment.

▶ *Calcitonin*

Calcitonin is a naturally occurring mammalian hormone that plays a major role in regulating calcium levels. It inhibits bone resorption by binding to osteoclast receptors. Calcitonin is considered a last-line agent for the treatment of osteoporosis due to limited fracture prevention data.[2] Calcitonin produces a modest increase in BMD at the spine of 1% to 3% and reduces vertebral fracture risk by up to 30%.[39] However, no benefit has been demonstrated in reducing nonvertebral fractures.[2] Calcitonin is generally reserved for patients unable to tolerate or take other agents. However, it is sometimes used for relief of back pain from vertebral fractures due to data suggesting benefit for this purpose.[2]

Although salmon calcitonin is approved and available in injectable and intranasal formulations, only the intranasal formulation has documented benefit in clinical trials for management of osteoporosis. Adverse effects associated with the intranasal formulation include rhinitis, nasal irritation, and dryness. Hypersensitivity can develop with either formulation and should be considered before administering to patients with suspected risk.[2]

▶ *Hormone Therapy*

Estrogen, either alone or in combination with a progestin as hormone replacement therapy (HRT), has a long history as an effective treatment of osteoporosis. The Women's Health Initiative (WHI) trial found a 34% reduction in both vertebral and hip fractures and a 23% reduction in other fractures in postmenopausal women receiving conjugated estrogens and medroxyprogesterone.[40] However, significant risks associated with long-term HRT, including breast cancer and venous thromboembolism, have limited its use in osteoporosis.[40,41]

▶ *Combination Therapy*

Combination therapy is based on the premise that two more antiresorptive therapies with different mechanisms of action may provide more benefit on bone than monotherapy. However, this practice is currently not recommended for most patients due to high cost and lack of long-term safety and efficacy data. Combination therapy with a bisphosphonate, denosumab, or an osteoanabolic agent may be considered in cases when indications exist for raloxifene to reduce breast cancer risk or HRT to treat menopausal symptoms.[2]

▶ *Investigational Therapy*

Romosozumab, a monoclonal antisclerostin antibody administered by subcutaneous injection, has shown promising results in clinical trials.[42,43] It promotes bone formation and reduces resorption by binding to and inhibiting sclerostin, resulting in significant decreases in vertebral and nonvertebral fractures. Early adverse effects include injection site reactions, arthralgias, and skin-related hypersensitivity reactions. ONJ and atypical femur fracture were also noted. Additionally, recent clinical trials have reported mixed data on the risk of cardiovascular events.[43,44] This prompted the FDA to initially deny approval of romosozumab in 2017 and to ask for more data.[45]

Treatment of Special Populations

▶ *Glucocorticoid-Induced Osteoporosis*

Glucocorticoids (eg, prednisone, hydrocortisone, methylprednisolone, and dexamethasone) play a significant role in bone remodeling, including increasing bone resorption, inhibiting bone formation, and changing bone quality. They promote bone resorption through reduced calcium absorption from the GI tract and increased renal calcium excretion. Bone formation is reduced through inhibition of osteoblasts and decreased estrogen and testosterone production.[46] Up to 40% of patients receiving long-term oral glucocorticoids have evidence of vertebral fracture.[47] Most bone mass is lost during the initial 3 to 6 months of therapy and continues to decline slowly thereafter.[47] Fracture risk is affected by other osteoporotic risk factors, and this risk is largely reversible once glucocorticoids are discontinued.

Patient Encounter Part 3: Development of a Treatment Plan

Considering all of the information presented, develop a treatment plan for this patient. Include the following information:

Recommendations for patient-specific drug therapy including dose and frequency.

Patient education about the chosen regimen, including administration directions.

Monitoring plan for efficacy and adverse effects.

Consideration of alternate therapies if the initial therapy fails or is intolerable.

KEY CONCEPT The American College of Rheumatology (ACR) recommends oral bisphosphonate therapy for all patients age 40 and over at moderate to high risk of fracture receiving glucocorticoids (prednisone 2.5 mg or more daily or equivalent) for 3 months or longer. Nonpharmacologic therapy and optimal calcium and vitamin D intake are also recommended. For patients unable to take oral bisphosphonates, alternative therapy recommendations include IV bisphosphonates, teriparatide, denosumab, and raloxifene in that order.[47] Frequent clinical fracture risk assessment with BMD testing every 1 to 3 years is recommended while receiving glucocorticoids.[47]

OUTCOME EVALUATION

- Evaluate patients for progression of osteoporosis, including signs and symptoms of new fragility fracture (eg, localized pain), loss of height, and physical deformity (eg, kyphosis). Assess patients on an annual basis or more often if new symptoms present
- Monitor for beneficial effects on bone density. The NOF recommends a follow-up DXA scan every 2 years to monitor the effects of therapy
- Assess patients for adverse effects of therapy:
  - Oral bisphosphonates: Dyspepsia, esophageal reflux, esophageal pain, or burning, ONJ (rare), subtrochanteric fracture (rare)
  - Injectable zoledronic acid: Influenza-type symptoms related to infusion, ONJ (rare), subtrochanteric fracture (rare)
  - Denosumab: Arthralgias, dermatologic reactions, and hypocalcemia, ONJ (rare)
  - Abaloparatide and teriparatide: Nausea, headache, leg cramps, hypercalcemia, and orthostatic hypotension; also palpitations with abaloparatide
  - Raloxifene: Hot flushes, signs, or symptoms of thromboembolic disease (eg, pain, redness, or swelling in one extremity, chest pain, and shortness of breath)
  - Calcitonin salmon: Nasal irritation or burning

Patient Care Process

Collect Information:

- Perform a thorough medication history, including prescription, over-the-counter, and alternative therapies.
- Determine the patient's average daily intake of calcium and sources of vitamin D; frequency, duration and type of physical activity; and history of smoking and/or alcohol consumption.
- Review past medical and family history, recent laboratory and procedure reports, and medication allergies/intolerances.
- Test bone densitometry in patients at risk for having low bone mass or bone loss. If *T*-score is between –1.0 and –2.5, use FRAX to estimate fracture risk.
- If the patient is already receiving pharmacotherapy, assess efficacy, safety, and patient adherence. How long has the patient been on each agent? Was the patient previously treated with other agents?

Assess the Information:

- Assess risk factors for osteoporosis and the presence of secondary causes of osteoporosis.
- Assess nonpharmacologic interventions for preventing osteoporotic fractures, including nutrition and weight-bearing and muscle-strengthening exercise regimens. What is the patient's fall risk? What medications is the patient taking that could increase fall risk?
- Determine the feasible options available for the patient. Does the patient have prescription coverage? What agents are recommended on the formulary? Are there any contraindications to available treatment options?

Develop a Care Plan:

- Select therapy (including agent and dose) likely to be safe and effective for the patient (see Table 56–6).

Implement the Care Plan:

- If pharmacologic therapy is indicated, discuss therapeutic goals and expectations (eg, changes in individual *T*-scores may not necessarily correlate with benefit in fracture risk reduction).
- Educate the patient on drug therapy selected, including drug name, dose, route and method of administration, common or serious adverse reactions, adherence, and monitoring.
- Educate the patient about nonpharmacologic measures to prevent osteoporotic fractures.

Follow up: Monitor and Evaluate:

- Annually review the need for continued medication. Assess appropriate drug administration and adherence efficacy, adverse effects, and nonpharmacologic measures to prevent fractures.
- Reassess BMD every 2 years in patients on pharmacologic agents to treat osteoporosis. Vertebral imaging is appropriate if there is a documented loss in height of 2 cm or greater.

Abbreviations Introduced in This Chapter

AACE	American Association of Clinical Endocrinologists
ACR	American College of Rheumatology
BMD	Bone mineral density
BMI	Body mass index
DXA	Dual-energy x-ray absorptiometry
FDA	Food and Drug Administration
HRT	Hormone replacement therapy
NOF	National Osteoporosis Foundation
ONJ	Osteonecrosis of the jaw
WHI	Women's Health Initiative
VFA	Vertebral fracture assessment

REFERENCES

1. Cosman F, de Beur SJ, Lewiecki EM, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25:2359-2381.
2. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis—2016. Endocr Pract. 2016;22(suppl 4):1–42.
3. Wilk A, Sajjan S, Modi A, Fan CPS, Mavros P. Post-fracture pharmacotherapy for women with osteoporotic fracture: analysis of a managed care population in the USA. Osteoporos Int. 2014;25:2777–2786.
4. The North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of the North American Menopause Society. Menopause. 2010;17:25–54.
5. Cauley JA. Public health impact of osteoporosis. J Gerontol A Biol Sci Med Sci. 2013;68:1243–1251.
6. Khosla S. Update in male osteoporosis. J Clin Endocrinol Metab. 2010;95:3–10.
7. Ammann P, Rizzoli R. Bone strength and its determinants. Osteoporos Int. 2003;14(suppl 3):S13–S18.
8. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow WH, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA Intern Med. 2013;173:639–646.
9. Michaelsson K, Melhus H, Warensjo E, et al. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. BMJ. 2013;346:f228.
10. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96:53–58.
11. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–1930.
12. Demas PD, Recker RR, Chesnut CH, et al. Daily and intermittent oral ibandronate normalize bone turnover and provide significant reduction in vertebral fracture risk: results from the BONE study. Osteoporos Int. 2004;14:792–798.

13. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med. 1995;333:1437–1443.
14. Brown JP, Kendler DL, McClung MR, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int. 2002;71:103–111.
15. Boe HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004;350:1189–1199.
16. Mellström DD, Sörensen OH, Goemaere S, et al. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int. 2004;75:462–468.
17. Boe DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809–1822.
18. Lyles KW, Colón-Emeric CS, Magaziner JS, et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med. 2007;357:1799–1809.
19. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg. 2004;62:527–534.
20. Rizoli R, Akesson K, Bouxsein M, et al. Subtrochanteric fractures after long-term treatment with bisphosphonates: a European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation Working Group Report. Osteoporos Int. 2011;22:373–390.
21. Ot SM. Long term safety of bisphosphonates. J Clin Endocrinol Metab. 2005;90:1897–1899.
22. Ovina CV, Zerwekh JE, Rao DS, et al. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab. 2005;90:1294–1301.
23. Adler RA, El-Hajj Fuleihan G, Bauer DC, et al. Managing osteoporosis in patients on long-term bisphosphonate treatment: report of a task force of the American Society for Bone and Mineral Research. JBMR. 2016;31:15–35.
24. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on the medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72:1938–1956.
25. Par-Wyllie YL, Mamdani MM, Juurlink DN, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. JAMA. 2011;305:783–789.
26. FDA Drug Safety Communication: Ongoing Safety Review of Oral Bisphosphonates and Atypical Subtrochanteric Femur Fractures. U.S. Food & Drug Administration. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203891.htm. Accessed August 24, 2015.
27. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756–765.
28. McClung MR, Lewiecki EM, Geller ML, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: 8 year results of a phase 2 clinical trial. Osteoporos Int. 2013;24:227–235.
29. Bone HG, Chapurlat R, Brandi ML, et al. The effect of three or six years of denosumab exposure in women with postmenopausal osteoporosis: results from the FREEDOM extension. J Clin Endocrinol Metab. 2013;98:4483–4492.
30. Prolia (Denosumab) Risk Evaluation and Mitigation Strategy. Amgen. Available from: http://www.proliahcp.com/risk-evaluation-mitigation-strategy/. Accessed September 6, 2017.
31. Harslof T, Langdahl B. New horizons in osteoporosis therapies. Curr Opin Pharmacol. 2016;28:38–42.
32. Lexicomp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2017, August 12, 2017.
33. Ner RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434–1441.
34. Leder BZ, O'Dea LS, Zanchetta JR, et al. Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. J Clin Endocrinol Metab. 2015;100:697–706.
35. Miller PD, Hattersley G, Riis BJ, et al, for the ACTIVE study investigators. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. JAMA. 2016;316:722–733.
36. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. JAMA. 1999;282:637–645.
37. Barrett-Connor E, Mosca L, Collins P, et al. For the Raloxifene Use for The Heart (RUTH) Trial Investigators. Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women. N Engl J Med. 2006;355:125–137.
38. Grady D, Cauley JA, Stock JL, et al. Effect of raloxifene on all-cause mortality. Am J Med. 2010;123:469:e1–e7.
39. Chestnut CH, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. Am J Med. 2000;109:267–276.
40. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321–333.
41. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998;280:605–613.
42. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med. 2014;370:412–420.
43. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016;375:1532–1543.
44. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med. 2017;377:1417–1427.
45. Nainoggolan L. FDA Rejects Romosozumab for Osteoporosis, Wants More Data. Available from: https://www.medscape.com/viewarticle/882966. Accessed December 20, 2017.
46. Weinstein RS. Glucocorticoid-induced bone disease. N Engl J Med. 2011;365:62–70.
47. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol. 2017;69:1521–1537.

57 Rheumatoid Arthritis

Susan P. Bruce

LEARNING OBJECTIVES

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

LO

1. Identify risk factors for developing adult rheumatoid arthritis (RA) or juvenile idiopathic arthritis (JIA).
2. Describe the pathophysiology of RA, with emphasis on the specific immunologic components.
3. Discuss the comorbidities associated with RA.
4. Recognize the typical clinical presentation of RA or JIA.
5. Create treatment goals for a patient with RA or JIA.
6. Compare the available pharmacotherapeutic options, selecting the most appropriate regimen for a given patient.
7. Propose a patient education plan that includes nonpharmacologic and pharmacologic treatment measures.
8. Formulate a monitoring plan to evaluate the safety and efficacy of a therapeutic regimen designed for an individual patient with RA or JIA.

INTRODUCTION

Rheumatoid arthritis (RA) is a complex systemic inflammatory condition manifesting initially as symmetric swollen and tender joints of the hands and/or feet. Some patients may experience low disease activity, whereas others may present with high disease activity and/or extraarticular manifestations. The systemic inflammation of RA leads to joint destruction, disability, and premature death. Juvenile idiopathic arthritis (JIA) is the most common form of arthritis in children.

EPIDEMIOLOGY AND ETIOLOGY

RA has a prevalence of 0.5% to 1%.[1,2] Patients with RA have a 50% increased risk of premature death and a decreased life expectancy of 3 to 10 years compared with individuals without RA.[3] The underlying causes of increased mortality are unclear. RA arises from an immunologic reaction, perhaps in response to a genetic or infectious antigen. Risk factors associated with the development of RA include the following:

LO 1

- Female gender (3:1 females to males)
- Increasing age (peak onset 35–50 years of age)
- Current tobacco smoking.[4] Tobacco users are more likely to have extraarticular manifestations and to experience treatment nonresponsiveness. This risk is reduced when a patient has remained tobacco-free for at least 10 years.
- Family history of RA. Genetic studies demonstrate a strong correlation between RA and the presence of major histocompatibility complex class II **human leukocyte antigens** (HLA), specifically HLA-DRB1 haplotypes.[5] HLA is a molecule associated with the presentation of antigens to T lymphocytes.
- Emerging evidence suggests that stress may influence RA onset and disease activity. It appears that individual major stressful life events do not play a significant role. Instead, chronic presence of minor stressors (daily hassles, work and relationship stress, financial pressures) may affect the immune response and RA disease activity.[6]
- The prevalence of JIA is approximately 1 in 1000 children.[7] There are no known risk factors for JIA.

PATHOPHYSIOLOGY

LO 2

The characteristics of a **synovium** affected by RA are: (a) the presence of a thickened, inflamed membrane lining called **pannus**; (b) development of new blood vessels; and (c) influx of inflammatory cells in the synovial fluid, predominantly T lymphocytes. The pathogenesis of RA is driven by T lymphocytes, but the initial catalyst causing this response is unknown. Understanding specific components of the immune system and their involvement in the pathogenesis of RA will facilitate understanding of current and emerging treatment options for RA. The components of most significance are T lymphocytes, cytokines, B lymphocytes, and kinases.[5,8]

T Lymphocytes

The development and activation of T lymphocytes are important to maintain protection from infection without causing harm to the host. Activation of mature T lymphocytes requires two signals. The first is the presentation of an antigen by antigen-presenting cells to the T-lymphocyte receptor. Second, a ligand-receptor complex (ie, CD80/CD86) on antigen-presenting cells binds to CD28 receptors on T lymphocytes.[5]

Table 57–1

Cytokines Involved in the Pathogenesis of RA[5,8,9]

Cytokine	Source	Activity
Proinflammatory		
TNF-α	Macrophages, monocytes, B lymphocytes, T lymphocytes, fibroblasts	Induces IL-1, IL-6, IL-8, GM-CSF; stimulates fibroblasts to release adhesion molecules
IL-1	Macrophages, monocytes, endothelial cells, B lymphocytes, activated T lymphocytes	Stimulates fibroblasts and chondrocytes to release matrix metalloproteinases
IL-6	T lymphocytes, monocytes, macrophages, synovial fibroblasts	Activates T lymphocytes, induces acute-phase response, stimulates growth and differentiation of hematopoietic precursor cells; stimulates synovial fibroblasts
IL-17	T lymphocytes in synovium	Synergistic effect with IL-1 and TNF leading to increased production of proinflammatory cytokines
Anti-Inflammatory		
IL-4	CD4+ type 2 helper T lymphocytes	Inhibits activation of type 1 helper T lymphocytes, decreases production of IL-1, TNF-α, IL-6, IL-8
IL-10	Monocytes, macrophages, B lymphocytes, T lymphocytes	Inhibits production of IL-1, TNF-α, and proliferation of T lymphocytes

LO 2 Once a cell successfully passes through both stages, the inflammatory cascade is activated. Activation of T lymphocytes: (a) stimulates the release of macrophages or monocytes, which subsequently causes the release of inflammatory cytokines; (b) activates osteoclasts; (c) activates release of matrix metalloproteinases or enzymes responsible for the degradation of connective tissue; and (d) stimulates B lymphocytes and the production of antibodies.[5,8,9]

Cytokines

LO 2 Cytokines are proteins secreted by cells that serve as intercellular mediators (Table 57–1). An imbalance of proinflammatory and anti-inflammatory cytokines in the synovium leads to inflammation and joint destruction. Some of the proinflammatory cytokines are interleukin 1 (IL-1), tumor necrosis factor-α (TNF-α), IL-6, and IL-17. These proinflammatory cytokines cause activation of other cytokines and adhesion molecules responsible for recruitment of lymphocytes to the site of inflammation. Anti-inflammatory cytokines and mediators (IL-4, IL-10, and IL-1 receptor antagonist) are present in the synovium, although concentrations are not high enough to overcome the effects of the proinflammatory cytokines.[5,8,9]

B Lymphocytes

LO 2 In addition to serving as antigen-presenting cells to T lymphocytes, B lymphocytes may produce proinflammatory cytokines and antibodies.[8] Antibodies of significance in RA are **rheumatoid factors** (antibodies reactive with the Fc region of IgG) and **anticitrullinated protein antibodies** (ACPA). Rheumatoid factors are not present in all patients with RA, but their presence is indicative of disease severity and structural progression. ACPA are produced early in the course of disease. High levels of ACPA are indicative of aggressive disease and a greater likelihood of poor outcomes. Monitoring RF and ACPA may be useful to match the intensity of treatment appropriately.[10]

Kinases

LO 2 Kinases are enzymes involved in communication or signaling activities within and between cells. Activated kinases lead to cell activation and proliferation. Examples include Janus-associated kinases (JAKs) and spleen tyrosine kinase. Research is ongoing to identify additional therapeutic targets to interrupt signaling and thereby halt the inflammatory process.[11]

Comorbidities Associated with RA

LO 3 RA reduces a patient's average life expectancy, but RA alone rarely causes death. Instead, specific **comorbidities** contribute to premature death independent of safety issues surrounding the use of immunomodulating medications. KEY CONCEPT The comorbidities with the greatest impact on morbidity and mortality associated with RA are: (a) cardiovascular disease, (b) infections, (c) malignancy, and (d) osteoporosis.

▶ *Cardiovascular Disease*

More than half of all deaths in RA patients are cardiovascular related. Because a patient with RA experiences inflammation and swelling in joints, it is likely that there is inflammation elsewhere, such as in the blood vessels, termed **vasculitis**. C-reactive protein (CRP), a nonspecific marker of inflammation, is associated with an increased risk of cardiovascular disease; CRP is elevated in patients with RA. Traditional cardiovascular risk factors alone cannot explain the increased cardiovascular mortality in patients with RA. Increasing evidence suggests that the presence of RA is a cardiovascular risk similar to diabetes. Aggressive management of systemic inflammation and traditional cardiovascular risk factors (eg, blood pressure, cholesterol, tobacco use) may reduce cardiovascular mortality in this population.[12-14]

▶ *Infections*

Patients with RA have an increased risk of infections due to the underlying disease process. Older age, disease activity, and concomitant conditions (ie, renal failure, lung disease) may increase risk of infection. Additionally, prolonged glucocorticoid use may contribute to infection risk. Patients and clinicians must pay close attention to signs and symptoms of infection.[15]

▶ *Malignancy*

Cancer is the second most common cause of death in RA patients. There is an overall increased risk of malignancy and an increased risk of developing **lymphoproliferative** malignancy (eg, lymphoma, leukemia, multiple myeloma), melanoma, and lung cancer but decreased risk of developing cancer of the cervix, prostate, and digestive tract. Research is underway to understand

Table 57–2

Comparison of RA and Osteoarthritis

Characteristic	RA	Osteoarthritis
Speed of onset	Rapid (weeks to months)	Slow (years)
Gender prevalence (women:men)	3:1	1:1
Usual age of onset	Juvenile or adult (35–50 years)	Greater than 50 years
Most common joints affected	Small joints of hands (MCPs, PIPs), feet	Hands (DIPs), large weight-bearing joints (hips, knees)
Joint symptoms	Pain, swelling, warmth, stiffness	Pain, bony enlargement
Presence of inflammation	Local and systemic	None or mild, local
Duration of morning joint stiffness	Usually 60 minutes or longer	Usually less than 30 minutes
Joint pattern	Symmetric	Symmetric or asymmetric
ESR	Elevated	Normal
Synovial fluid	Leukocytosis, slightly cloudy	Mild leukocytosis
Systemic manifestations	Yes	No

DIPs, distal interphalangeal joints; ESR, erythrocyte sedimentation rate; MCPs, metacarpophalangeal joints; PIPs, proximal interphalangeal joints.

the mechanisms that increase or decrease risk of specific cancers, and how medication use independently contributes to individual risk.[15,16]

▶ *Osteoporosis*

Cytokines involved in the inflammatory process directly stimulate **osteoclast** and inhibit **osteoblast** activity. Additionally, arthritis medications can lead to increased bone loss. Bone mineral density should be evaluated at baseline and routinely using dual-energy x-ray absorptiometry.

CLINICAL PRESENTATION AND DIAGNOSIS

See the box on next page for the clinical presentation of RA.

Diagnosis

Both osteoarthritis and RA are prevalent in the US population, but they differ in presentation (Table 57–2). Because management of the two conditions differs significantly, early evaluation and diagnosis are essential to maximize an individual's care.

In 2010, The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) released classification criteria for RA (Table 57–3).[1] The goal was to identify a subset of patients with undifferentiated synovitis who were at high risk for chronic and erosive disease. The criteria are intended to help identify patients earlier in the course of disease. This will allow researchers to determine whether earlier introduction of medications alters the disease process. The criteria were developed as a tool for research purposes, but they are also helpful to guide clinical diagnosis. Patients with at least one joint with definite clinical synovitis that is not explained by another disease should be evaluated for RA.

Certain clinical features of RA are considered in diagnosis and treatment decisions because they may be related to rapid disease progression. KEY CONCEPT The most clinically important features associated with poor long-term outcomes include: (a) high disease activity, (b) positive autoantibodies (RF or ACPA), and (c) early presence of bony erosions by radiography.[18]

▶ *Diagnosis of Juvenile Idiopathic Arthritis*

Diagnostic criteria for JIA include: (a) age less than 16 years at disease onset, (b) arthritis in one or more joints for more than 6 weeks, and (c) exclusion of other types of arthritis. JIA can be divided into three main types:

1. *Systemic (4%–17% of cases)*: Occurs equally in girls and boys. There are characteristic fever spikes twice daily (> 38.3°C or 101°F) and the presence of a pale, pink, transient rash. The peak onset is between ages 1 and 6 years.
2. *Polyarticular (approximately 40% of cases)*: More likely to affect girls than boys (3:1). Arthritis is present in five or more joints. The disorder resembles adult RA more than the other types of JIA.

Table 57–3

ACR/EULAR 2010 Classification Criteria for Rheumatoid Arthritis[1]

Criteria	Score
Joint involvement	
1 large joint (hips, knees, ankles, elbows, shoulders)	0
2–10 large joints	1
1–3 small joints (MCPs, PIPs, MTPs, wrists)	2
4–10 small joints	3
More than 10 joints (at least one small joint)	5
Serology (need at least one result for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-phase reactants (need at least one result for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
Duration of symptoms	
Less than 6 weeks	0
More than 6 weeks	1
TOTAL:	6 or greater indicates definite RA

ACPA, anticitrullinated protein antibodies; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; MCPs, metacarpophalangeal joints; MTPs, metatarsophalangeal joints; PIPs, proximal interphalangeal joints; RA, rheumatoid arthritis; RF, rheumatoid factor.

LO 4

Clinical Presentation of RA

General

- About 60% of patients develop symptoms gradually over several weeks to months.
- Patients may present with systemic findings, joint findings, or both.

Symptoms

- Nonspecific systemic symptoms may include fatigue, weakness, anorexia, and diffuse musculoskeletal pain.
- Patients complain of pain in involved joints and prolonged morning joint stiffness.

Signs

- The metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP), and wrist joints are involved frequently.
- Joint involvement is usually symmetric.
- There is often limited joint function.
- Swan neck and/or boutonniere deformities may be present (see Figure 57–1).
- Signs of joint inflammation are present (tenderness, warmth, swelling, and erythema).
- Low-grade fever may be present.
- Extraarticular manifestations:
  - *Skin:* Subcutaneous nodules
  - *Ocular:* Keratoconjunctivitis sicca, scleritis
  - *Pulmonary:* Interstitial fibrosis, pulmonary nodules, pleuritis, pleural effusions
  - *Vasculitis:* Ischemic ulcers, skin lesions, leukocytoclastic vasculitis
  - *Neurologic:* Peripheral neuropathy, Felty syndrome
  - *Hematologic:* Anemia, thrombocytosis

Laboratory Tests

- Positive rheumatoid factor (RF) (the test is negative in up to 30% of patients)
- Elevated ESR (Westergren ESR: > 20 mm/hour in men; > 30 mm/hour in women)
- Elevated C-reactive protein (CRP) (> 0.7 mg/dL or 7 mg/L)
- Complete blood count: Slight elevation in WBC count with a normal differential; slight anemia; thrombocytosis
- Positive anticitrullinated protein antibodies (ACPA)

Other Diagnostic Tests

- *Synovial fluid analysis:* Straw colored, slightly cloudy, WBC 5–25 × 10^3/mm^3 (10^9/L), no bacterial growth if cultured
- *Joint x-rays:* To establish baseline and evaluate joint damage
- *MRI:* May detect erosions earlier in the course of disease than x-rays but is not required for diagnosis

Assessing Disease Activity

- Common tools to assess disease activity include Patient Activity Scale, Clinical Disease Activity Index, Simplified Disease Activity Index, and Disease Activity in 28 joints (DAS-28).[17] Components involved in calculating a DAS-28 score are the number of swollen and tender joints, ESR or CRP, and a subjective measure of the patient's general health. A DAS-28 score of 3.2 or less indicates low disease activity, between 3.2 and 5.1 is considered moderate activity, and 5.1 or more is considered to be high activity. Remission as defined by DAS-28 is a score of less than 2.6.[17] An online DAS-28 calculator is available at www.4s-dawn.com/DAS28/.

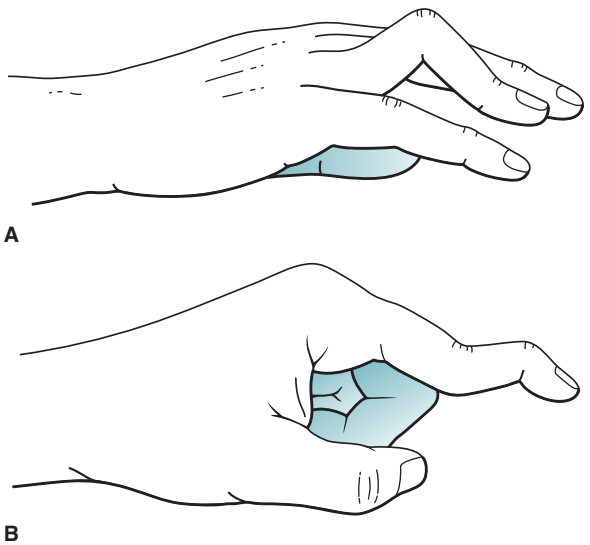

FIGURE 57–1. Boutonnière **(A)** and swan-neck **(B)** deformities. (Reproduced with permission from: Toy EC, Patlan Jr JT, Warner MT. Case Files: Internal Medicine 5e; 2017. http://accessmedicine.mhmedical.com/ViewLarge.aspx?figid=140919481.)

Patient Encounter Part 1

A 47-year-old woman presents to her rheumatologist for routine follow-up. She was diagnosed with RF-positive RA 10 years ago and presents today with concerns of increased morning stiffness (average 90 minutes daily) and symmetrical tenderness/swelling in her hands. She wishes to improve function as soon as possible. She maintains a stressful career in the banking industry. She tries to eat healthy, although she travels frequently and relies on many fast food meals. She smokes one pack per day and consumes alcohol socially. She has been taking medications for RA since diagnosis, although she admits to missing doses often because of her busy lifestyle.

What additional information do you need to assess disease activity?

What variables in this scenario may inhibit optimal patient care?

Which features suggest that the patient is experiencing symptoms of RA rather than OA?

What additional information do you need before creating a care plan for this patient?

3. *Oligoarticular (about 50% of cases)*: More likely to affect girls than boys (5:1). Uveitis is more likely to be present. Arthritis is present in four or fewer joints. The peak onset is between ages 1 and 3 years.

TREATMENT

Desired Outcomes

LO 5

KEY CONCEPT The goals of treatment in RA are to: (a) reduce or eliminate pain, (b) reduce disease activity to the lowest possible level, ideally remission, as soon as possible, (c) protect articular structures and function, (d) control systemic complications, and (e) improve/maintain quality of life. The goals for JIA are the same, with the added goals of maintaining normal growth, development, and activity level.[19,20] It is a common misconception that patients with JIA grow out of the disease. Many children with JIA become adults with JIA. Knowing this, it is essential that early, aggressive treatment is initiated to achieve the goals of therapy.

General Approach to Treatment

LO 6

The clinician must evaluate patient-specific factors and select appropriate treatment to maximize the care of each patient. Joint damage accumulates over time; therefore, early diagnosis and early aggressive treatment are necessary to reduce disease progression and prevent joint damage. Aggressive treatment is defined as one or more disease-modifying antirheumatic drugs (DMARDs) at effective doses. Delaying treatment will result in more destructive disease that is very difficult to delay or reverse to preserve joint function.

KEY CONCEPT It is imperative that one or more DMARDs be initiated in all patients as soon as possible to reduce disease activity. DMARDs are the mainstay of RA treatment because modifying the disease process can prevent or reduce joint damage. The umbrella term DMARD includes traditional nonbiologic DMARDs, biologic DMARDs, and Janus-kinase inhibitors. The drugs in these classes modify the underlying disease process rather than merely providing symptomatic relief. In addition to safety and efficacy data, the initial DMARD choice depends on disease severity, patient characteristics (ie, comorbidities, likelihood of adherence), cost, and clinician experience with the medication.[7,17] Methotrexate alone or in combination therapy is the initial treatment of choice.

Depending on disease severity, combination therapy may be initiated at the time of diagnosis or after an adequate trial of DMARD monotherapy. If a patient has evidence of rapid disease progression (eg, worsening radiographic erosions), a more aggressive treatment plan may be warranted with more frequent follow-up to achieve the goal of remission or low disease activity.

Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids also have specific roles in the treatment of RA, as discussed below. Agents such as azathioprine, cyclosporine, minocycline, gold salts, and anakinra are used rarely today.[17]

Figures 57–2 and 57–3 outline the course of treatment for adult RA according to the ACR 2015 Recommendations.[17] The recommendations are based on the disease activity level and duration of disease activity (early vs established). Figure 57–2 applies to patients with early RA (defined as < 6 months). Nonbiologic DMARD monotherapy includes methotrexate (preferred), hydroxychloroquine, leflunomide, or sulfasalazine. Examples of combination nonbiologic DMARD therapy include methotrexate/sulfasalazine, methotrexate/hydroxychloroquine, or methotrexate/sulfasalazine/hydroxychloroquine.

Figure 57–3 outlines the course of treatment for patients with established RA (disease duration 6 months or longer). Combination biologic DMARDs should be avoided because of the increased risk of infection due to excessive immunosuppression. There is no evidence that the benefits of combination biologic DMARD therapy outweigh the potential risks, especially the increased risk of infections.

Sarilumab does not appear in either figure because it was not FDA approved until after the guidelines were published. Anakinra does not appear in the 2015 treatment guidelines due to limited efficacy and infrequent use in RA.

Nonpharmacologic Therapy

All patients should receive education about the nonpharmacologic and pharmacologic measures to help manage RA and JIA. Empowered patients take an active role in care by participating in therapy-related decisions. Certain forms of nonpharmacologic therapy benefit all levels of severity, whereas others (ie, surgery) are reserved for severe cases only.

Occupational and physical therapy may help patients preserve joint function, extend joint range of motion, and strengthen joints and muscles through strengthening exercises. Patients with joint deformities may benefit from the use of mobility or assistive devices that help to minimize disability and allow continued activities of daily living. When appropriate, patients should also be counseled about stress management. In situations where the disease has progressed to a severe form with extensive joint erosions, surgery to replace or reconstruct the joint may be necessary.

Pharmacologic Therapy

LO 7

► *Bridge Therapy/Symptomatic Relief*

The current standard of care for RA treatment is to initiate disease-modifying therapy immediately. While this step is critical to control the underlying disease activity, it may take weeks to months for the patient to experience relief. It is acceptable to initiate "bridge therapy" or short-term use of certain medications to provide symptomatic relief until the disease modifying drug reaches its therapeutic effect. The most common classes used for bridge therapy are NSAIDs and glucocorticoids.

NSAIDs These agents provide analgesic and anti-inflammatory benefits for joint pain and swelling. However, they do not prevent joint damage or change the underlying disease. Selecting an NSAID depends on multiple patient-specific factors, including cardiovascular risk, potential for GI-related adverse events, adherence to medication regimens, and insurance coverage or lack thereof. NSAID monotherapy is recommended as initial treatment in children with JIA without prior treatment for a duration of 1 month.[19] Clinicians must carefully evaluate the potential risks of NSAID therapy against the potential benefits. See Chapter 58 for additional discussion of NSAID therapy.

Glucocorticoids In contrast to NSAIDs, low-dose glucocorticoid treatment (equivalent to prednisone 10 mg/day or less) effectively reduces inflammation through inhibition of cytokines and inflammatory mediators and prevents disease progression.[21] However, due to the adverse effect profile, the goal of glucocorticoid use is to keep doses low and use the drugs as infrequently as possible. For the purposes of bridge therapy, the recommended duration is 3 months or less. Patients taking more than 2.5 mg/day of prednisone or equivalent are at increased risk for clinically significant adverse reactions, especially bone loss leading to osteoporosis. Other glucocorticoid-related adverse reactions include Cushing syndrome, peptic ulcer disease,

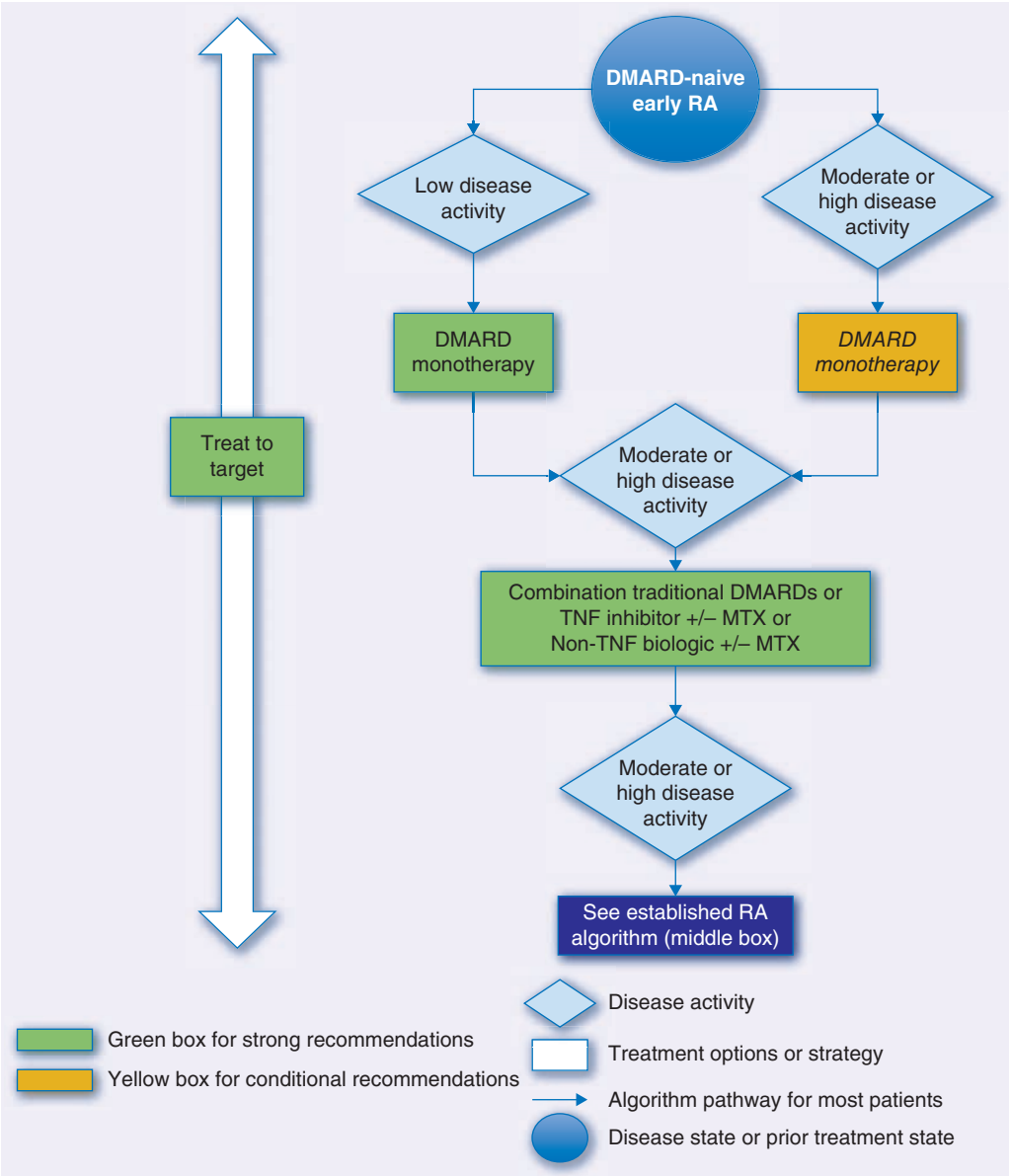

FIGURE 57–2. 2015 American College of Rheumatology recommendations for the treatment of the treatment of early RA (disease duration < 6 months). (Reproduced, with permission, from Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016;68:1–25.)

hypertension, weight gain, infection, mood changes, cataracts, dyslipidemia, and hyperglycemia.[21] Intraarticular administration of glucocorticoids may be considered in RA for rapid control of inflammation if a limited number of joints are affected. Intraarticular glucocorticoid injections are recommended as initial treatment of JIA for disease affecting four or fewer joints.[19]

▶ *Nonbiologic DMARDs*

Methotrexate KEY CONCEPT Methotrexate is the nonbiologic DMARD of choice in RA because of its documented efficacy and safety profile when monitored appropriately. Methotrexate exerts its anti-inflammatory effect through inhibition of dihydrofolate reductase, which causes inhibition of purines and thymidylic acid, and by inhibiting production of certain cytokines. Unless the patient has contraindications to methotrexate or takes other medications that should be used with caution or avoided in combination with methotrexate, once-weekly doses should be initiated and increased steadily until the patient has symptomatic improvement or a maximum dose of 20 mg/week is reached. It is important to emphasize to patients and health care providers that the dosing is once weekly (not once daily) to avoid medication errors resulting in serious complications from profound myelosuppression (eg, infections, bleeding). If monotherapy does not produce complete resolution of symptoms, methotrexate may be used in combination with other nonbiologic or biologic DMARDs. If a patient experiences intolerable gastrointestinal effects, switching to subcutaneous methotrexate will reduce those effects. Concomitant folic acid is given routinely to reduce the risk of folate-depleting reactions induced by methotrexate therapy (eg, **stomatitis**, diarrhea, nausea, **alopecia**, **myelosuppression**, and elevated liver function tests).

Methotrexate is recommended as initial treatment for JIA in patients with more than four active joints.[19] There are insufficient published data to assess the risk of serious toxicity in children

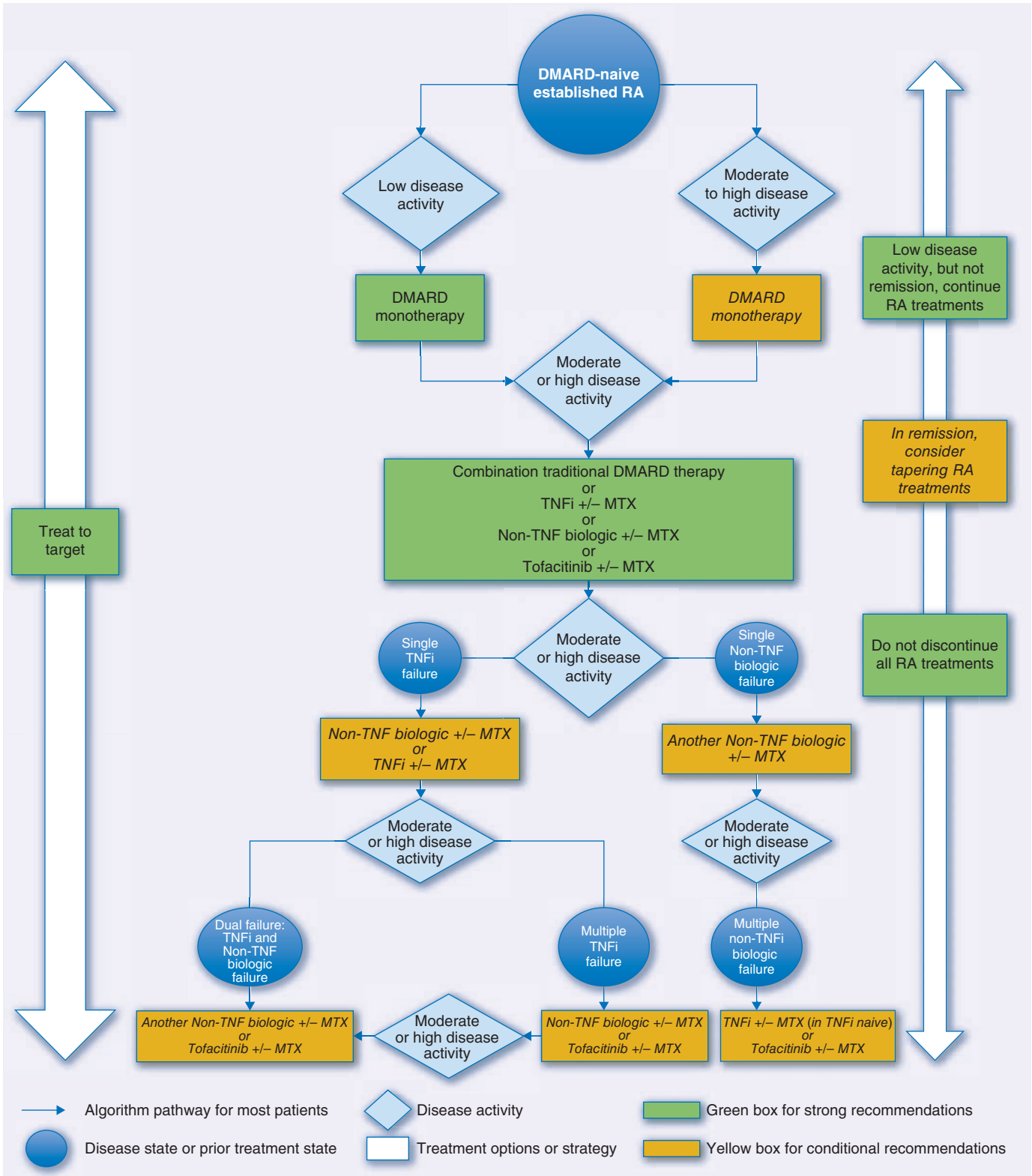

FIGURE 57–3. 2015 American College of Rheumatology recommendations for the treatment of established RA (disease duration 6 month or longer). (Reproduced, with permission, from Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res. 2016;68:1–25.)

receiving doses greater than 20 mg/m^2/week. Methotrexate therapy in children should be monitored the same way that is recommended in adults.

Hydroxychloroquine and Sulfasalazine The exact mechanism of action of these drugs is unknown, but both agents are fairly well tolerated. Because of their slow onset of action, each drug must be given at therapeutic doses for at least 6 months before it can be deemed a treatment failure. If a patient does not respond to methotrexate monotherapy, adding one of these two drugs may provide the benefit necessary to reduce symptoms satisfactorily and ideally induce remission.[17]

Hydroxychloroquine is not associated with renal, hepatic, or bone marrow suppression and therefore may be an acceptable treatment option for patients with contraindications to other DMARDs because of their toxicities.

Starting sulfasalazine at low doses and titrating slowly will minimize the nausea and abdominal discomfort caused by the drug. Patients with a sulfa allergy should not receive sulfasalazine.

In patients with JIA, sulfasalazine is recommended only for patients with the **enthesitis**-related category. Enthesitis-related arthritis is a less common form of JIA that affects boys more than girls and is characterized by lower extremity joint involvement, including heel pain and enthesitis. Hydroxychloroquine is not recommended in JIA patients with active arthritis.[17,22]

Leflunomide This drug inhibits dihydroorotate dehydrogenase, an enzyme within mitochondria that supplies T lymphocytes with the necessary components to respond to cytokine stimulation. Thus, leflunomide inhibits the T-lymphocyte response to various stimuli and halts the cell cycle. Its efficacy is similar to that of moderate doses of methotrexate or sulfasalazine. Because of its extended half-life, leflunomide therapy begins with a loading dose followed by a maintenance dose. Leflunomide may be used in combination with methotrexate, but the added efficacy comes with a dramatic rise in the risk of hepatotoxicity. If therapy requires abrupt discontinuation (eg, due to toxicity or pregnancy), administering cholestyramine will accelerate leflunomide removal from the body.[22]

Leflunomide is recommended as an alternative to methotrexate in patients with JIA experiencing disease activity in five or more joints.[21] However, leflunomide does not have an FDA-approved indication for this use.

▶ *Biologic DMARDs and Associated Biosimilars*

Biologic DMARDs are indicated in patients who have received an adequate trial of nonbiologic DMARD monotherapy or combination therapy but have failed to achieve treatment goals. These agents may be added to nonbiologic DMARD monotherapy (eg, methotrexate), replace ineffective nonbiologic DMARD therapy, or even be considered for initial therapy, based on current guidelines.

"Biosimilars" are highly similar to an FDA-approved biologic agent (called the reference product) and have been shown to have no clinically meaningful differences in efficacy or adverse effects from the reference product. They are not completely identical to the originator compound because of molecular complexity and production using recombinant DNA techniques in living organ systems. The FDA will approve a biosimilar product only if it has the same mechanism of action, route of administration, dosage form, and strength as the reference product. Also, a biosimilar can only be approved for indications that were previously approved for the reference product. Biosimilars have a nonproprietary name plus an FDA-designated suffix consisting of four lower-case letters that have no intended meaning. Five biosimilars are now approved for use in RA: etanercept-szzs, infliximab-dyyb, infliximab-abda, adalimumab-adbm, and adalimumab-atto. Biosimilars are not considered to be interchangeable with the reference product unless the manufacturer fulfills additional requirements for interchangeability.

Patients with concomitant serious infections, lymphoproliferative disorders, hepatitis, history of malignancy, or heart failure should be evaluated thoroughly to determine if or which biologic DMARD is appropriate, preferred, or contraindicated in their treatment regimen. The 2015 treatment guidelines provide recommendations for those scenarios based on available evidence.[17]

Tumor Necrosis Factor (TNF) Antagonists There are currently five reference TNF antagonists approved for the treatment of RA: etanercept, adalimumab, infliximab, golimumab, and certolizumab.

Etanercept is a recombinant form of human T receptor. Etanercept provides a therapeutic effect by binding to soluble TNF and preventing its binding with TNF receptors. Etanercept is very effective as monotherapy or in combination with other nonbiologic DMARDs. Etanercept has an FDA-approved indication for treatment of JIA.

Adalimumab is a recombinant human IgG1 monoclonal antibody specific for human TNF. Adalimumab binds to soluble and bound TNF-α. It can be administered in combination with methotrexate or other DMARDs. Adalimumab has an FDA-approved indication for JIA.

Infliximab is a **chimeric** IgG1 monoclonal antibody that binds to soluble and bound TNF-α. Methotrexate is given with it to suppress antibody production against the mouse-derived portion of the molecule. Qualified health care personnel must be present during the infliximab infusion to respond to infusion-related reactions, if they occur (rash, urticaria, flushing, headache, fever, chills, nausea, tachycardia, dyspnea). These reactions may be treated by: (a) temporarily discontinuing the infusion, (b) slowing the infusion rate, or (c) administering corticosteroids or antihistamines. Patients may be pretreated with corticosteroids or antihistamines if they continue to experience infusion reactions. Infliximab was shown in clinical trials to be effective for treatment of JIA, but it has not yet received FDA approval for this indication.

Golimumab is a human monoclonal antibody that binds to membrane-bound and soluble TNF. Golimumab can be administered in combination with methotrexate in patients with moderate to severe RA. One advantage of this agent over others in the class may be the once-monthly SC dosing or every-other-month IV dosing. Golimumab is not FDA approved for use in JIA.

Certolizumab is a humanized antibody Fab fragment conjugated to polyethylene glycol, which delays its metabolism and elimination. Certolizumab can be administered alone or in combination with methotrexate in patients with moderate to severe RA. Certolizumab is not FDA approved for use in JIA.[23]

Interleukin-1 Antagonists Anakinra is a recombinant form of human IL-1 receptor antagonist. Anakinra inhibits the activity of IL-1 by binding to it and preventing cell signaling. It is indicated for adults with RA who have failed one or more nonbiologic DMARDs. Regarding treatment of JIA, anakinra is recommended in the ACR treatment guidelines for patients with systemic arthritis with continued disease activity following an adequate trial of glucocorticoids or NSAIDs.[18] Anakinra is not FDA approved for the treatment of JIA.[23]

Canakinumab is a human monoclonal antibody that binds to IL-1 and blocks binding with the IL-1 receptor, thereby neutralizing

its activity. Canakinumab is not indicated for treatment of adult RA. Canakinumab is indicated for the treatment of systemic JIA in patients 2 years and older. The recommended dose is 4 mg/kg (maximum 300 mg) subcutaneously every 4 weeks.[24]

Costimulation Modulators Abatacept interferes with T-cell signaling, ultimately blocking T-cell activation and leading to anergy, or lack of response to an antigen. Abatacept is indicated as monotherapy or in combination with nonbiologic DMARDs following inadequate response to methotrexate or anti-TNF agents. Abatacept is FDA approved for the treatment of moderate to severe JIA; it is recommended as an option for patients who did not respond to an adequate trial of methotrexate, leflunomide, or anakinra.[19,23]

Anti-CD20 Monoclonal Antibody Rituximab is a genetically engineered chimeric anti-CD20 monoclonal antibody that causes B-lymphocyte depletion in bone marrow and synovial tissue. Rituximab is indicated for patients with moderate to severe RA and a history of inadequate response to one or more TNF antagonist therapies. Patients with RF-positive RA tend to respond more favorably to rituximab than patients with RF-negative disease. Rituximab carries a black-box warning of fatal infusion reactions, severe mucocutaneous reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy. The benefits of rituximab must be tempered against the safety concerns reported with use of rituximab in the oncology setting. The role of rituximab in JIA is unclear, and the medication is not FDA approved for this purpose.[19,23]

Interleukin-6 Antagonists Interleukin-6 (IL-6) production is increased in patients with RA. High levels are indicative of joint damage and disease activity. In addition, IL-6 plays a significant role in the pathogenesis of anemia associated with RA. Tocilizumab, an anti–IL-6 receptor monoclonal antibody, inhibits the binding of IL-6 to the IL-6 receptor.[25] Tocilizumab is FDA approved for the treatment of moderate to severe RA and JIA. In JIA, it is recommended for patients with inadequate response to glucocorticoid monotherapy, methotrexate, leflunomide, or anakinra.[19]

Sarilumab is an IL-6 receptor antagonist that binds to soluble and membrane-bound IL-6 receptors. It is indicated for treatment of moderate to severe RA following inadequate response or intolerance to one or more DMARDs. It is not FDA approved for JIA.[24]

▶ *Janus-Kinase (JAK) Inhibitors*

Tofacitinib selectively inhibits Janus kinases, with greatest affinity for JAK3.[26] Tofacitinib is indicated for the treatment of moderate to severe RA as monotherapy or in combination with nonbiologic DMARDs. Combination administration with biologic DMARDs is inappropriate due to increased immunosuppression and subsequent increased infection risk. One distinct advantage of tofacitinib over biologic DMARDs is that it is given orally because it is a synthetic small molecule rather than a large protein produced by recombinant DNA techniques. It may be initiated if a patient does not have an adequate response to or is otherwise unable to receive nonbiologic or biologic DMARDs.[26] Baricitinib is an inhibitor of JAK 1 and 2 undergoing review by the FDA for treatment of RA.

▶ *Selecting Disease-Modifying Therapy*

The decision to select a particular agent generally is based on the prescriber's comfort level with monitoring medication safety and efficacy, severity of disease activity, presence of factors suggestive of poor prognosis, the frequency and route of administration, the patient's comfort level or manual dexterity to self-administer subcutaneous injections, the cost, and the availability of insurance coverage. Table 57–4 highlights dosing, safety, monitoring, and patient counseling information for DMARDs used in the treatment of RA. Together, Figures 57–2 and 57–3 and Table 57–4 can be used to build an individualized treatment plan. While monotherapy is preferred, combination therapy may be necessary to achieve the target of low disease activity or remission. When selecting a treatment plan, cost should also be considered. The expense of biologic DMARDs can limit their use in patients without adequate insurance or other means of covering the drug cost. Cost analyses indicate that the increased expenses associated with biologic DMARDs may be offset by the costs avoided for treatment of advanced RA. It is anticipated that introduction of biosimilars will reduce RA treatment costs because they are expected to be less costly than the reference products.

KEY CONCEPT The risk of infection in patients treated with biologic DMARDs must be considered when selecting and monitoring therapy.[17,27] Influencing the immune response to reduce symptoms of RA may influence the body's response to pathogens. Of particular concern is use of TNF antagonists in patients with a history of tuberculosis exposure. TNF is important in the formation of granulomas that wall off tuberculosis infection. In theory, if TNF is inhibited, patients with latent tuberculosis may have a reactivated infection. Patients receiving any biologic DMARD should be screened for tuberculosis and other infections (hepatitis B, hepatitis C). Antituberculosis therapy should be initiated in patients with active or latent tuberculosis.[17] Patients with active tuberculosis should receive the full course of antituberculosis treatment prior to initiating biologic DMARDs. If there is latent infection, biologic DMARD therapy may be initiated after at least 1 month of antituberculosis treatment. Biologic DMARDs should not be initiated and should be discontinued temporarily during an acute, serious infection. Biologic DMARD therapy can be continued during nonserious infections.[28] Concomitant use of two biologic DMARDs or use of a biologic DMARD in combination with a JAK inhibitor is contraindicated due to increased infection risk.

▶ *Vaccinations*

Initiation of biologic DMARD therapy suppresses the immune system and reduces the body's ability to mount a response to a pathogen or a vaccine. Prior to initiation of an immunosuppressant, a patient's immunization status should be determined, and recommended vaccines should be administered. Specifically, administration of killed vaccines (pneumococcal, influenza, hepatitis B), recombinant vaccines (human papillomavirus, recombinant zoster vaccine [Shingrix]), and live attenuated vaccines (zoster vaccine live [Zostavax]) should be considered prior to and reevaluated during treatment with DMARDs. Herpes zoster status should be determined prior to initiation of biologic DMARDs or tofacitinib and the vaccine administered, if appropriate. In October 2017, the CDC Advisory Committee on Immunization Practices (ACIP) preferentially recommended Shingrix over Zostavax for prevention of herpes zoster and related complications in immunocompetent adults aged 50 years or more. Live vaccines (eg, Zostavax) should be avoided in patients already taking biologic DMARDs or tofacitinib because they may result in disseminated varicella-zoster virus disease, including fatal outcomes.[17] At the time of this writing, the CDC ACIP had not made recommendations about use of the newer recombinant zoster vaccine (Shingrix) in immunocompromised persons and

Table 57–4

FDA-Approved DMARDs for Treatment of RA[1,2,20,23,24]

Drug	Dose[a]	Time to Effect (weeks)	ADRs	Dosing in Hepatic Impairment	Dosing in Renal Impairment	Monitoring	Counseling Points
Nonbiologic DMARDs							
Methotrexate	Adults: 7.5–20 mg orally, SC or IM once weekly Polyarticular-course JIA: Recommended starting dose: 10 mg/m^2 oral, IM, or SC once weekly; usual max dose: 20 mg/m^2 once weekly	4–8	N, D, hepatotoxicity, alopecia, new-onset cough or SOB, MYL	Contraindicated	CrCl (mL/min)[b]: 61–80: 75% of dose 51–60: 70% of dose 10–50: 50% of dose Less than 10: Avoid use	CBC, creatinine, LFTs every 4–8 weeks; monitor for signs of infection	Use of folic acid concomitantly Avoid alcohol Use contraception if childbearing potential
Hydroxychloroquine	Adults: 200 mg orally twice daily or 400 mg once daily	8–24	N, D, HA, vision changes, skin pigmentation	Use with caution	No change	Specialized retinal eye examination every 5 years	
Sulfasalazine	Adults: 1000 mg orally two to three times daily Polyarticular-course JIA: Initial: 10 mg/kg/day orally; increase weekly by 10 mg/kg/day; usual dose: 30–50 mg/kg/day orally in two divided doses; max 2 g/day	8–12	N, D, rash, yellow-orange discoloration, photosensitivity, MYL	Avoid use	CrCl (mL/min)[b]: 10–30: Give twice daily Less than 10: Give once daily	CBC, LFTs, creatinine every 2–4 weeks for 3 months, then every 8–12 weeks	Sunscreen use
Leflunomide (Arava)	Adults: 100 mg orally daily for 3 days; then 20 mg daily	4–12	Hepatotoxicity, D, N, HTN, rash, HA, abdominal pain	Avoid use	Guidelines not available	CBC, LFTs, creatinine every 2–4 weeks for 3 months, then every 8–12 weeks Monitor for signs of infection	Avoid alcohol Use contraception if childbearing potential
Biologic DMARDs and Associated Biosimilars							
Etanercept (Enbrel) Biosimilar: Etanercept-szzs (Erelzi)	Adults: 25 mg SC twice weekly or 50 mg SC once weekly Children ages 2–17: 0.8 mg/kg SC once weekly; max 50 mg/week	1–4	ISR	No change	No change	Monitor for infection	ISR—topical corticosteroids, antipruritics, analgesics, rotate injection sites Screen for tuberculosis, Hepatitis B
Infliximab (Remicade) Biosimilars: Infliximab-dyyb (Inflectra) Influximab-abda (Renflexis)	Adults: 3–10 mg/kg by IV infusion at 0, 2, and 6 weeks; then every 8 weeks	1–4	IR (rash, urticaria, flushing, HA, fever, chills, nausea, tachycardia, dyspnea)	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
Adalimumab (Humira) Biosimilar: Adalimumab-atto (Amjevita) Adalimumab-adbm (Cyltezo)	Adults: 40 mg SC every other week Children older than 4 years and weighing 15–29 kg: 20 mg SC every other week Children weighing 30 kg or more: 40 mg SC every other week	1–4	ISR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B

Golimumab (Simponi)	Adults: 50 mg SC once monthly 2 mg/kg IV infusion at weeks 0, 4, then every 8 weeks	1–4	ISR, IR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
Certolizumab (Cimzia)	Adults: 400 mg SC initially, at 2 weeks, 4 weeks, then every 4 weeks thereafter	1–4	ISR	No change	No change	Monitor for infection	Screen for tuberculosis, Hepatitis B
Anakinra (Kineret)	Adults: 100 mg SC daily	2–4	HA, N, V, D, ISR	No data available	CrCl < 30 mL/min[b]: consider 100 mg every other day	Monitor for infection	
Abatacept (Orencia)	Adult IV infusion: < 60 kg, 500 mg; 60–100 kg, 750 mg; > 100 kg, 1000 mg IV on days 1, 15 and every 28 days thereafter SC Injection: Weight-based loading dose, then 125 mg SC within 1 day, 125 mg SC once weekly; or 125 mg once weekly in patients unable to receive IV. JIA (> 6 years of age): < 75 kg: 10 mg/kg; 75–100 kg: 750 mg; > 100 kg: 1000 mg IV infusion on days 1, 15, 28 and every 28 days thereafter	2	HA, infection, IR, ISR	No change	No change	Monitor for infection	
Rituximab (Rituxan)	Adults: Two 1000-mg IV infusions separated by 2 weeks; timing of the third dose is based on patient symptoms (no earlier than 16 weeks)	4	IR	No change	No change	Monitor for infection	
Tocilizumab (Actemra)	Adults: 8 mg/kg IV infusion every 4 weeks SC: if > 100 kg, 162 every week; if < 100 kg, 162 every other week JIA (2 years and older): < 30 kg: 12 mg/kg IV infusion every 2 weeks; > 30 kg: 8 mg/kg every 2 weeks		Elevated LFTs, total cholesterol, triglycerides, and high-density lipoprotein; nasopharyngitis, infection	No data available	No data available	Monitor for infection; LFTs	
Sarilumab (Kevzara)	Adults: 200 mg SC every 2 weeks		ISR, elevated LFTs, neutropenia	Not recommended in patients with hepatic impairment	CrCl < 30 mL/min[b]: no data available	Monitor for infection, LFTs, lipids	Screen for tuberculosis
Janus-Kinase Inhibitors							
Tofacitinib (Xeljanz) Tofacitinib extended-release (Xeljanz-XR)	Adults: 5 mg orally twice daily Adults: 11 mg orally once daily		Infection, headache, HTN, elevated LFTs, D, worsening lipid profile	Mild impairment: no adjustment Moderate: 5 mg once daily Severe: Use not recommended	Mild: no adjustment; Moderate/severe: 5 mg once daily	CBC, Hgb, lipids, LFTs, monitor for infection	

[a]Geriatric patients should receive the usual adult dose unless renal or hepatic impairment is present. Pediatric doses are provided for drugs that have FDA-approved indications for juvenile idiopathic arthritis (JIA).

[b]To convert to SI units of mL/s, multiply by 0.0167.

CBC, complete blood count; D, diarrhea; HA, headache; Hgb, hemoglobin; HTN, hypertension; IR, infusion reactions; ISR, injection site reactions; LFTs, liver function tests; MYL, myelosuppression (watch for fever, symptoms of infection, easy bruisability, and bleeding); N, nausea; SC, subcutaneous injection; SOB, shortness of breath.

those on moderate to high doses of immunosuppressive therapy because these patients were excluded from the efficacy studies. Additional vaccine information is available on the Centers for Disease Control and Prevention website (www.cdc.gov).

▶ *Fertility, Pregnancy, and Fetal Development*

Women of childbearing potential should be counseled about the impact of antirheumatic drugs on fertility, pregnancy, fetal development, and lactation. Some women may experience a reduction in disease symptoms during pregnancy; however, many agents used to treat RA are known teratogens. In addition, some women may present with signs and symptoms of RA for the first time during the postpartum period. Women desiring motherhood must consult with their physicians to carefully plan for the pregnancy and reduce risks to the developing fetus.[29,30]

Treatment plans must also consider the potential effects on breastfeeding babies. Low-dose corticosteroids, certain NSAIDs, hydroxychloroquine, sulfasalazine, and certain biologic DMARDs described below may be considered during pregnancy. Health care providers and patients are encouraged to visit MotherToBaby (https://mothertobaby.org) for educational information regarding medication use in pregnancy and ongoing studies designed to learn more about medication exposure during pregnancy.

Methotrexate use is associated with spontaneous abortion, fetal myelosuppression, limb defects, and CNS abnormalities; therefore, pregnancy must be avoided. Methotrexate should be discontinued 3 months prior to attempting conception.[30] Patients of childbearing potential receiving methotrexate should be counseled on the importance of effective contraception (ie, oral contraceptives, condoms plus spermicidal foam). If pregnancy occurs, the patient should notify their health care providers immediately. Leflunomide is teratogenic in animal studies, and discontinuation prior to conception is recommended.[30]

Although data on safety of biologic DMARD use in pregnant women are limited, TNF antagonists are considered safe in the first trimester. Etanercept and certolizumab may be continued throughout the pregnancy because the transfer of medication across the placenta is very low. Rituximab should be discontinued 1 year prior to planned conception. Abatacept should be discontinued 10 weeks prior to planned conception. Insufficient data exist regarding use of tocilizumab and tofacitinib during pregnancy.[29,30]

Male patients with RA must receive counseling about the effects of certain medications on their fertility and potential harm to the fetus. It is difficult to establish causality between use of a medication by a male and the effect on fertility or fetal development; therefore, a conservative approach must be taken. KEY CONCEPT Women of childbearing potential and their partners must be counseled to: (a) use proper birth control while undergoing treatment for RA, and (b) involve health care providers in discussions regarding family planning to carefully consider all treatment options.[29,30]

OUTCOME EVALUATION

- Rheumatologists rely on standardized criteria to assess treatment interventions through measurement of disease activity. The ACR uses criteria for improvement based on percentage improvement in tender and swollen joint count, and the presence of at least three or more of the following measures: (a) pain, (b) patient global assessment, (c) physician global assessment, (d) self-assessed physical disability, and (e) acute-phase reactants.[32] ACR20, ACR50, and ACR70 are common efficacy endpoints in clinical trials. The number corresponds with the percentage improvement. As drug development continues to evolve, the acceptable criteria for 20% improvement may be too low.
- Physical disability from RA can be measured through the Stanford Health Assessment Questionnaire (HAQ).[33,34] This patient self-assessment tool was developed to evaluate patient outcomes in five dimensions of chronic conditions: (a) disability, (b) discomfort, (c) drug adverse effects, (d) dollar costs, and (e) death. Clinicians and clinical studies in rheumatology use the HAQ to assess longitudinal changes that influence the patient's quality of life.[33,34]

Patient Encounter Part 2: Medical History, Physical Examination, and Laboratory Tests

PMH: Hypertension (15 years), depression (5 years), rheumatoid arthritis (10 years)

FH: Mother died age 65 from lung cancer; father died age 82 from lymphoma

Allergies: Sulfa

Meds: Metoprolol 50 mg once daily, lisinopril 20 mg once daily; hydrochlorothiazide 25 mg once daily; citalopram 40 mg once daily; methotrexate 20 mg orally once weekly; abatacept 125 mg SC once weekly (initiated 1 year ago); folic acid 1 mg daily; prednisone 5 mg every morning

Previous Meds: Etanercept, infliximab

ROS: (+) Fatigue, (–) N/V/D, HA, SOB, chest pain, cough

PE:

VS: BP 174/86 mm Hg, P 78 beats/min, RR 18 breaths/min, T 38.0°C (100.4°F); Ht 5'7" (170 cm), Wt 87 kg (192 lb)

Skin: Warm, dry

HEENT: NC/AT, PERRLA, TMs intact

CV: RRR, normal S_1 and S_2, no m/r/g

Chest: CTA

Abd: Soft, NT/ND

Neuro: A&O × 3; CN II to XII intact

Ext: Bilateral tender and swollen PIPs and MCPs

Labs: ESR 58 mm/hour, RF (+), ACPA (high +)

Synovial fluid analysis: Yellow, cloudy, decreased viscosity

Hand x-rays: Soft-tissue swelling, joint space narrowing, evidence of erosions

Disease Activity Score 28 (DAS-28): 4.85

How would you categorize this patient's disease activity—low, moderate, or high? Why? How does this affect your treatment plan?

What nonpharmacologic and pharmacologic alternatives are appropriate for this patient?

Patient Encounter Part 3: Creating a Care Plan

Based on the information available, create a care plan for this patient's RA. The plan should include the following:

(a) A statement of the drug-related needs and/or problems

(b) A patient-specific detailed care plan (including specific medications and associated doses)

(c) Monitoring parameters to assess safety and efficacy

(d) Key patient education topics

Patient Encounter Part 4: Patient Counseling

While meeting with the patient, she admits that she forgets to administer the abatacept 2 to 3 times a month due to her busy schedule. Also, the prednisone was initiated about 5 years ago. She rarely forgets to take it in the morning.

How does this information change your care plan?

Patient Care Process

Collect Information:

- Perform a medication history to determine current prescription, nonprescription, and dietary supplements. Inquire about previous medications for RA and reasons why they were discontinued. Ask about allergies (and the associated reaction) and immunizations.
- Determine whether physical examination findings and patient-reported symptoms are consistent with RA. Evaluate the duration of symptoms and impact on daily living.
- Review the medical history. Determine if comorbidities are present.

Assess the Information:

- Determine if any of the patient's medications are causing the signs or symptoms.
- Review laboratory test results to establish baseline renal and hepatic function and blood cell status. Review other findings specific to RA (RF, ACPA, etc.).
- Determine disease severity.
- If the patient is already receiving pharmacotherapy for RA, assess efficacy, safety, and patient adherence.
- Review immunization history and determine if vaccinations are necessary prior to initiating new medications.

Develop a Care Plan:

LO 6

- If newly diagnosed with RA, make sure the patient receives DMARD therapy immediately to minimize disease progression and joint destruction.
- Consider bridge therapy with an NSAID or glucocorticoid to provide symptomatic relief until the DMARD reaches its time to effect (Table 57–4).
- Review current medications to proactively identify potential drug interactions with the addition of one more DMARDs.
- Select DMARD therapy that is likely to be safe and effective (see Figures 57–2 and 57–3).
- Ensure that drug doses are optimal (see Table 57–4).
- Incorporate measures to control the increased risk of present comorbidities.
  - *Cardiovascular*: Keep doses of NSAIDs and glucocorticoids low; consider initiating folic acid, low-dose aspirin, hypertensive and/or lipid therapy; encourage tobacco cessation, physical activity and a healthy diet.[13,14] Screen and aggressively treat elevated blood pressure and lipids.
  - *Infection*: Inform the patient to wash hands routinely, limit contact with individuals who are ill, and report signs and symptoms of infection immediately (eg, fever, weight loss, and night sweats).
  - *Malignancy*: Have the patient report new signs and symptoms (eg, fever, chills, anorexia, and night sweats) immediately.
  - *Osteoporosis*: Encourage the patient to ingest adequate amounts of calcium and vitamin D; consider initiating medications for prevention/treatment of osteoporosis if the patient is taking glucocorticoids chronically or has evidence of low bone mineral density.[30] Review glucocorticoid-induced osteoporosis guidelines.[31]

Implement the Care Plan:

LO 7

- Educate the patient on pharmacologic and nonpharmacologic measures, including medication administration.
- Screen for tuberculosis if initiation of a biologic DMARD or tofacitinib is under consideration.
- Stress the importance of adherence with medications and laboratory monitoring.
- Determine whether the patient has prescription coverage. If not, determine if the patient is eligible for prescription assistance programs.

Follow-up: Monitor and Evaluate:

LO 8

- Assess the patient's response to initiation of DMARD therapy after allowing adequate time for the medication to achieve its therapeutic effect.
- Determine whether any adverse reactions to medications are present.
- Reevaluate need for bridge therapy and discontinue if possible.
- Monitor laboratory parameters to ensure patient safety and reduce the risk of adverse reactions.
- Longitudinally evaluate the patient's clinical response to therapy and the impact on quality of life and mobility.
- Assess patient understanding of RA and their medications. Provide additional education where appropriate.

- Before starting treatment for RA, assess the subjective and objective evidence of disease. For joint findings, this includes the number of tender and swollen joints, pain, limitations on use, duration of morning stiffness, and presence of joint erosions. Systemic findings may include fatigue and the presence of extraarticular manifestations. Obtain laboratory measurements of CRP and ESR. The impact of the disease on quality of life and functional status is also important.
- At follow-up visits, compare the patient's status to baseline or previous visits using standardized criteria for improvement of disease activity (ie, DAS-28) and the influence on quality of life.
- KEY CONCEPT In addition to designing an individualized therapeutic regimen to control the progression of RA, the clinician must evaluate the presence of comorbidities and implement measures to control the increased risk.

Abbreviations Introduced in This Chapter

ACPA	Anticitrullinated protein antibodies
ACR	American College of Rheumatology
CRP	C-reactive protein
DAS	Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism
HAQ	Health Assessment Questionnaire
HLA	Human leukocyte antigen
IL	Interleukin
JIA	Juvenile idiopathic arthritis
MCP	Metacarpophalangeal joint
MTP	Metatarsophalangeal joint
NSAID	Nonsteroidal anti-inflammatory drug
PIP	Proximal interphalangeal joint
RA	Rheumatoid arthritis
TNF	Tumor necrosis factor

REFERENCES

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–2581.
2. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388:2023–2038.
3. Myasoedova E, Davis JM, 3rd, Crowson CS, Gabriel SE. Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. Curr Rheumatol Rep. 2010;12:379–385.
4. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun. 2010;34:J258–J265.
5. Burmester GR, Feist E, Dorner T. Emerging cell and cytokine targets in rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:77–88.
6. McCray CJ, Agarwal SK. Stress and autoimmunity. Immunol Allergy Clin North Am. 2011;31:1–18.
7. Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011;63:465–482.
8. Veale DJ, Orr C, Fearon U. Cellular and molecular perspectives in rheumatoid arthritis. Semin Immunopathol. 2017;39:343–354.
9. Boissier MC. Cell and cytokine imbalances in rheumatoid synovitis. Joint Bone Spine. 2011;78:230–234.
10. Aletaha D, Bluml S. Therapeutic implications of autoantibodies in rheumatoid arthritis. RMD Open. 2016;2:e000009.
11. Kelly V, Genovese M. Novel small molecule therapeutics in rheumatoid arthritis. Rheumatology (Oxford). 2013;52:1155–1162.
12. Pieringer H, Pichler M. Cardiovascular morbidity and mortality in patients with rheumatoid arthritis: vascular alterations and possible clinical implications. QJM. 2011;104:13–26.
13. Chodara AM, Wattiaux A, Bartels CM. Managing cardiovascular disease risk in rheumatoid arthritis: clinical updates and three strategic paproaches. Curr Rheumatol Rep. 2017;19:16.
14. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76:17–28.
15. Turesson C. Comorbidity in rheumatoid arthritis. Swiss Med Wkly. 2016;146:w14290.
16. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2015;17:212.
17. Singh JA, Saag KG, Bridges SL Jr., et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1–26.
18. Albrecht K, Zink A. Poor prognostic factors guiding treatment decisions in rheumatoid arthritis patients: a review of data from randomized clinical trials and cohort studies. Arthritis Res Ther. 2017;19:68.
19. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013;65:2499–2512.
20. Coulson EJ, Hanson HJ, Foster HE. What does an adult rheumatologist need to know about juvenile idiopathic arthritis? Rheumatology (Oxford). 2014;53:2155–2166.
21. Caporali R, Todoerti M, Sakellariou G, Montecucco C. Glucocorticoids in rheumatoid arthritis. Drugs. 2013;73:31–43.
22. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis: a revolution in care. Pediatr Rheumatol Online J. 2014;12:13.
23. Meier FM, Frerix M, Hermann W, Muller-Ladner U. Current immunotherapy in rheumatoid arthritis. Immunotherapy. 2013;5:955–974.
24. Lexi-Comp Online™, Lexi-Drugs™, Hudson, Ohio: Lexi-Comp Inc., August 2017.
25. Al-Shakarchi I, Gullick NJ, Scott DL. Current perspectives on tocilizumab for the treatment of rheumatoid arthritis: a review. Patient Prefer Adherence. 2013;7:653–666.
26. Scott LJ. Tofacitinib: a review of its use in adult patients with rheumatoid arthritis. Drugs. 2013;73:857–874.
27. Winthrop KL. Infections and biologic therapy in rheumatoid arthritis: our changing understanding of risk and prevention. Rheum Dis Clin North Am. 2012;38:727–745.
28. Dao KH, Herbert M, Habal N, Cush JJ. Nonserious infections: should there be cause for serious concerns? Rheum Dis Clin North Am. 2012;38:707–725.
29. Krause ML, Makol A. Management of rheumatoid arthritis during pregnancy: challenges and solutions. Open Access Rheumatol. 2016;8:23–36.
30. de Jong PH, Dolhain RJ. Fertility, pregnancy, and lactation in rheumatoid arthritis. Rheum Dis Clin North Am. 2017;43:227–237.

31. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheum. 2017;69:1521–1537.
32. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38:727–735.
33. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol. 2003;30:167–178.
34. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003;1:20.

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58 Osteoarthritis

Scott G. Garland, Nicholas W. Carris, and Steven M. Smith

LEARNING OBJECTIVES

LO

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

1. Explain the pathophysiologic mechanisms involved in the development of osteoarthritis (OA).
2. Identify risk factors associated with OA.
3. Recognize the clinical presentation of OA.
4. Determine the goals of therapy for individual patients with OA.
5. Formulate a rational nonpharmacologic plan for patients with OA.
6. Recommend a pharmacologic plan for treating OA, taking into consideration patient-specific factors.
7. Develop monitoring parameters to assess effectiveness and adverse effects of pharmacotherapy for OA.
8. Modify an unsuccessful treatment strategy for OA.
9. Deliver effective patient counseling, including lifestyle modifications and drug therapy, to facilitate effective and safe management of OA.

INTRODUCTION

KEY CONCEPT

Osteoarthritis is the most common form of arthritis and is strongly related to age. Weight-bearing joints (eg, hips, knees) are most susceptible, but non–weight-bearing joints, especially hands, may be involved. OA causes tremendous morbidity and financial burden because of its high prevalence and effect on joints critical for daily functioning.[1] OA is the leading cause of chronic mobility disability and the most common reason for total-hip and total-knee replacement.[2]

EPIDEMIOLOGY AND ETIOLOGY

Approximately 27 million Americans have signs and symptoms of OA.[3] OA is more common in females and older persons, affecting an estimated 10% of men and 18% of women over age 60 years. Approximately 7% of Americans experience daily symptomatic hand OA, 6% experience daily symptomatic knee OA, and 3% experience daily symptomatic hip OA.[3] Hip OA occurs more frequently in men.[4] However, women tend to have more generalized disease and joint inflammation. Some patients can develop bony enlargements of the hands, called **Bouchard nodes** or **Heberden nodes**, in the absence of inflammation. The prevalence of OA in African Americans is similar to whites, but African Americans often experience more severe and disabling disease.

PATHOPHYSIOLOGY

LO 1

OA is characterized by damage to **diarthrodial joints** and joint structures (**Figure 58–1**). The pathophysiology is multifactorial and typified by progressive destruction of joint cartilage, erratic new bone formation, thickening of **subchondral** bone and the joint capsule, bony remodeling, development of **osteophytes**, variable degrees of mild **synovitis**, and other changes.[5]

The earliest stages of OA are characterized by increasing water content and softening of cartilage in weight-bearing joints. As the disease progresses, **proteoglycan** content of cartilage declines, and eventually, cartilage becomes hypocellular. Procatabolic and proinflammatory changes precede cartilage degradation and are thought to play important roles in OA development and progression.[6]

Subchondral bone undergoes metabolic changes, including increased bone turnover, that appear to be precursors to tissue destruction. The normally contiguous bony surface becomes fissured. Persistent use of the joint eventually results in loss of cartilage, permitting bone-to-bone contact that ultimately promotes thickening and **eburnation** of exposed bone. Microfractures may appear in subchondral bone, and **osteonecrosis** may develop beneath the surface, especially in advanced disease.

New bone is formed haphazardly, creating osteophytes that extend into the joint capsule and ligament attachments and may encroach on joint space. Progressive loss of joint cartilage, subchondral damage, joint space narrowing, and changes in underlying bone and soft tissue may culminate in deformed, painful joints.

Classification

OA is classified as primary (idiopathic) or secondary. *Primary OA* is the predominant form, occurring in the absence of a known precipitating event. Primary OA may be localized, generalized, or erosive. Localized OA is distinguished from generalized disease by the number of sites involved. Erosive disease—typically in hand or foot joints—is characterized by erosive bone destruction and in some cases bony proliferations. Secondary OA results from congenital or developmental disorders or inflammatory, metabolic, or endocrine diseases.

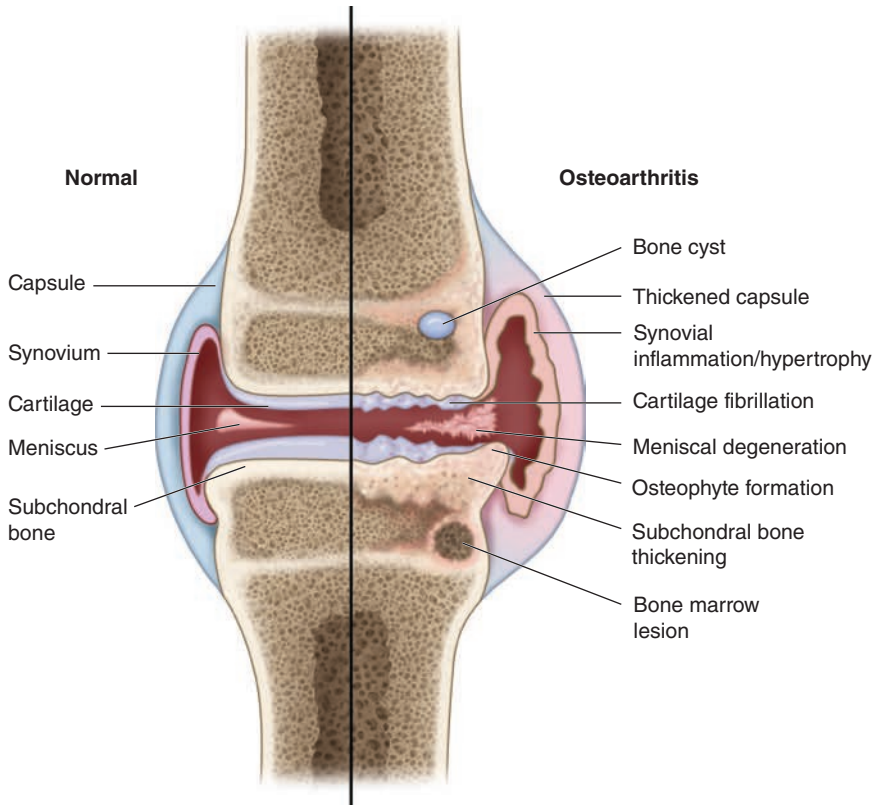

FIGURE 58–1. Characteristics of osteoarthritis in the diarthrodial joint. (From DiPiro JT, Talbert RL, Yee GC, et al., [eds.] Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017:1601, Fig. 90–2; with permission.)

Risk Factors

LO 2

OA develops when systemic factors and biomechanical vulnerabilities combine. Systemic factors include increased age, female sex, genetic predisposition, and nutritional status. Age is the strongest predictor of OA, although advanced age alone is insufficient to cause OA.

Joints exposed to biomechanical factors are at increased risk. Occupational and recreational activities involving repetitive motion or injury can provoke OA, although most daily activities do not produce enough joint trauma to cause OA. However, daily activities may lead to OA if a joint is susceptible because of previous injury, joint deformity, muscle weakness, or systemic

Clinical Presentation of OA

General

- Patients usually are more than 50 years old.
- Presentation may range from asymptomatic to severe joint pain and stiffness with functional limitations.
- Joint involvement has an asymmetric local distribution without systemic manifestations.
- Unlike some other arthritic conditions (eg, rheumatoid arthritis, gout), inflammation is usually absent or mild and localized.

Symptoms

LO 3

- KEY CONCEPT The most common symptoms are joint pain, reduced range of motion, and brief joint stiffness after inactivity.
- The cardinal symptoms are use-related joint pain, typically described as deep and aching in character, and stiffness. In advanced cases, pain may occur continuously and at rest.
- Joint stiffness ("gelling") abates with motion and recurs with rest.
- Joint stiffness generally lasts fewer than 30 minutes after extended periods of inactivity, limits the range of joint motion, impairs daily activities, and may be related to weather.
- Weight-bearing joints may be unstable.

Signs

- One or more joints may be involved, usually in an asymmetric pattern.
- The following sites are most often involved in primary OA:
  - Distal interphalangeal finger joints (Heberden nodes)
  - Proximal interphalangeal finger joints (Bouchard nodes)
  - First carpometacarpal joint
  - Knees, hips, and cervicolumbar spine
  - Metatarsophalangeal joint of the great toe
- Joint examination may reveal local tenderness, bony prominence, soft tissue swelling, crepitus, muscle atrophy, limited motion with passive/active movement, and effusion.

factors. Heavy physical activity is a stronger predictor of OA than light-to-moderate activities, especially for older individuals, in whom joint structures are less capable of coping with highly stressful activities.[7] Obesity increases load-bearing stress on hip and knee joints. OA risk increases by 10% for each kilogram above ideal body weight.[8]

CLINICAL PRESENTATION AND DIAGNOSIS

OA is diagnosed clinically from symptoms and physical examination of the joint(s), sometimes supported by radiographic evidence (see Clinical Presentation of OA). Radiographic changes are often absent in early OA. As OA progresses, joint space narrowing, subchondral bone sclerosis, and osteophytes may develop. Laboratory tests are not helpful for diagnosing OA but may rule out related diseases. The erythrocyte sedimentation rate (ESR) and the hematologic and chemistry panels are usually unremarkable in OA. Synovial fluid aspirated from an affected joint should be sterile, without crystals, and with a WBC count less than $1.5 \times 10^3/mm^3$ ($1.5 \times 10^9/L$). Gross joint deformity and joint effusions may occur in late severe OA.

TREATMENT

Desired Outcomes

LO 4

KEY CONCEPT Goals of therapy include: (a) educating the patient and caregivers, (b) relieving pain, (c) maintaining or restoring mobility, (d) minimizing functional impairment and associated adverse outcomes (eg, falls), (e) preserving joint integrity, and (f) improving quality of life.

General Approach to Treatment

Treatment is individualized considering medical history, physical examination, radiographic findings, distribution and severity of joint involvement, and response to previous treatment. Comorbid diseases, concomitant medications, and allergies are integrated into a holistic treatment approach.

Patient Encounter Part 1

A 68-year-old obese white woman presents to her primary care physician with left hip pain that has significantly worsened over the past several years. She describes the pain as dull and achy, and it is most severe in the morning after awakening until she "loosens up" 10 to 15 minutes later. She believes the morning stiffness is worse when it is overcast or raining. She has tried heating pads without relief. She also reports feeling "down" because she is no longer able to go on walks with her grandchildren when they come to visit. She is a retired store clerk in a position that required her to be on her feet for long hours in addition to lifting heavy boxes.

What information is suggestive of osteoarthritis (OA)?

What risk factors for OA does this patient have?

What other information will you need to differentiate OA from rheumatoid arthritis?

What potential comorbidities should be considered in this patient?

What other information will be required before formulating a treatment plan?

As shown in Figure 58–2, nonpharmacologic treatment is integral to achieving optimal outcomes. Pharmacologic therapy is an adjunctive measure to relieve pain; available medications do not substantially modify the disease course. Surgical intervention generally is reserved for patients with advanced disease complicated by unremitting pain or severely compromised function.

Nonpharmacologic Therapy

LO 5

KEY CONCEPT Nonpharmacologic therapy is the cornerstone of treatment: education, exercise, weight loss, and cognitive behavioral intervention are integral components.

Educational programs are designed to improve health behaviors and health status, thereby slowing OA progression. The goal is to increase patient knowledge and self-confidence in adjusting daily activities in the face of evolving symptoms. Effective programs produce positive behavioral changes, decrease pain and disability, and improve functioning and psychological outcomes (eg, depression, self-efficacy, life satisfaction). Patients can be referred to the Arthritis Foundation (www.arthritis.org) for educational materials and information on support groups.

Lifestyle modification should be encouraged for all patients at risk for, or with established OA. Low-impact exercise is advisable for most patients, especially with knee or hip OA. Aerobic exercise and strength-training programs improve functional capacity in older adults. Stretching and strengthening exercises should target affected and vulnerable joints. Isokinetic and isotonic exercises performed at least three to four times weekly improve physical functioning and decrease disability, pain, and analgesic use.

The association between body weight and OA onset and progression make weight loss a pivotal goal in overweight and obese patients. Women who reduce body weight by 5 kg (11 lb) can halve their risk of developing OA. Weight loss improves symptoms and quality of life in patients with knee OA. Weight loss should be pursued through diet modification and increased physical activity (see Chapter 102, Overweight and Obesity). Knee braces may delay the progression of knee OA. Clinicians should consider the patient's physical capabilities when implementing any exercise program. Application of heat or cold to involved joints improves range of motion, reduces pain, and decreases muscle spasms. Applications of heat include warm baths or warm water soaks. Heating pads should be used cautiously, especially in older persons, and patients must be warned of the potential for burns if used inappropriately.

Referral to a physical or occupational therapist may be helpful, particularly in patients with functional disabilities. Physical therapy is tailored to the patient and may include assessment of muscle strength, joint stability, and mobility; use of heat (especially prior to increased activity); structured exercise regimens; and assistive devices such as canes, crutches, and walkers. Occupational therapists advise on optimal joint protection and function, energy conservation, and use of splints and other assistive devices.

Pharmacologic Therapy

Simple analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line agents for treating OA (Table 58–1).

▶ *Acetaminophen*

Acetaminophen is a centrally acting analgesic that inhibits prostaglandin production in the brain and spinal cord.

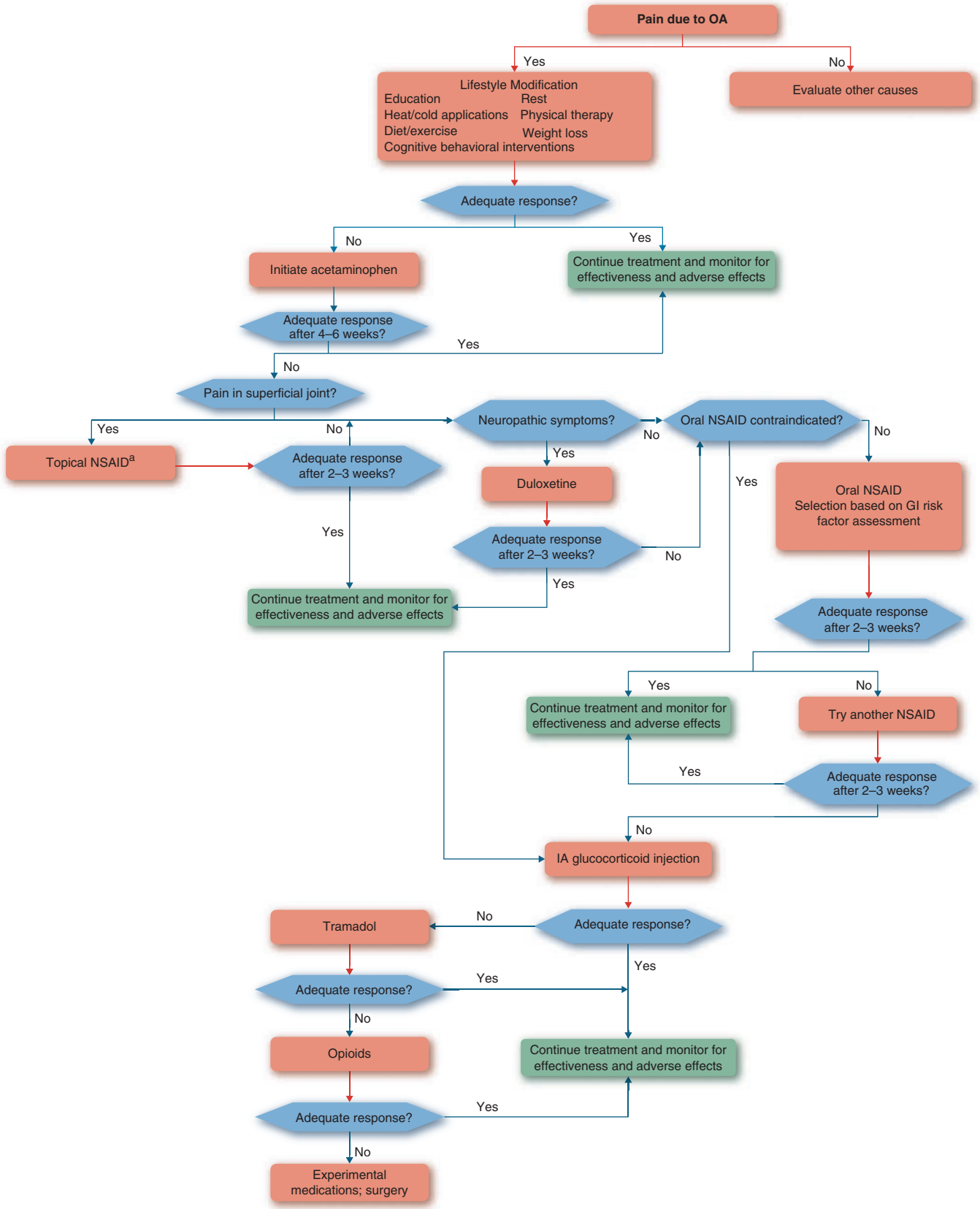

FIGURE 58–2. Treatment of osteoarthritis. (OA, osteoarthritis; CV, cardiovascular; IA, intraarticular; NSAID, nonsteroidal anti-inflammatory drug.)

[a]Topical NSAIDs can be considered before acetaminophen for superficial joints due to their favorable side effect profile and their potentially greater effect than acetaminophen.

Table 58–1

Dosing Parameters of Select Agents Used to Treat OA

Medication	Dosage and Frequency
Oral Analgesics	
Acetaminophen	325 mg every 4–6 hours or 1000 mg every 6–8 hours; max 4000 mg/day (from all sources)
Tramadol	50–100 mg every 4–6 hours; max 400 mg/day (300 mg in elderly) CrCl < 30 mL/min (0.50 mL/s): 50–100 mg every 12 hours; max 200 mg/day
Oxycodone	5–15 mg every 4–6 hours (initial dose for opioid naïve); dose depends on degree of opioid tolerance and patient response
Serotonin-Norepinephrine Reuptake Inhibitors	
Duloxetine	30–60 mg once daily; max 60 mg/day
Intraarticular Corticosteroid Injection	
Triamcinolone acetonide	2.5–15 mg for single injection; doses can be adjusted to 20–40 mg; administered not more often than every 3 months
Triamcinolone acetonide extended-release	32 mg for a single knee injection
Methylprednisolone acetate	Small joints 4–10 mg; medium joints 10–40 mg; large joints 20–80 mg; administered no more often than every 3 months
Intraarticular Hyaluronic Acid Injection	
Hyaluronic Acid	16–30 mg injected into the affected knee every week for a total of 3–5 weeks, depending on the product (see text)
Oral NSAIDs by Chemical Class	
Carboxylic acid (salicylates)	
Aspirin	325–650 mg every 4–6 hours; max 3600 mg/day
Salsalate	500–1000 mg two to three times daily; max 3000 mg/day
Acetic acid	
Etodolac	300–600 mg twice daily; max 1200 mg/day 400–1000 mg once daily (extended-release)
Diclofenac	50 mg two to three times daily 75 mg twice daily (delayed-release tablets) 100 mg once daily (extended-release tablets) 35 mg three times daily (submicron particle capsules) Max 150 mg/day from any formulation
Indomethacin	25 mg two to three times daily 75 mg one to two times daily (sustained-release) Max 200 mg/day from any formulation
Nabumetone	500–1000 mg one to two times daily; max 2000 mg/day
Propionic acid	
Ibuprofen	400–800 mg three to four times daily; max 3200 mg/day
Naproxen	250–500 mg two times daily 750–1000 mg once daily (controlled-release) 275–550 mg two times daily (naproxen sodium) Max 1650 mg/day from any formulation
Enolic acid	
Meloxicam	7.5–15 mg once daily; max 15 mg/day
Piroxicam[c]	20 mg once daily; max 20 mg/day
Coxibs	
Celecoxib[c]	100 mg twice daily or 200 mg once daily; max 200 mg/day
Topical Analgesics	
Capsaicin 0.025% or 0.075% cream	Apply to affected joint every 6–8 hours
Diclofenac sodium 1% gel	Upper extremity joints: 2 g four times daily; max 8 g[b] per upper extremity joint per day Lower extremity joints: 4 g four times daily; max 16 g[b] per joint per day
Diclofenac sodium 1.5% solution	40 drops per affected knee, four times per day; max 160 drops per day per knee
Diclofenac sodium 2% solution	40 mg (2 pump actuations) on each painful knee, two times a day; max 80 mg per day per knee
Dietary Supplements	
Glucosamine sulfate	500 mg three times daily or 1500 mg once daily
Chondroitin	400–800 mg up to three times daily with glucosamine

[a]Serum salicylate levels should be monitored for doses greater than 3 g/day.

[b]Total daily dose of diclofenac 1% gel should not exceed 32 g for all affected joints.

[c]Substrate for CYP2C9, consider a 50% reduction in the initial dose in known or suspected poor metabolizers.

CrCl, creatinine clearance.

KEY CONCEPT Acetaminophen is an inexpensive analgesic with a favorable risk–benefit profile. Although less effective than NSAIDs, acetaminophen may be tried initially at an adequate dose and duration in patients with mild-to-moderate pain, before considering an oral NSAID.[9-12]

Acetaminophen should be administered initially on an as-needed basis in divided doses up to 4 g daily. Single doses should not exceed 1 g. Some patients may require scheduled dosing to achieve adequate pain relief. Periodic assessment of pain control should be performed to maintain the lowest effective dose. Insufficient acetaminophen dose or duration are common reasons for inadequate response. A sufficient trial is defined as up to 4 g daily in divided doses for 4 to 6 weeks.

Despite being among the safest analgesics, acetaminophen can cause significant adverse effects, including hepatic and renal toxicity.[13] Acetaminophen overdose, both intentional and unintentional, is the leading cause of acute liver injury in the United States.[14] Doses greater than 4 g are associated with increased risk of hepatotoxicity. Total daily doses of 4 g have been associated with significant liver enzyme elevations, but such elevations do not necessarily portend hepatotoxicity.[15] Concomitant use of alcohol may increase risk of hepatic injury; a maximum acetaminophen dose of 2.5 g daily is recommended in patients who consume more than 2 to 3 alcoholic beverages daily. Acetaminophen does not appear to exacerbate stable, chronic liver disease, but liver function should be monitored regularly in this population.[13] Careful inventory should be taken of all concomitant prescription and over-the-counter (OTC) products to minimize the risk of inadvertent acetaminophen overdose.

Acetaminophen may worsen kidney function and increase blood pressure.[16,17] Nevertheless, acetaminophen remains the preferred oral analgesic for mild-to-moderate pain in patients with hypertension or kidney disease because of the greater risks associated with systemic NSAIDs.[18] Monitoring specifically for these adverse effects generally is unnecessary.

▶ *Nonsteroidal Anti-inflammatory Drugs*

Prostaglandins play an important role in the function of several organ systems. These compounds are synthesized via the interaction of two isoforms of the **cyclooxygenase** enzyme (COX-1 and COX-2) with their substrate, arachidonic acid.

The COX-1 enzyme is expressed constitutively in various body tissues (eg, gastric mucosa, kidney, platelets). Prostaglandins produced by the actions of the COX-1 enzyme in the gastrointestinal (GI) tract preserve GI mucosal integrity by increasing mucous and bicarbonate secretion, maintaining mucosal blood flow, and decreasing gastric acid secretion. Prostaglandins associated with COX-1 also promote normal platelet activity and function. In the kidney, COX-1–mediated prostaglandins dilate the afferent arteriole, thereby maintaining intraglomerular pressure and glomerular filtration rate when renal blood flow is reduced.

In contrast, the COX-2 enzyme is normally undetectable in most tissues, but its expression can be induced rapidly in the presence of inflammation and local tissue injury. This change leads to the synthesis of prostaglandins involved in pain and inflammation. Consequently, blocking the COX-2 enzyme is thought to result in analgesic and anti-inflammatory effects. All NSAIDs inhibit both the COX-1 and COX-2 enzyme isoforms, but nonselective NSAIDs (eg, ibuprofen, naproxen) are not particularly selective for one isoform, whereas COX-2 inhibitors (ie, celecoxib) preferentially inhibit COX-2.

KEY CONCEPT NSAIDs are a reasonable first-line therapy in patients with moderate-to-severe OA or as adjunctive or alternative therapy when acetaminophen fails to provide an acceptable analgesic response. NSAIDs reduce pain and improve functioning in patients with OA, although individual responses vary widely. Pooled analyses suggest that NSAIDs improve OA pain more than acetaminophen, although direct comparisons have yielded mixed results.[10] Consensus guidelines support the use of NSAIDs as an alternative to acetaminophen if clinical features of peripheral inflammation or severe pain are present.[9] The route of administration (ie, oral or topical) should be based on affected joint(s), patient preference, ability to administer, and an assessment of risk for adverse effects of systemic NSAIDs.

Topical NSAID administration minimizes systemic exposure while providing pain relief comparable to oral NSAIDs. Consequently, topical NSAIDs may be an acceptable alternative first-line treatment to acetaminophen for patients with OA in a superficial joint, including hands, wrists, elbows, knees, ankles, and feet. Currently, the only commercially available topical NSAID in the United States is diclofenac, which is marketed in a variety of preparations (ie, solution, gel, topical patch). These products decrease pain and improve joint function without demonstrated superiority for any one product.[19,20] Systemic absorption of topical diclofenac is significantly less than that of oral diclofenac. Thus, with proper administration, GI, cardiovascular, and renal adverse effects are rare and similar in incidence to placebo.[19,20] The most common adverse effects are application site dermatitis, pruritus, and phototoxicity.

For patients with OA affecting deeper joints (ie, hip, shoulder, spine), or who have not achieved adequate response to topical NSAIDs, an oral NSAID should be considered. KEY CONCEPT At equipotent doses, the analgesic and anti-inflammatory activities of all oral NSAIDs, including COX-2–selective inhibitors, are similar. The selection of a specific oral NSAID should be based on patient preference, previous response, tolerability, side-effect profile, dosing frequency, cost, and underlying GI risk. Pain relief occurs rapidly (within hours), but anti-inflammatory response occurs after 2 to 3 weeks of continuous therapy. This latter period is the minimal duration that should be considered an adequate NSAID trial. If an insufficient response is achieved with one oral NSAID, another oral agent should be tried.

KEY CONCEPT All systemic NSAIDs are associated with adverse GI, renal, hepatic, cardiovascular, central nervous system (CNS), and hypertensive effects, particularly in older individuals. Inhibition of the COX-1 enzyme is thought to be responsible primarily for the adverse effects on the gastric mucosa, kidney, and platelets. Direct irritant effects also may contribute to adverse GI events. Minor GI complaints, including nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea, are reported by 10% to 60% of patients treated with oral nonselective NSAIDs. Asymptomatic gastric and duodenal mucosal ulceration can be detected in 15% to 45% of patients.[21] Perforation, gastric outlet obstruction, and GI bleeding are the most severe complications and occur in 1.5% to 4% of patients annually.[21]

KEY CONCEPT COX-2 inhibitors are preferred for patients at high risk for GI complications.[22] Several risk factors predict a greater likelihood of GI complications in NSAID-treated patients (see Chapter 18, Peptic Ulcer Disease). Identifying at-risk patients based on symptoms alone is impractical because the presence of symptoms and actual gastroduodenal damage are poorly correlated. For patients at particularly high GI risk (eg, previous history of NSAID-induced GI bleed), a selective

COX-2 inhibitor combined with a proton pump inhibitor reduces risk for GI bleeds more than a COX-2 inhibitor alone, which in turn has lower GI bleed risk than a nonselective NSAID combined with a proton pump inhibitor.[23–26] See Chapter 17 (Gastroesophageal Reflux Disease) for more information on proton pump inhibitors.

COX-2 inhibitors have historically been associated with a greater risk of MI than nonselective NSAIDs, which led to removal of rofecoxib and valdecoxib from the market.[27] However, direct comparison of naproxen, ibuprofen, and celecoxib suggests similar cardiovascular risk between these agents.[28] Nevertheless, all NSAIDs, except low-dose aspirin, increase cardiovascular risk.[29] Accordingly, NSAIDs should be used at the lowest effective dose for the shortest duration, consistent with individual patient treatment goals, to limit risk. All oral NSAIDs can increase blood pressure, and patients with hypertension should be monitored within the first 2 to 4 weeks of initiation and periodically thereafter.[30]

All NSAIDs can cause adverse renal effects. Patients who are particularly susceptible include older persons and patients with chronic renal insufficiency, left ventricular dysfunction, and those taking diuretics or drugs that interfere with the renin–angiotensin system. These effects include decreased glomerular filtration, hyperkalemia, and sodium and water retention. Therefore, both nonselective NSAIDs and selective COX-2 inhibitors should be used with caution in patients with hypertension, heart failure, or chronic renal insufficiency. NSAIDs rarely cause **tubulointerstitial** nephropathy and renal papillary necrosis.

Like most medications, NSAIDs should be avoided if possible during pregnancy due to potential risks to the fetus. However, all NSAIDs should be strictly avoided starting at 30 weeks gestation to prevent premature closure of the ductus arteriosus in the fetus.

Nonselective NSAIDs and selective COX-2 inhibitors are prone to drug interactions due to high protein binding, detrimental renal effects, and antiplatelet activity. Interactions are encountered frequently with aspirin, warfarin, oral hypoglycemics, antihypertensives, and lithium. When potential interactions are present, vigilant monitoring is warranted for therapeutic efficacy (eg, NSAIDs blunt the antihypertensive efficacy of diuretics) and adverse effects (eg, NSAIDs increase the risk of bleeding in anticoagulated patients).

▶ *Tramadol*

Tramadol is an oral, centrally acting synthetic opioid analgesic that also weakly inhibits serotonin and norepinephrine reuptake. Tramadol has been shown to relieve OA pain (albeit minimally), and is a reasonable option for patients with contraindications to NSAIDs or in those who have failed to respond to other oral therapies.[31,32] The addition of tramadol to NSAIDs or acetaminophen may augment the analgesic effects of a failing regimen and provide sufficient pain relief in some patients.[32] Moreover, concomitant tramadol may permit lower NSAID doses. However, the increased side effect risk associated with tramadol may offset these benefits.[31]

Common adverse events include dizziness, vertigo, nausea, vomiting, constipation, and lethargy. These effects are more pronounced for several days after initiation or a dose increase. Seizures have been reported rarely; the risk is dose-related and appears to increase with concomitant use of antidepressants, such as tricyclics or selective serotonin reuptake inhibitors. Tramadol should be avoided in patients receiving monoamine oxidase inhibitors due to the potential for serotonin syndrome.

▶ *Other Opioid Analgesics*

Opioid analgesics other than tramadol are reserved for patients experiencing pain severe enough to require opioid treatment for which alternative options are inadequate or contraindicated (eg, renal failure, heart failure, anticoagulation). Opioids may decrease pain, improve sleep patterns, and increase functioning in patients with OA who are unresponsive to nonpharmacologic therapy and nonopioid analgesics. However, opioids also increase the risk for addiction and other serious adverse effects that limit their use in most patients.[32] Small improvement in OA pain has been demonstrated with oxycodone, oxymorphone, morphine, hydromorphone, codeine, buprenorphine, and transdermal fentanyl, but with significant increased risk of serious side effects.[33]

Opioids should be initiated with short-acting agents at low doses and titrated to the lowest effective dose to minimize adverse events. When feasible, opioids should be combined with acetaminophen or NSAIDs to reduce the opioid requirement. However, adverse effects from opioids are common even with the lowest effective doses.[33] Common or serious adverse effects include nausea, constipation, sedation, and respiratory depression. Use of combination opioid-acetaminophen products should be accompanied by clear instructions to limit additional use of OTC acetaminophen to avoid unintentional overdose.

Clinicians should establish realistic pain and function goals for all patients before starting opioid therapy. The Centers for Disease Control and Prevention recommends taking a detailed history, providing information regarding treatment expectations, and developing a management plan with goals and safeguards, including how opioid therapy will be discontinued if benefits do not outweigh risks (see Chapter 34, Pain Management). Additional recommendations to mitigate the risk of opioid therapy misuse include frequent follow-up, urine drug testing initially and at least yearly thereafter to assess use of prescribed medications or other illicit substances, and use of prescription drug monitoring programs to identify filling of opioid prescriptions from other providers. Patient response to opioid therapy should be assessed within 1 to 4 weeks of initiation or dose increase and every 3 months thereafter. Clinicians should use both nonopioid analgesics and nondrug therapies, as appropriate, to lower opioid doses or taper to opioid discontinuation.[32]

▶ *Duloxetine*

Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is an effective adjunctive therapy for knee OA in patients achieving a suboptimal response to acetaminophen or oral NSAIDs alone.[34] Benefits typically are observed only after several weeks of therapy with moderate doses (ie, 60 mg/day); larger doses do not provide additional benefit.[35] Duloxetine may be the preferred adjunctive treatment in patients experiencing concurrent neuropathic and musculoskeletal pain. The most common adverse events are nausea, dry mouth, somnolence, constipation, decreased appetite, and hyperhidrosis.[35] Concomitant use with tramadol should be pursued cautiously owing to an increased risk of serotonin syndrome. For more duloxetine information, see Chapters 38 (Major Depressive Disorder) and 39 (Bipolar Disorder).

▶ *Intraarticular Therapy*

Intraarticular (IA) therapy is an alternative to oral and topical agents for joint pain treatment. Two IA therapies, corticosteroids and hyaluronic acid, have been used as second-line therapy in OA. However, the ideal injection agent is still debated.[36]

IA injection, per se, appears to be remarkably effective, at least for knee OA, where IA placebo injections have similar efficacy to oral NSAIDs.[36] Whether injection of specific agents improve on the substantial placebo effect remains a subject of debate. Nevertheless, these injections are used to improve symptoms but do not reverse disease progression.[4] Therefore, IA injections are usually reserved for patients unresponsive to other treatments because they are more invasive, have a small infection risk, and the procedure may be expensive.

Corticosteroids KEY CONCEPT Current evidence suggests limited benefit of intraarticular corticosteroids over placebo in the general OA population.[37] However, IA corticosteroids may still play a role in the subset of patients with significant inflammation or effusion. Corticosteroids with reduced solubility, such as methylprednisolone and triamcinolone, are usually preferred. The affected joint can be aspirated and subsequently injected with the corticosteroid. The aspirate should be examined for the presence of crystal formation and infection. Pain relief begins within days after the injection but may wane beyond 3 weeks for most agents. The triamcinolone acetonide extended-release product may provide pain relief for up to 12 weeks. Corticosteroid injections should be administered as infrequently as possible to avoid joint damage. Specifically, a single joint should not be treated more than 3 to 5 times per year to reduce the risk of corticosteroid-induced cartilage and joint damage. Because the recommended dosing interval exceeds the typical duration of benefit for most agents, IA corticosteroids are usually ineffective as monotherapy for chronic OA treatment.

The crystalline nature of corticosteroid suspensions can provoke a postinjection flare that mimics the flare of arthritis and inflammation that accompanies infection. Cold compresses and analgesics are recommended to treat symptoms in affected patients.

Hyaluronic Acid The mechanism of action of hyaluronic acid is not fully understood. Healthy cartilage and synovial fluid are replete with hyaluronic acid, a viscous substance believed to facilitate lubrication and shock absorbency under varying load-bearing conditions. Patients with OA demonstrate an absolute and functional decline in hyaluronic acid; thus, exogenous administration is referred to as viscosupplementation.

Pain and joint function following IA hyaluronic acid injections have been evaluated frequently in clinical trials, most of which were of low quality. Evidence is conflicting, but hyaluronic acid appears to offer no substantial benefit over placebo injections, and treatment courses are relatively expensive. Hyaluronic acid is not recommended in current treatment guidelines.[9]

Several hyaluronic acid formulations are available in the United States for knee OA:

- Euflexxa: 20 mg (2 mL) injected every week for a total of 3 weeks
- Hyalgan: 20 mg (2 mL) injected every week for a total of 5 injections
- Orthovisc: 30 mg (2 mL) injected every week for a total of 3 to 4 weeks
- Synvisc: 16 mg (2 mL) injected every week for a total of 3 weeks
- Synvisc-One: 48 mg (6 mL) for a single injection

Injections are generally well tolerated, although patients may report local reactions. Rarely, postinjection flares or anaphylaxis has been reported. Patients should be counseled to minimize activity and stress on the joint for several days after each injection.

▶ *Over-the-Counter Agents*

Glucosamine and Chondroitin Glucosamine is believed to function as a "chondroprotective" agent, stimulating the cartilage matrix and protecting against oxidative chemical damage. Chondroitin, often administered with glucosamine, is thought to inhibit degradative enzymes and serve as a substrate for proteoglycan production. Previous high-quality evidence suggested no clinically important benefit with the combination of chondroitin-glucosamine compared to placebo in patients with knee OA.[38] However, recent evidence suggests that monotherapy with chondroitin may improve knee OA symptoms similarly to celecoxib.[39] If used, these agents should be adjuncts to traditional nonpharmacologic and pharmacologic therapies and discontinued after 3 to 6 months if no benefit is achieved.[9]

Patients with shellfish allergies should be warned of the potential for severe anaphylactic reactions with the use of glucosamine products (derived from crab, lobster, or shrimp shells). Because the allergic reaction is caused by shellfish proteins rather than the animal shell, most products pose little risk.[40,41] However, patients should be aware that products may be contaminated with shellfish proteins given that these agents are loosely regulated in the United States as dietary supplements, product standards are inconsistent, and the constituents are not validated by any regulatory agency. Additionally, glucosamine may alter cellular glucose uptake, thus elevating blood glucose levels in patients with diabetes.[42] Because the clinical significance of this is unclear, blood glucose levels in diabetic patients should be monitored closely after glucosamine initiation or dosage adjustments.

Other Topical Agents Limited data support use of salicylate-containing **rubefacients** (eg, methyl salicylate, trolamine salicylate) or other **counterirritants** (eg, menthol, camphor, methyl nicotinate) in OA.[43] See Chapter 60 (Musculoskeletal Disorders) for more information on these products.

Capsaicin relieves pain by depleting substance P from spinal sensory neurons, thereby decreasing pain transmission. Capsaicin is not effective for acute pain; it may take up to 2 weeks of daily administration to relieve pain. As with other topical products, capsaicin is best suited for treating superficial joints (eg, hand OA). The lower concentration (0.025%) is better tolerated, but most patients experience a localized burning sensation. The discomfort usually does not result in discontinuation and often abates within the first week with regular use. Contact with eyes or mucous membranes should be avoided and patients should be counseled to wash their hands after application.

Surgery

Surgery generally is reserved for patients who fail medical therapy and have progressive limitations in activities of daily living. In joint replacement surgery (arthroplasty), the damaged joint surfaces are replaced with metal or plastic prostheses. Hip and knee joints are most commonly replaced, but arthroplasty may also be performed on shoulders, elbows, fingers, and ankles. Total knee arthroplasty combined with physical and medical therapy improves knee OA symptoms more than physical and medical therapy alone.[44] Most patients achieve significant pain relief and functional restoration after arthroplasty, and it is a reasonable option in carefully selected patients.

Surgical debridement may be performed arthroscopically. With this procedure, a tiny video camera is inserted into the affected joint through a small incision, and the surgeon removes

torn cartilage or other debris from the joint. The long-term benefits of arthroscopic surgery for OA are unclear, and it may be no better than optimized physical and medical therapy.[45]

OUTCOME EVALUATION

- At baseline, quantify pain using a visual analog scale, assess range of motion of affected joints, and identify activities of daily living that are impaired.
- In patients treated with acetaminophen or oral NSAIDs, assess pain control after 2 to 3 weeks. Full anti-inflammatory effects of NSAIDs may take longer to occur.
- Incorporate other measures to track disease progress. Use radiography to assess severity of joint destruction, determine 50-ft (~15-m) walking time and grip strength, and administer the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Stanford Health Assessment Questionnaire, where appropriate, to assess activities of daily living.
- If pain control is adequate, continue the current therapy at the lowest effective dose. If pain is improving but still inadequate, titrate to maximum therapeutic dose or consider adjunctive agents. If the patient has no improvement after 2 weeks, assess medication adherence and consider switching therapy.
- Ask patients if they are experiencing side effects or other problems with their medications and respond with more specific questions.
- Educate patients to not exceed maximum daily doses of medications.

Patient Encounter Part 3: Creating a Care Plan

Based on the available information, create a care plan for this patient's OA. The plan should include:

(a) A statement of the drug-related needs and/or problems

(b) An individualized, detailed therapeutic plan

(c) A plan for follow-up monitoring to document the patient's response and identify adverse reactions

- Consider baseline liver function tests in patients being prescribed acetaminophen who are at high risk for hepatoxicity.
- Assess acetaminophen exposure from all sources, including OTC products.
- In patients with hypertension, who are taking oral NSAIDs, monitor blood pressure at baseline, every 2 to 4 weeks for 1 to 2 months, and then periodically thereafter.
- For patients prescribed NSAIDs, monitor for weight gain, edema, and skin rash, and inquire about CNS adverse effects such as headaches and drowsiness at baseline and at least every 6 to 12 months.
- Evaluate serum creatinine, complete blood count, and serum transaminases at baseline and at every 6 to 12 months in patients treated with oral NSAIDs or acetaminophen.
- Perform stool guaiac in patients taking oral NSAIDs when clinically indicated.
- Monitor for drug interactions, including with alcohol, at every visit.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Obesity (BMI 32 kg/m^2), HTN for 24 years, dyslipidemia, coronary artery disease, COPD

PSH: Hysterectomy 12 years ago

FH: Father had OA of the hip and knee; mother died of MI at age 68

SH: Retired clerk. Consumes one glass of wine per day; denies illicit drug use; smoked one pack of cigarettes per day for 35 years but quit 3 years ago

Allergies: NKDA; shellfish allergy (hives)

Meds: Losartan 50 mg once daily; rosuvastatin 20 mg once daily; enteric-coated aspirin 81 mg once daily; tiotropium 18 mcg by inhalation once daily; albuterol 1 to 2 puffs as needed for wheezing/shortness of breath; acetaminophen 500 mg, one tablet 2 to 4 times per day as needed for pain

ROS: (+) SOB on exertion, left hip pain 6 out of 10 with movement

PE:

VS: BP 138/85 mm Hg, Pulse 70 beats/min, RR 13 breaths/min, T 98.6°F (37.0°C)

Skin: Warm, dry, cracked skin on feet bilaterally

HEENT: NC/AT, PERRLA, TMs intact

CV: RRR, normal S_1 and S_2, no m/r/g

Chest: CTA

Abd: Soft, NT/ND

Neuro: A&O × 3; CN II to XII intact

Ext: No edema, swelling, or tenderness of the soft tissue surrounding left hip. Noticeable crepitus and decreased range of motion of the left hip. No other joint involvement.

Labs: ESR 12 mm/hour; basic metabolic panel within normal limits

Hip x-rays: Left hip shows joint space narrowing, minor osteophyte formation, and subchondral bone sclerosis

What clinical parameters are consistent with a diagnosis of OA?

What are the treatment goals for this patient?

What nondrug options are available to treat this patient?

What pharmacologic options are available to treat this patient?

What factors are important to consider when selecting medications for this patient?

Pharmacist's Patient Care Process

Collect Information:

- Obtain a thorough history of previous device and drug use, including prescription drugs, OTC drugs, and dietary supplements.
- Ask the patient about known allergies to medications and other substances, including type and severity of reaction.
- Determine lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect overall patient care.
- Consider obtaining laboratory tests depending on degree of clinical suspicion for inflammatory etiology (eg, ESR, C-reactive protein [CRP], rheumatoid factor [RF], antinuclear antibodies [ANA]).

Assess the Information:

- Determine whether the patient's symptoms are consistent with OA. Review the medical history to determine whether other rheumatic diseases may be involved.
- Assess symptoms to determine whether pain warrants additional attention. Does the pain affect quality of life or interfere with activities of daily living?
- Assess radiographs for diagnosis and disease severity (joint-space narrowing, subchondral bone sclerosis, osteophyte formation, joint deformity, joint effusion).

Develop a Care Plan:

- At baseline, quantify pain using a visual analog scale, assess range of motion of affected joints, and identify activities of daily living that are impaired.
- Evaluate the effectiveness of current or previous pharmacotherapy, including dose, frequency, and duration to determine whether an adequate trial was given.
- Establish realistic treatment goals with the patient, including acceptable levels of pain and function.
- Formulate a plan for lifestyle modifications and alteration/addition of pharmacotherapy that considers risks, benefits, and patient preference, given the patient's medical history, concomitant medications, and previous response to OA therapies.

Implement the Care Plan:

- Discuss with the patient any modifications to nondrug or pharmacological treatment plans and how to implement the new care plan.
- Address patient concerns related to OA and its treatment, with special focus on the expected benefits and potential adverse effects of medications.
- Emphasize the value of adherence to medication regimens and lifestyle modifications.
- Facilitate adherence by implementing medication regimens and lifestyle plans that are simple and consistent with the patient's lifestyle.

Follow-up: Monitor and Evaluate:

- Schedule follow-up within 1 to 2 weeks to assess the effectiveness of therapy and associated adverse effects; the specific time frame depends on patient factors and the treatment regimen chosen.
- If laboratory tests (eg, renal function for NSAIDs) are appropriate for monitoring drug therapy, provide the patient with an order for the laboratory test(s) and instructions to complete them before the follow-up appointment.
- If the patient has hypertension and is taking an oral NSAID, monitor blood pressure at each follow-up visit within 2 to 4 weeks of initiating therapy and then every 1 to 2 months.
- Document whether the patient has had improvements in pain, quality of life measures, mobility and functioning, ability to perform activities of daily living, and well-being.
- If pain control is adequate, continue the current therapy at the lowest effective dose. If pain is improving but still inadequate, titrate as needed to the maximum therapeutic dose or consider adjunctive agents. If the patient has no improvement after 2 weeks, assess medication adherence and consider switching therapy.
- Ascertain new OTC medication use; for patients prescribed acetaminophen or oral NSAIDs, pay particular attention to OTC sources of these drugs.
- Evaluate for the presence of adverse drug reactions, drug hypersensitivity, and potential drug interactions.

Abbreviations Introduced in This Chapter

ANA	Antinuclear antibodies
BMI	Body mass index
CNS	Central nervous system
COX	Cyclooxygenase
CRP	C-reactive protein
CYP	Cytochrome P450
ESR	Erythrocyte sedimentation rate
GI	Gastrointestinal
IA	Intraarticular
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OTC	Over-the-counter
RF	Rheumatoid factor

REFERENCES

1. Centers for Disease Control and Prevention. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions—United States, 2003. MMWR Morb Mortal Wkly Rep. 2007;56:4–7.
2. Centers for Disease Control and Prevention. Prevalence of disability and disability type among adults—United States, 2013. MMWR Morb Mortal Wkly Rep. 2015;64:777–783.
3. The National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II. Arthritis Rheum. 2008;58:26–35.
4. Glyn-Jones S, Palmer AJ, Agricola R, et al. Osteoarthritis. Lancet. 2015;386:376–387.
5. Bijlsma JWJ, Berenbaum F, Lafeber FPJG. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377:2115–2126.

6. Loeser, RF, Collins JA, Kiekman BO. Aging and pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12:412–420.
7. McAlindon TE, Wilson PW, Aliabadi P, et al. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham Study. Am J Med. 1999;106:151–157.
8. Fife RS. Epidemiology, pathology, and pathogenesis. In: Klippel JH, ed. Primer on Rheumatic Diseases, 11th ed. Atlanta, GA: Arthritis Foundation; 1997:216–217.
9. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012;64:465–474.
10. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390:e21–e33.
11. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015;350:h1225. doi: 10.1136/bmj.h1225.
12. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med. 2015;162(1):46–54.
13. Graham GG, Scott KF, Day RO. Tolerability of paracetamol. Drug Saf. 2005;28:227–240.
14. Larson AM, Polson J, Fontana RJ, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter prospective study. Hepatology. 2005;42:1364–1372.
15. Watkins PB, Kaplowitz N, Slattery JT, et al. Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily. JAMA. 2006;296:87–93.
16. Fored CM, Ejerblad E, Lindblad P, et al. Acetaminophen, aspirin, and chronic renal failure. N Engl J Med. 2001;345:1801–1808.
17. Curhan GC, Knight EL, Rosner B, et al. Lifetime non-narcotic analgesic use and decline in renal function in women. Arch Intern Med. 2004;164:1519–1524.
18. Forman JP, Stampfer MJ, Curhan GC. Non-narcotic analgesic dose and risk of incident hypertension in U.S. women. Hypertension. 2005;46:500–507.
19. Baraf HS, Gloth FM, Barthel HR, et al. Safety and efficacy of topical diclofenac sodium gel for knee osteoarthritis in elderly and younger patients: pooled data from three randomized, double-blind, parallel-group, placebo-controlled, multicentre trials. Drugs Aging. 2011;28:27–40.
20. Derry, S, Conaghan P, Da Silva JAP. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2016;(4):CD007400.
21. Laine L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. Gastroenterology. 2001;120:594–606.
22. Lanza FL, Chan FKL, Quigley EMM. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728–738.
23. Chan FKL, Wong VWS, Suen BY, et al. Combination of a cyclo- oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomized trial. Lancet. 2007;369:1621–1626.
24. Rahme E, Barkun AN, Toubouti Y, et al. Do proton-pump inhibitors confer additional gastrointestinal protection in patients given celecoxib? Arthritis Rheum. 2007;57:748–755.
25. Chan FK, Lanas A, Scheiman J, Berger MF, Nguyen H, Goldstein JL. Celecoxib versus omeprazole and diclofenac in patients with osteoarthritis and rheumatoid arthritis (CONDOR): a randomised trial. Lancet. 2010;376:173–179.
26. Chan FK, Ching JY, Tse YK, et al. Gastrointestinal safety of celecoxib versus naproxen in patients with cardiothrombotic diseases and arthritis after upper gastrointestinal bleeding (CONCERN): an industry-independent, double-blind, double-dummy, randomised trial. Lancet. 2017;389:2375–2382.
27. Drazen JM. COX-2 inhibitors—a lesson in unexpected problems. N Engl J Med. 2005;352:1131–1132.
28. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med. 2016;375:2519–2529.
29. Kohli P, Steg PG, Cannon CP, et al. NSAID use and association with cardiovascular outcomes in outpatients with stable atherothrombotic disease. Am J Med. 2014;127:53–60.
30. Lovell AR, Ernst ME. Drug-induced hypertension: focus on mechanisms and management. Curr Hypertens Rep. 2017;19(5):39.
31. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database Syst Rev. 2006;(3): CD005522.
32. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315:1624–1645.
33. da Costa BR, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2014;(9):CD003115.
34. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22:363–388.
35. Cymbalta [package insert]. Indianapolis, IN: Eli Lilly and Company; 2012. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=2f7d4d67-10c1-4bf4-a7f2-c185fbad64ba#s145. Accessed July 15, 2017.
36. Bannuru RR, McAlindon TE, Sullivan MC, et al. Effectiveness and implications of alternative placebo treatments: a systematic review and network meta-analysis of osteoarthritis trials. Ann Intern Med. 2015;163:365–372.
37. Jüni P, Hari R, Rutjes AW, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev. 2015;(10):CD005328.
38. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006;354:795–808.
39. Reginster JY, Dudler J, Blicharski T, Pavelka K. Pharmaceutical-grade Chondroitin sulfate is as effective as celecoxib and superior to placebo in symptomatic knee osteoarthritis: the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT). Ann Rheum Dis. 2017;76:1537–1543.
40. Gray HC, Hutcheson PS, Gray RG. Is glucosamine safe in patients with seafood allergy? J Allergy Clin Immunol. 2004;114:459–460.
41. Sicherer SH, Sampson HA. Food allergy: epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291–307.
42. Dostrovsky NR, Towheed TE, Hudson RW, Anastassiades TP. The effect of glucosamine on glucose metabolism in humans: a systematic review of the literature. Osteoarthritis Cartilage. 2011;19:375–380.
43. Mason L, Moore RA, Edwards JE, et al. Systematic review of efficacy of topical rubefacients containing salicylates for the treatment of acute and chronic pain. BMJ. 2004;328:995–998.
44. Skou ST, Roos EM, Laursen MB, et al. A randomized, controlled trial of total knee replacement. N Engl J Med. 2015;373:1597–1606.
45. Kirkley A, Birmingham TB, Litchfield RB, et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med. 2008;359:1097–1107.

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59 Gout and Hyperuricemia

Maria Miller Thurston

LEARNING OBJECTIVES

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

LO

1. Explain the pathophysiologic mechanisms underlying gout and hyperuricemia.
2. Recognize major risk factors for developing gout in a given person.
3. Assess the signs and symptoms of an acute gout attack.
4. List the treatment goals for a patient with gout.
5. Develop a pharmacotherapeutic plan for a patient with acute gouty arthritis that includes individualized drug selection and monitoring for efficacy and safety.
6. Identify patients for whom prophylactic urate-lowering therapy for gout and hyperuricemia is warranted.
7. Formulate appropriate educational information for a patient on lifestyle modifications to help prevent gouty arthritis attacks.
8. Select an appropriate drug to reduce serum uric acid (SUA) levels in patients with gout, and outline a plan for monitoring efficacy and toxicity.

INTRODUCTION

KEY CONCEPT Gout is an inflammatory condition of the arthritis-type that results from deposition of uric acid crystals in joint spaces or surrounding tissues, leading to an inflammatory reaction that causes intense pain, erythema, and joint swelling. It is associated with hyperuricemia, defined as a SUA level of 6.8 mg/dL (404 μmol/L) or greater, but not all patients with hyperuricemia demonstrate symptoms.[1] Four organizations publish guidelines that provide recommendations for the diagnosis and/or management of gout.[2-9] There is much similarity in the recommendations, and this chapter focuses primarily on the consensus expert panel recommendations of the American College of Rheumatology (ACR).[5,6] However, the American College of Physicians (ACP) guideline includes updated clinical trial data and some distinct and controversial differences.[8-10]

EPIDEMIOLOGY AND ETIOLOGY

Gout is the most common inflammatory arthritis in men, with a male:female incidence of about 4:1; it affects over 3% of US adults.[1,11] The National Health and Nutrition Examination Survey (NHANES) 2007–2008 estimated the prevalence of gout among US adults to be 8.3 million.[12] The incidence increases with age and is rising in part due to a larger number of patients with risk factors for gout.[13] There is also a significant economic cost and humanistic burden associated with gout, which increases with worsening disease severity.[14]

In order to lessen the incidence and disease severity of gout, it is important to be mindful of risk factors and pharmacologic agents that can influence the disease. Dietary risk factors involve ingestion of animal purines, fructose, and alcohol (especially beer). Patients experiencing frequent attacks and those with poorly controlled advanced disease should be educated to avoid sweetbreads (organ meats such as thymus and pancreas), liver, and kidney meat; high-fructose corn syrup; and alcohol use.[5] Other risk factors include male sex, obesity, hypertension, dyslipidemia, and the metabolic syndrome.[11] Gout also occurs frequently in patients with type 2 diabetes mellitus, chronic kidney disease (CKD), and coronary artery disease.[15] Prospective data indicate that gout is an independent risk factor for coronary heart disease,[16] and the cardiovascular impact of urate-lowering therapy continues to be investigated.[17-19] Uric acid excretion is reduced in patients with CKD, putting them at risk for hyperuricemia.

LO 2

KEY CONCEPT Some drugs can cause hyperuricemia and precipitate gout, such as thiazide and loop diuretics, niacin, pyrazinamide, calcineurin inhibitors, and aspirin. In most cases, these drugs block uric acid secretion in the kidney. The effect of aspirin on uric acid is dose-dependent. Aspirin in high analgesic doses (600–2400 mg/day) blocks uric acid reabsorption by the kidneys, increasing uric acid excretion. Aspirin doses below 600 mg/day inhibit uric acid excretion and can elevate serum uric acid levels.[4] However, patients with hyperuricemia or gout and cardiovascular risk factors should continue low-dose aspirin (eg, 81–325 mg/day) for myocardial infarction or stroke prevention because the cardiovascular benefit outweighs the minimal effect on serum urate.[5]

PATHOPHYSIOLOGY

LO 1

Gout is caused by an abnormality in uric acid metabolism. Uric acid is a waste product of purine breakdown contained in the DNA of degraded body cells and dietary protein. It is water soluble and excreted primarily by the kidneys, although some is broken down by colonic bacteria and excreted via the

gastrointestinal (GI) tract. Uric acid solubility is dependent on concentration and temperature. At high serum concentrations, lower body temperature causes the precipitation of **monosodium urate** (MSU) crystals. Collections of these crystals (called microtophi) can form in joint spaces in distal extremities as well as soft tissues such as tendons and ligaments. Larger **tophi** may take 10 years or longer to develop. LO1

Free urate crystals can activate neutrophils and macrophages, which release proinflammatory mediators, including tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), and IL-8. This signals chemotactic movement of neutrophils into the joint space that phagocytize MSU crystals. These neutrophils are then lysed, releasing proteolytic enzymes that trigger the clinical manifestations of an acute gout attack, such as pain and swelling. Inflammatory mechanisms in gout, especially in untreated disease, can lead to cartilage and joint destruction. LO1

The increased SUA involves either the underexcretion of uric acid (90% of patients) or its overproduction. The cause of overproduction or underexcretion of uric acid in most gout patients is unknown; this is referred to as primary gout.[1] The reference range for SUA is 3.6 to 6.8 mg/dL (214–404 μmol/L). The risk of gout increases as the SUA concentration increases. Uric acid **nephrolithiasis** can occur in patients with persistently acidic urine and hyperuricemia. In severe cases, uric acid stones can cause nephropathy and renal failure. LO1 LO2

KEY CONCEPT Long-term consequences of gout and hyperuricemia include joint destruction, tophi, nephrolithiasis, and nephropathy.

CLINICAL PRESENTATION AND DIAGNOSIS

Refer to the accompanying box for the clinical presentation of acute gouty arthritis.

Diagnosis

A presumptive diagnosis is often based on presenting symptoms and may be confirmed later with laboratory and other diagnostic tests. However, in younger patients (< 25 years of age) with evidence of clinical disease, screening for uric acid overproduction is recommended.[5] Severe joint pain, swelling, tenderness, and erythema that rapidly peak are highly suggestive of, but not specific for, gout. Gout is a reasonably accurate clinical diagnosis in patients with recurrent **podagra** and hyperuricemia.[1] While gout classification criteria are available to identify patients potentially suitable for clinical trial enrollment, the point-based system should not be used clinically to diagnose gout.[20] Rather, severity of symptoms and proper categorization as delineated in the ACR guidelines should be assessed.[5,6] LO3

The SUA level is often elevated but may be normal during an acute attack; an elevated SUA alone is not diagnostic for gout. The peripheral white blood cell (WBC) count may be only mildly elevated. Other laboratory markers of inflammation (eg, increased erythrocyte sedimentation rate) are often present. Although difficult to perform, aspiration of affected joint fluid or a tophus is essential for a definitive diagnosis.[8] Needle-shaped negatively birefringent MSU crystals in the aspirate confirm the diagnosis (**Figure 59–1**). Joint fluid may also have an elevated WBC count with neutrophils predominating.[2]

Radiographs of affected joints may have characteristic cystic changes, punched-out lytic lesions with overhanging bony edges, and soft-tissue calcified masses. These signs may also appear in other arthropathies and are generally not apparent with the first acute gout attack.[21] Therefore, radiographs are often reserved for patients with long-standing disease.

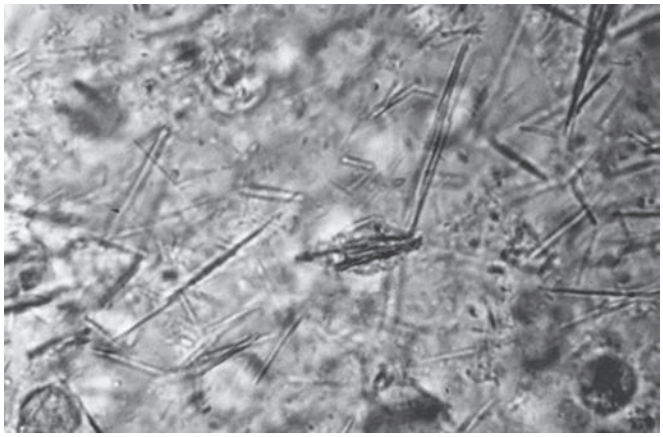

FIGURE 59–1. Synovial fluid containing extracellular and intracellular needle-like, negative birefringent monosodium urate crystals. (Reprinted with permission from: Schumacher HR, Chen LX. Chapter 395. Gout and Other Crystal-Associated Arthropathies. In: Kasper DL, Fauci AS, Hauser SL et al., eds. Harrison's Principles of Internal Medicine, 19th ed. New York, NY: McGraw-Hill; 2015. http://accesspharmacy.com)

A 24-hour urine collection can determine whether the patient is an overproducer or an underexcretor of uric acid. Individuals who excrete more than 800 mg (4.8 mmol) of uric acid are overproducers. Patients with hyperuricemia who excrete less than 600 mg/day (3.6 mmol/day) are classified as underexcretors. However, this approach is not often used because the urine collection is inconvenient for patients and clinicians and does not identify patients who may be both overproducers and underexcretors.

TREATMENT OF ACUTE GOUTY ARTHRITIS

KEY CONCEPT Treatment of gout involves: (a) acute relief of a gouty arthritis attack with topical application of ice and drug therapy commonly including NSAIDs, colchicine, corticosteroids, or

Clinical Presentation of Acute Gouty Arthritis

General

- Acute inflammatory monoarthritis.
- Patients are usually in acute distress.

Symptoms

- There is severe pain and swelling in the affected joint(s).
- Symptoms reach maximal intensity within 6 to 12 hours.
- The attack is usually monoarticular; the most common site is the metatarsophalangeal joint.
- In older patients, gouty attacks may be atypical with insidious and polyarticular onset, often involving hand or wrist joints.

Signs

- Affected joint(s) are warm, erythematous, and swollen.
- Mild fever may be present.
- Tophi (usually on hands, wrists, elbows, or knees) may be present in chronic, severe disease.

Patient Encounter Part 1

A 62-year-old Korean woman presents to the charitable rheumatology clinic with complaints of excruciating pain in her right wrist that has progressed quickly since onset late yesterday afternoon. She is a poor historian but reports no recent injuries and states that these symptoms "happen every couple of months in my ankle, toe, and wrist and I take whatever strong pain medicine I can get because the other stuff makes me break out." On examination, she can barely move her wrist due to pain and it is red, swollen, tender, and warm to the touch. She also has multiple small, firm nodules under the skin on her right hand. She is unemployed, homeless, and has difficulty reading and completing clinic intake paperwork due to limited English. She is concerned that she cannot carry her personal items between shelters with this reoccurring pain.

What information is suggestive of acute gouty arthritis?

What additional information is necessary to differentiate gout from other joint abnormalities?

What additional information do you need before creating a treatment plan for this patient?

What are aspects to consider when providing care for a patient who speaks limited English and has socioeconomic difficulties?

a combination thereof, and (b) in some patients, long-term prophylactic treatment with urate-lowering therapy (ULT) to prevent subsequent attacks.

Desired Outcomes

LO 4 Treatment goals for an acute attack are to: (a) achieve rapid and effective pain relief, (b) maintain joint function, (c) prevent disease complications, (d) avoid treatment-related adverse effects, (e) provide cost-effective therapy, and (f) improve quality of life.[3] Infrequent gouty arthritis is a self-limited disease, and treatment usually focuses on symptomatic relief.

Nonpharmacologic Therapy

Nondrug modalities play an adjunctive role and usually are not effective when used alone. Immobilization of the affected extremity speeds resolution of the attack. Applying ice packs to the joint is most effective in decreasing pain and swelling.[6]

Pharmacologic Therapy

LO 5 KEY CONCEPT Nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids are considered first-line monotherapy options for acute attacks.[6] Selection depends on number of joints affected, presence/absence of infection, clinician/patient preference, prior response, and patient factors such as comorbidities and renal function (Figure 59–2). Each drug class has a unique safety and efficacy profile in gout that should be considered carefully before choosing a specific agent (Table 59–1). Generally, the earlier in the course of the arthritic attack these agents are employed (ie, within 24 hours), the better the outcome.[6] Therefore, fully informed patients are encouraged to self-medicate at the first sign of an attack.[7] Corticotropin (adrenocorticotropic hormone, ACTH) and IL-1 inhibitors are alternatives in select cases.[6] Opioid analgesics have little to no role in acute gout, which results from overwhelming inflammation.

▶ *Nonsteroidal Anti-inflammatory Drugs*

NSAIDs, which reduce the pain and inflammation associated with an acute attack, have largely supplanted colchicine as the treatment of choice (see Chapter 58, Osteoarthritis, for more detailed information on NSAIDs). These agents are most LO 5 effective when given within the first 24 hours of the onset of pain. Most studies have shown similar results among agents, and no one NSAID is preferred over another. Doses at the higher LO 5 end of the therapeutic range are often needed.[6] NSAIDs are usually continued at full doses until 24 hours after symptoms subside. Clinicians may consider tapering the dose if a patient has multiple comorbidities, including hepatic or renal failure.

Only naproxen, indomethacin, and sulindac are FDA approved for treatment of acute gout. Although indomethacin has been used traditionally, its relative cyclooxygenase-1 (COX-1) selectivity increases its gastropathy risk. Studies comparing indomethacin to other NSAIDs consistently show similar efficacy with higher side effects with indomethacin; thus, other generic NSAIDs may be preferred. The patient's overall clinical status should LO 5 be evaluated prior to NSAID initiation because adverse effects include gastropathy (primarily peptic ulcers), renal dysfunction, and fluid retention.[6] In general, NSAIDs should be avoided in patients at risk for peptic ulcers; those taking anticoagulants; and those with renal insufficiency, uncontrolled hypertension, or heart failure. Gastroprotective agents such as proton pump inhibitors may protect against ulcer development in patients receiving NSAIDs for acute gout.

Cyclooxygenase-2 (COX-2)–selective inhibitors produce results comparable to those of traditional NSAIDs, with celecoxib being the only available product in the US market currently.[22] However, the need for large COX-2 inhibitor doses during an acute gouty attack (ie, celecoxib 800 mg daily), cardiovascular safety concerns, and high cost make the risk-benefit ratio unclear for this disorder.

▶ *Colchicine*

Colchicine has a long history of successful use and was the treatment of choice for many years. It is used less commonly today because of its low therapeutic index and more recently, increased cost. Colchicine is thought to exert its anti-inflammatory effects by interfering with the function of mitotic spindles in neutrophils by binding of tubulin dimers; this inhibits phagocytic activity.[23] Colchicine is not considered to be an analgesic.

About two-thirds of patients with acute gout respond favorably LO 5 if colchicine is given within the first 24 hours of symptom onset.[24] Presently, colchicine is only indicated if given within 36 hours of attack onset.[6] Gastrointestinal effects (eg, nausea, vomiting, diarrhea, and abdominal pain) are most common and are considered a forerunner of more serious systemic toxicity, including myopathy and bone marrow suppression (usually neutropenia). However, systemic colchicine toxicity can occur without prior GI effects, especially with renal insufficiency. In the presence of severe renal impairment (creatinine clearance [CrCl] < 30 mL/min [0.5 mL/s]), dosing should be repeated no more than once every 2 weeks. Dose reductions are required when coadministered with p-glycoprotein or strong CYP3A4 inhibitors (eg, clarithromycin, verapamil, ritonavir, cyclosporine, ranolazine).[23] Because of these problems, colchicine may be reserved for patients who are at risk for NSAID-induced gastropathy or who have failed NSAID therapy.

Until recently, Colcrys was the only single-ingredient oral colchicine product FDA approved for treatment of acute gout attacks. For many years prior to its release, generic colchicine

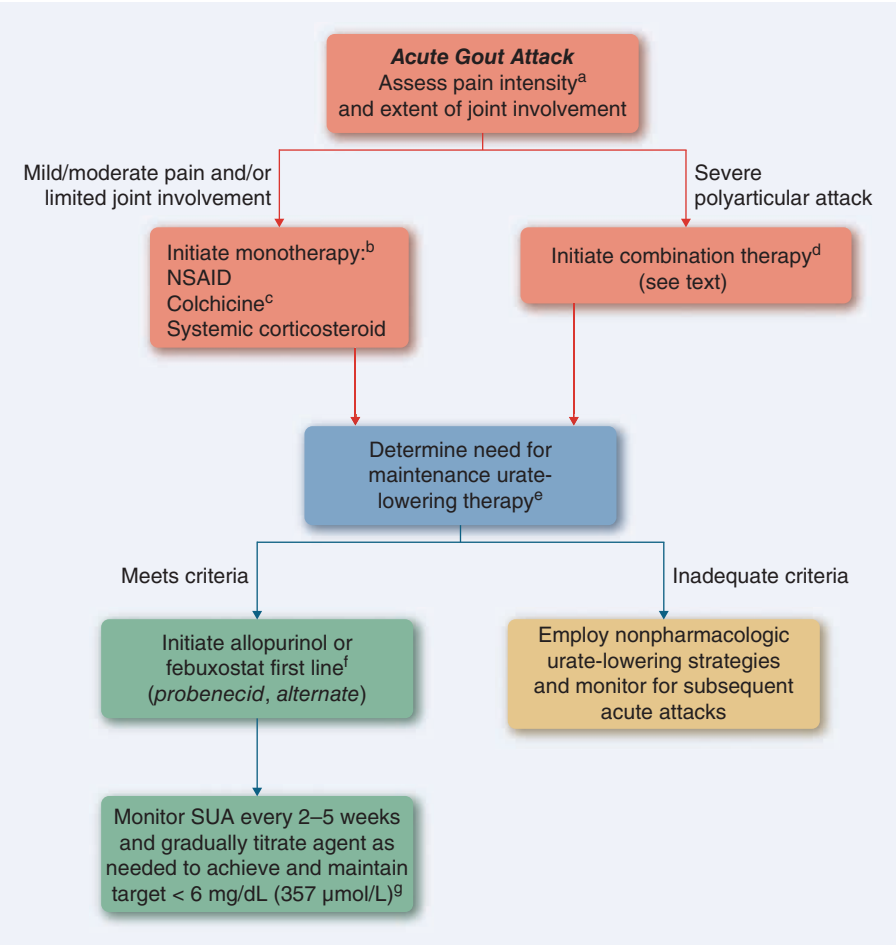

FIGURE 59–2. Treatment algorithm for hyperuricemia in gout. (NSAID, nonsteroidal anti-inflammatory drug; SUA, serum uric acid.)

[a]Self-reported pain score using a visual analog scale of 6 or less is considered mild/moderate pain and 7 or more is considered severe pain.

[b]May consider switch to alternate monotherapy, add-on combination therapy, or off-label therapy for inadequate response (< 20% improvement in pain score within 24 hours or < 50% at 24 hours or longer).

[c]Colchicine recommended only if started within 36 hours of symptom onset.

[d]Intraarticular corticosteroids may be used in combination when only one or two large joints are affected.

[e]Criteria for ult initiation include: Recurrent attacks (2 or more per year), evidence of tophus or tophi, chronic kidney disease stage 2 or worse, or past urolithiasis.

[f]Initiate concomitant anti-inflammatory prophylaxis and continue for indicated duration.

[g]May add on uricosuric therapy if unable to achieve target SUA on maximally dosed xanthine oxidase inhibitor therapy; addition of lesinurad only recommended with febuxostat (40 or 80 mg) or allopurinol doses above 200–300 mg based on renal function; switch to pegloticase for refractory cases.

products were available without FDA approval, but the FDA mandated their discontinuation in 2010. Colcrys is significantly more expensive than the generic compounds it replaced but has evidence-based labeling and safety data. In 2015, a generic form of colchicine was approved for use, helping to enhance affordability.

As part of the Colcrys approval process, a dosing study showed that one dose initially and a single additional dose after 1 hour was just as effective as and less toxic than continued hourly colchicine dosing.[25] Thus, the approved dosage regimen is 1.2 mg (two 0.6-mg tablets) at the onset of an acute flare, followed by 0.6 mg 1 hour later.[23] The ACR guidelines suggest it can then be continued starting 12 hours later at a dose of 0.6 mg once or twice daily (prophylaxis dosing) until the gout attack is resolved.[6] This is not part of the FDA-approved labeling but is an off-label recommendation based on pharmacokinetic data.[25] Dose adjustment is required for renal insufficiency.

Colchicine should not be used for an acute attack if the patient is currently prescribed colchicine for prophylaxis and was previously treated with colchicine for an acute attack within the last 14 days. Intravenous colchicine (no longer commercially available) should never be used in gout management.[6]

► *Corticosteroids*

It is important to determine the number of joints affected when considering a corticosteroid for first-line therapy. Systemic corticosteroids are a useful option in patients with contraindications to NSAIDs or colchicine (primarily renal impairment) or polyarticular attacks, especially in older patients. Furthermore, corticosteroids and NSAIDs have been shown equally effective in acute gout treatment.[26,27] The ACR recommends initiating oral prednisone or prednisolone at a dose of at least 0.5 mg/kg daily for 5 to 10 days, followed by abrupt

Table 59–1

Pharmacotherapy Regimens for Acute Gout Treatment

Drug	Usual Dosage Range
NSAIDs	
Etodolac	300–500 mg po two times daily
Fenoprofen	400–600 mg po three to four times daily
Ibuprofen	400–800 mg po three to four times daily
Indomethacin[a]	50 mg po three times daily initially until pain is tolerable, then quickly taper to discontinue
Ketoprofen	50 mg po four times daily or 75 mg po three times daily
Naproxen[a]	750 mg po initially, then 250 mg po every 8 hours
Piroxicam	20 mg po once daily or 10 mg po twice daily
Sulindac[a]	150–200 mg po two times daily for 7–10 days
Celecoxib	800 mg po followed by 400 mg po on day 1, then 400 mg po twice daily for 1 week
Colchicine[b]	1.2 mg po at the onset of attack, then 0.6 mg po 1 hour later
Corticosteroids	
Local corticosteroid	
Triamcinolone acetonide	10–40 mg (large joint), 5–20 mg (small joint) for one dose by intraarticular injection
Systemic corticosteroid	
Prednisone (example)	30–60 mg po once daily for 3–5 days, then taper to discontinue by 5 mg decrements over 10–14 days
Triamcinolone acetonide	60 mg by IM injection for one dose[c]
Methylprednisolone	100–150 mg by IM injection once daily for 1–2 days
Corticotropin[d]	40–80 units IM or SC every 24–72 hours
Interleukin-1 Inhibitors[d]	
Anakinra	100 mg SC once daily for 3 days
Canakinumab	150 mg SC for 1 dose

[a]This drug has FDA approval for the treatment of acute gout.

[b]Dose reduction recommended for renal impairment.

[c]Administration of IM triamcinolone should be followed by oral prednisone or prednisolone.

[d]Not FDA approved for this indication.

Drug regimens derived from various sources.

IM, intramuscular; NSAIDs, nonsteroidal anti-inflammatory drugs; po, by mouth; SC, subcutaneous.

discontinuation, or full dose therapy for 2 to 5 days with a 7- to 10-day taper to discontinue.[6] Oral methylprednisolone (ie, the 6-day dose pack consisting of a 21-tablet taper of 4 mg tablets, starting with 6 tablets on day 1 [divided into three separate doses] and ending with one tablet on day 6) and naproxen have been shown to be equivalent in treating acute gout attacks.[28]

When only one or two large joints are affected, an **intraarticular** corticosteroid injection can provide rapid relief with a relatively low incidence of side effects, and it may be used in combination with either an NSAID, colchicine, or oral corticosteroid. Joint fluid obtained by **arthrocentesis** should be examined for evidence of joint space infection and crystal identification. If uric acid crystals are present and there is no infection, intraarticular injection can proceed. Finally, an alternative regimen consisting of a single intramuscular injection of a long-acting corticosteroid such as triamcinolone acetonide, followed by oral prednisone or prednisolone, may also be used.[6]

LOS

Adverse effects from systemic corticosteroids include fluid retention, hyperglycemia, CNS stimulation, weight gain, GI upset, and increased risk of infection. Patients with diabetes should have blood glucose levels monitored carefully during the corticosteroid course, and caution should be exercised when treating patients with a history of peptic ulcer disease.

▶ *Corticotropin (Adrenocorticotropic Hormone)*

Exogenous administration of intramuscular adrenocorticotropic hormone (ACTH) stimulates production of cortisol and corticosterone by the adrenal cortex. Clinical studies have shown efficacy similar to other agents for acute gout. Although not a first-line option (or FDA approved for this use), the ACR supports its use for patients unable to take medications orally.[6] The product is available in the United States only through specialty pharmacy distribution.

▶ *Interleukin-1 Inhibitors*

Several small clinical trials have demonstrated efficacy of IL-1 inhibitors in inhibiting inflammation associated with acute gout attacks. While their role is unclear and the available products (anakinra and canakinumab) are not FDA approved for this purpose, the ACR guidelines include off-label use as an option for severe acute attacks or for patients refractory to other agents.[6]

▶ *Combination Therapy*

In severe polyarticular attacks, particularly attacks involving multiple large joints, colchicine may be used in combination with an NSAID or oral corticosteroid. Intraarticular corticosteroid injections may be used in combination with any other first-line agent (NSAID, colchicine, oral corticosteroid).[6]

URATE-LOWERING THERAPY FOR GOUT PROPHYLAXIS

Gout is an episodic disease, and the number of attacks varies widely among patients. Thus, the benefit of long-term acute attack prophylaxis must be weighed against the cost and potential toxicity of therapy that may not be necessary in all patients.

The benefits of long-term use (> 12 months) in patients with single or infrequent gout attacks have not been evaluated, and the time at which therapy could be discontinued is unclear.[9] KEY CONCEPT Asymptomatic hyperuricemia generally does not require treatment.

Nonpharmacologic Therapy

LO 7

Historically, lifestyle modifications alone have been insufficient for lowering SUA levels, and low purine diets are not well tolerated. Patients should be educated on general nutrition principles and advised to engage in regular exercise to lose weight if obese, strictly limit or discontinue ethanol consumption, maintain hydration, and manage other comorbidities (eg, hypertension, diabetes). Evidence suggests that men who follow the Dietary Approaches to Stop Hypertension (DASH) diet have a reduced risk for gout compared to those who eat a Western diet.[29] While the ACR guidelines encourage patients to consume low/non-fat dairy products and vegetables, they also cite a lack of specific evidence[5] (similar to the ACP guidelines) that judge the available evidence insufficient to recommend specific dietary changes.[9] Complementary therapies are considered to be inappropriate for gout due to insufficient evidence of benefit, such as cherry juice/extract, flaxseed, and celery root.[6,11] Drugs that may cause or aggravate hyperuricemia should be discontinued if clinically appropriate. Clinical experience indicates that few patients adhere to lifestyle modifications long-term, and pharmacologic therapy usually is needed to treat hyperuricemia adequately.

Pharmacologic Therapy

LO 6

KEY CONCEPT Patients with recurrent attacks (2 or more per year), evidence of tophus or tophi, CKD stage 2 or worse, or past urolithiasis are candidates for *prophylactic* therapy with allopurinol, febuxostat, lesinurad, probenecid, and/or pegloticase to lower SUA levels (see Figure 59–2).[5] However, ULT may be considered sooner in patients younger than 40 years, those with comorbidities, or SUA levels above 8 mg/dL (480 µmol/L).[7] Because hyperuricemia is the strongest modifiable risk factor for acute gout, prophylactic therapy commonly involves either decreasing uric acid production or increasing excretion (Table 59–2). The goal of therapy is to decrease SUA levels significantly, leaving less uric acid available for conversion to MSU crystals.[3] KEY CONCEPT ULT may be started during an acute attack if anti-inflammatory treatment has been initiated. Similarly, ULT should be continued during acute flares.

LO 4

Ideally, the selection of long-term prophylactic therapy involves determining the cause of hyperuricemia (primarily by analyzing a 24-hour urine collection for uric acid) and tailoring therapy appropriately. Drugs used to increase uric acid excretion (**uricosuric** agents) generally are not as well tolerated as drugs that decrease production, and uricosurics increase the risk of uric acid nephrolithiasis.

LO 8

Because allopurinol (which reduces uric acid production) is effective in both overproducers and underexcretors and is generally well tolerated, many clinicians forego the 24-hour urine collection and treat patients empirically with it. Both allopurinol and febuxostat are xanthine oxidase inhibitors (XOIs) and are first-line ULT agents.[5] Probenecid, a uricosuric agent, is an alternative first-line option. Combination therapy with an XOI and probenecid or lesinurad may be used if single-agent XOI therapy is insufficient. Pegloticase, a recombinant urate oxidase, is reserved for refractory cases.[5]

Table 59–2

Pharmacotherapy Regimens for Urate Lowering

Drug	Usual Dosage Range
Xanthine Oxidase Inhibitors	
Allopurinol[a]	100 mg po initially, then titrate to achieve SUA level < 6 mg/dL (357 µmol/L); maximum 800 mg po daily
Febuxostat	40 mg po once daily initially, then increase to 80 mg po once daily if SUA does not decline to 6 mg/dL (357 µmol/L) or lower after 2 weeks of treatment
Uricosurics	
Probenecid	250 mg po two times daily for 1 week, then 500 mg po twice daily; may increase by 500 mg every 4 weeks to achieve SUA level < 6 mg/dL (357 µmol/L); maximum 2 g po daily
Lesinurad[b]	200 mg po once daily in combination with a xanthine oxidase inhibitor
Other	
Pegloticase	8 mg given as an IV infusion over at least 2 hours once every 2 weeks, optimal duration unknown

[a]Initial dose reduction recommended for renal impairment.

[b]Not recommended if patient is taking less than 300 mg of allopurinol (or 200 mg if creatinine clearance is less than 60 mL/min [(1 mL/s]).

Drug regimens derived from various sources.

po, by mouth; SUA, serum uric acid.

▶ *Allopurinol*

Most patients in the United States are treated with allopurinol, which usually is effective if the dosage is titrated appropriately. The drug and its primary active metabolite, oxypurinol, reduce SUA concentrations by inhibiting the enzyme xanthine oxidase, thereby blocking the two-phase oxidation of hypoxanthine and xanthine to uric acid.[3]

Allopurinol is well absorbed, with a short half-life of 2 to 3 hours. The half-life of oxypurinol approaches 24 hours, allowing allopurinol to be dosed once daily. Oxypurinol is primarily renally cleared and can accumulate in patients with reduced kidney function.

Allopurinol may be started during an acute gout attack only if anti-inflammatory treatment is also initiated, because sudden shifts in SUA levels from mobilization of tissue urate stores may precipitate or exacerbate gouty arthritis. Thus most clinicians provide anti-inflammatory prophylaxis during initiation of ULT with colchicine (0.6 mg once or twice daily or 0.3 mg daily if severe renal impairment) or a low-dose NSAID (eg, naproxen 250 mg twice daily) with acid-suppressing therapy (eg, omeprazole 20 mg once daily). If a patient is being treated with colchicine for an acute attack, the prophylactic colchicine dose may be administered 12 hours after the last treatment dose. This approach, with colchicine having a stronger evidence grade, is supported by the ACR guidelines. Guidelines recommend that all acute gout patients receive prophylaxis when ULT is started with continuation of therapy for at least 6 months or up to 3 to 6 months after no clinical evidence of gout activity and the target SUA has been achieved.[6] Patients receiving colchicine for prophylaxis should be screened for drug–drug interactions (via the cytochrome p-450 system) that may increase the risk of colchicine adverse effects. Low-dose prednisone or

prednisolone (< 10 mg/day) is an alternative for patients unable to take colchicine or NSAIDs. The IL-1 inhibitors have also been investigated off-label as potential alternatives.

The initial dose of allopurinol is based on the patient's renal function. If renal function is normal, an initial dose no greater than 100 mg daily is recommended. The initial dose should be reduced to 50 mg daily in patients with a CrCl less than 30 mL/min (0.5 mL/s).[6] The relationship between allopurinol dose and its most severe side effects, including allopurinol hypersensitivity syndrome (AHS), is controversial.[30] Patients should be screened for AHS risk factors (female sex, age above 60 years, renal or cardiovascular disease, treatment of asymptomatic hyperuricemia, or an initiation dose of allopurinol greater than 100 mg daily.)[31] However, the dose can be adjusted upward every 2 to 5 weeks as needed and tolerated to the SUA target, even in patients with renal insufficiency provided that they are monitored and educated appropriately.[5,32]

LO 8 SUA levels must be monitored every 2 to 5 weeks during titration, then every 6 months after the target SUA is achieved. The target SUA level is less than 6 mg/dL (357 μmol/L) in all cases and perhaps even less than 5 mg/dL (297 μmol/L) in more severe disease involving tophi.[5] It is not recommended to have a SUA level less than 3 mg/dL (178 μmol/L) long-term.[7] The allopurinol dose should be titrated upward (to a maximum of 800 mg/day) or downward as these levels dictate.[5] However, the ACP guideline does not support the ACR's proactive "treat-to-target" approach due to a lack of adequate supporting evidence; rather the ACP recommends "treating-to-avoid-symptoms."[9] Nevertheless, most clinicians likely follow the ACR recommendations and strategies at this time. The typical allopurinol dose prescribed is 300 mg/day in patients with normal renal function, but this dose often fails to achieve the target SUA level.[5]

LO 8 Allopurinol is typically well tolerated; nausea and diarrhea occur uncommonly. A generalized, maculopapular rash occurs in about 2% of patients. Although usually mild, this can progress to severe skin reactions such as Stevens-Johnson syndrome. The most serious side effect is AHS, which may involve severe desquamating skin lesions, high fever (usually greater than 39.0°C [102.2°F]), hepatic dysfunction, leukocytosis with predominant eosinophilia, and renal failure. The risk appears to be highest in the first few months of therapy, and although rare, this severe reaction has a 20% to 25% mortality rate.[5,33,34] Prior to initiating allopurinol, pharmacogenomic screening via human leukocyte antigen (HLA)-B*5801 testing is recommended for patients at an elevated risk for AHS (eg, Koreans with stage 3 or worse CKD and all individuals of Han Chinese and Thai descent). If results are positive, the patient should be provided with an alternative to allopurinol. Patients with a history of AHS should never again receive allopurinol (including desensitization) or oxypurinol (available outside the United States). Patients with a mild skin rash who require allopurinol can be desensitized to it using published protocols or be switched to febuxostat.[35]

There are several important drug–drug interactions with allopurinol. The effects of both theophylline and warfarin may be potentiated by allopurinol. Azathioprine and 6-mercaptopurine are purines whose metabolism is inhibited by concomitant allopurinol therapy; the dose of these drugs must be reduced by 75% with allopurinol cotherapy. Patients taking allopurinol who receive ampicillin are at increased risk of skin rashes.

▶ *Febuxostat*

Febuxostat is a nonpurine XOI structurally distinct from allopurinol that is FDA approved for chronic hyperuricemia associated with gout. The initial dose is 40 mg orally once daily. The dose may be increased to 80 mg orally once daily if the SUA does not decrease to 6 mg/dL (357 μmol/L) or less after 2 weeks of treatment. No dosage adjustment is necessary in patients with mild or moderate renal impairment (CrCl 30–89 mL/min [0.5–1.48 mL/s]); however, febuxostat is not recommended in severe renal insufficiency (CrCl < 30 mL/min [0.5 mL/s]).[36,37] Because of its potency and rapid reduction of SUA levels, anti-inflammatory prophylaxis with low-dose colchicine or an NSAID is also recommended during initiation and titration of therapy and for at least 6 months as previously discussed for allopurinol.

LO 8 Adverse effects of febuxostat include nausea, arthralgias, rash, transient elevation of hepatic transaminases, and cardiovascular events. Therefore, periodic liver function tests are recommended (eg, at baseline, 2 and 4 months after starting therapy, and then periodically thereafter). Additionally, preliminary results from a safety clinical trial demonstrated an increased risk of heart-related deaths and death from all causes with febuxostat compared to allopurinol.[38] Due to differences in chemical structure, febuxostat would not be expected to cross-react in patients with a history of AHS.

Due to cost concerns, febuxostat should generally be reserved for patients who do not tolerate allopurinol and those who cannot achieve SUA levels of 6 mg/dL (357 μmol/L) or less despite maximal allopurinol therapy.[1]

▶ *Probenecid*

Probenecid is a uricosuric agent that blocks the tubular reabsorption of uric acid, increasing its excretion. Because of its mechanism of action, probenecid is not recommended for urate overproducers and is contraindicated in patients with a history of urolithiasis or urate nephropathy. Probenecid loses its effectiveness as renal function declines and should be avoided when the CrCl is 50 mL/min (0.83 mL/s) or less.[39] Probenecid is

LO 8 an alternate first-line agent if XOI therapy is either not tolerated or contraindicated. It may also be added to XOI therapy that has been titrated to the maximum dose without attainment of the target SUA level.[6]

Although generally well tolerated, probenecid can cause GI side effects (nausea), as well as fever, rash, and rarely, hepatic toxicity.[39] Patients should maintain adequate fluid intake and urine output to decrease the risk of uric acid stone formation. Some experts advocate alkalinizing the urine to decrease this risk, but no specific recommendations are provided.

▶ *Escalating Urate-Lowering Therapy*

If the target SUA level is not achieved with single-agent XOI therapy (allopurinol or febuxostat) titrated to the maximum appropriate dose, a uricosuric (eg, probenecid) may be added and also titrated to the appropriate dose.[5] Other medications with mild uricosuric effects may be appropriate adjunctive therapy in some patients. Losartan increases both uric acid excretion and urine pH and may be an option in hypertensive patients with gout. Fenofibrate is also uricosuric and may be appropriate in select dyslipidemic patients with gout.[40] Either one of these agents may be combined with a XOI in patients who fail to achieve

LO 8 the target SUA level on maximized therapy.[5] Another option for patients failing to achieve the target SUA level with

Patient Encounter Part 2

PMH: Stage 3 chronic kidney disease, hypertension, dyslipidemia, asthma, prediabetes mellitus (type 2)

FH: Unknown—adopted as child. No siblings.

SH: Unemployed with "off and on" side jobs. She drinks soda during the day to stay awake and a 12-pack of beer on the weekends. She denies use of tobacco products, but buys illicit opioids occasionally for joint pain. She admits to a poor diet consisting of packaged and canned food donations and eats candy from the convenience store if she is unable to find a meal.

Allergies: NSAIDs (anaphylaxis), simvastatin (myopathy), allopurinol (severe rash)

Meds: Chlorthalidone 25 mg once daily, niacin ER 1000 mg at bedtime, aspirin 325 mg TID PRN pain, albuterol HFA MDI 1-2 puffs every 6 hours PRN

ROS: Aside from pain in her wrist, she reports occasional shortness of breath. No fatigue, N/V/D, chest pain, or cough.

PE:

VS: 155/92, P 79, RR 19, T 37.3°C (99.1°F), Ht 69 inches (175 cm), Wt 77.5 kg

Skin: Warm, dry with excessive warmth surrounding right wrist

HEENT: NC/AT, PERRLA, TMs intact

CV: RRR, normal S1 and S2, no m/r/g

Chest: CTA

Abd: Slightly overweight, but soft, NT/ND. Normal bowel sounds in all quadrants.

Ext: No c/c. Trace edema in both ankles. Erythematous, edematous right wrist joint. Joint is warm to the touch and extremely painful (9/10 on the pain scale). Signs of tophi on right hand. No swelling of other joints.

Neuro: A&O × 3, CN II to XII intact

Labs: Serum creatinine 1.4 mg/dL (124 µmol/L), SUA 13.4 mg/dL (797 µmol/L), WBC + diff WNL. AST/ALT WNL.

Other: 24-hour urine collection not performed. Joint aspirate from wrist tap: > 50 WBC/HPF, containing negatively birefringent monosodium urate crystals. Wrist and hand radiographs negative for break or trauma, but indicate cystic changes and calcified masses. (+) for HLA-B*5801.

What risk factors promote gout and hyperuricemia in this patient?

Given this additional information, what is your assessment of the patient's condition?

Identify your gout treatment goals for this patient.

What nonpharmacologic and pharmacologic alternatives are available for this patient's acute gouty attack?

What alternatives are available for urate-lowering therapy for gout prophylaxis in this patient?

an appropriately dosed XOI is to combine the XOI with the uricosuric lesinurad.[41]

► *Lesinurad*

Lesinurad is a uric acid transporter 1 (URAT1) inhibitor that increases renal excretion of SUA and is approved for co-administration with a XOI (allopurinol or febuxostat) in patients who fail to meet their SUA target on a XOI alone.[41] Its place in therapy was determined by recent clinical trials.[42-44] Lesinurad should never be used as monotherapy due to the boxed warning of acute renal failure when given alone. Lesinurad is recommended at a dose of 200 mg once daily in the morning with food and water. It is also available in a dual-mechanism combination product that contains lesinurad 200 mg plus allopurinol 200 or 300 mg.[45] Additional URAT1 inhibitors are still in development.[46]

LO 8 Common adverse events include headache, influenza, blood creatinine increase, and gastroesophageal reflux disease; cardiovascular events were also observed. Interactions with aspirin in doses above 325 mg daily, hormonal contraceptives, inhibitors of epoxide hydrolase, moderate CYP2C9 inhibitors and inducers, and CYP3A4 substrates are possible. Renal function should be monitored at initiation and during therapy, avoiding initiation and discontinuing the product if CrCl is below 45 mL/min (0.75 mL/s). Contraindications include **tumor lysis syndrome** (TLS) and **Lesch-Nyhan syndrome**. Patients should be instructed to stay well hydrated, and gout flare prophylaxis is also recommended when starting lesinurad.[41]

Patient Encounter Part 3

The charitable clinic stocks only brand name medications donated by pharmaceutical companies to dispense to patients without charge. Older generic medications are unavailable. Based on all the information provided, create a care plan for this patient's gout. The plan should include: (a) a statement of the drug-related needs and/or problems, (b) a patient-specific detailed therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

► *Pegloticase*

Gout does not occur in most nonprimate mammals because these species produce the enzyme uricase, which catalyzes oxidation of uric acid into the more soluble compound allantoin, which is readily excreted. Humans lack this enzyme, which allows uric acid to accumulate, leading to gout in some individuals.

Pegloticase is a recombinant form of uricase (also known as urate oxidase) conjugated to polyethylene glycol. It is FDA approved for treatment of chronic gout refractory to other therapies. The approved dose of 8 mg by IV infusion over at least 2 hours every 2 weeks rapidly (within 6 hours) decreased SUA in subjects in published trials.[47] However, pegloticase should be limited to patients with severe gout with tophi or nephropathy that has not responded to other agents because of significant adverse effects, including gout flares, infusion reactions, anaphylaxis (in up to 5% of patients) that mandates pretreatment with antihistamines and corticosteroids, the inconvenience of IV therapy, and its high cost. Pegloticase is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and methemoglobinemia; therefore, patients should be screened prior to initiation of therapy.

LO 8

Patient Care Process

Collect Information:

- Perform allergy assessment and medication history for prescription, nonprescription, and dietary supplement use.
- Review medical history for contributing lifestyle factors (ie, alcohol use) and comorbidities including CKD that may exacerbate hyperuricemia or help guide therapy.
- Review physical assessment findings and patient symptoms to determine time of attack onset, joint(s) affected, pain level, and observe signs (joint warmth, swelling, redness).
- Identify patient preferences, beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Identify risk factors and comorbidities associated with gout.
- Determine whether patient is taking products such as diuretic therapy that may contribute to hyperuricemia.
- Determine whether patient is experiencing signs/symptoms of an acute gout flare or long-term complications of hyperuricemia.
- If patient is currently receiving pharmacotherapy, assess efficacy (ie, frequency/severity of attacks), safety/adverse reactions, adherence, and potential drug interactions.
- Evaluate SUA level to confirm presence of hyperuricemia and document the level.
- If a gout diagnosis has not been confirmed previously, assess feasibility of aspirating the affected joint to identify uric acid crystals.

Develop a Care Plan: (Figure 59–2)

- Select a regimen for treatment of the acute attack, considering the patient's past response (if any) and comorbidities.
- Ensure patient has met criteria for ULT if already prescribed.
- Select appropriate lifestyle modifications and therapy based on comorbidities and potential safety/efficacy.
- Determine need for continuous ULT (Table 59–2). Use patient factors such as comorbidities to select an agent.
- Choose adjunctive therapy with low-dose colchicine or NSAID during initiation or titration of ULT to prevent rebound flare.
- Initiate ULT during acute attack only in conjunction with effective anti-inflammatory therapy.

Implement the Care Plan:

- Initiate therapy to treat acute gout attack within 24 hours (Table 59–1).
- Educate patient on hyperuricemia/gout, drug therapy, importance of adherence, and lifestyle modifications that may improve symptoms (eg, weight loss, alcohol avoidance).
- Address patient concerns about hyperuricemia/gout and its management.
- Determine if patient has prescription insurance and whether recommended agents (eg, colchicine) are included on formulary.
- Discontinue nonessential urate-elevating medications.

Follow-up: Monitor and Evaluate:

- Follow-up every 2 to 5 weeks to assess effectiveness, safety, and titrate ULT or add alternate agent to achieve target SUA; monitor SUA concentration during ULT titration and periodically thereafter.
- Review physical examination, lab tests, and results of other diagnostic tests to assess changes in clinical status.
- Once gout symptoms are controlled, monitor patient and SUA every 6 months; reinforce adherence with regimen to prevent future gout attacks and long-term complications (ie, development of tophi or nephrolithiasis).

OUTCOME EVALUATION

Acute Gout

- Monitor the patient for pain relief and decreased swelling of the affected joint(s). Both parameters improve significantly within 48 hours of starting therapy.
- Assess the patient's complaints and objective information for adverse effects:
  - NSAIDs: Be alert for new-onset epigastric pain, dark or tarry stools, blood in vomitus, dizziness or lightheadedness, development of edema, decreased urine output, or shortness of breath.
  - Colchicine: Monitor for nausea or vomiting, diarrhea, easy bruising, cold or flu-like symptoms, lightheadedness, muscle weakness, or pain. Advise the patient to inform you of any new medications started or stopped while taking colchicine.
  - Systemic corticosteroids: Assess for mental status changes, fluid retention, increased blood glucose, muscle weakness, or development of new infections.
  - Intraarticular corticosteroid injections: Monitor for increased swelling or pain at the injection site.

Urate-Lowering Therapy

- Monitor the SUA level every 2 to 5 weeks during ULT initiation and titration. Adjust the dose of ULT to achieve a target SUA level of less than 6 mg/dL (357 µmol/L) or optionally less than 5 mg/dL (297 µmol/L) in more severe disease. Then continue measurements every 6 months thereafter and evaluate need for additional therapy.
- Concomitantly initiate anti-inflammatory prophylaxis and continue for the greater of 6 months or 3 to 6 months after achieving target SUA level with no gout signs/symptoms.
- Assess for new gouty arthritis attacks or development of tophi.
- Evaluate patients for adverse medication effects:
  - Allopurinol: Assess for development of rash, nausea, or new fever. These symptoms usually appear within the first 3 months of therapy but can occur anytime.

- Febuxostat: Monitor for presence of nausea, arthralgias, rash, transient elevation of hepatic transaminases, and cardiovascular events.
- Lesinurad: Monitor for headache, influenza, serum creatinine increase, gastroesophageal reflux disease, and cardiovascular events.
- Probenecid: Assess for fever, nausea, or skin rash. Reevaluate therapy if a significant decrease in urine output occurs.
- Pegloticase: Monitor SUA levels before each 2-week IV infusion. Also evaluate patients on pegloticase for development of gouty flares and infusion reactions, which may include anaphylaxis. The manufacturer recommends giving an antihistamine and perhaps low-dose methylprednisolone before the infusion to minimize reactions.

Abbreviations Introduced in This Chapter

ACP	American College of Physicians
ACR	American College of Rheumatology
ACTH	Adrenocorticotropic hormone
AHS	Allopurinol hypersensitivity syndrome
COX	Cyclooxygenase
DASH	Dietary Approaches to Stop Hypertension
G6PD	Glucose-6-phosphate dehydrogenase
HLA	Human leukocyte antigen
IL-1	Interleukin-1
MSU	Monosodium urate
SUA	Serum uric acid
TLS	Tumor lysis syndrome
URAT1	Uric Acid Transporter 1
ULT	Urate-lowering therapy
XOI	Xanthine oxidase inhibitor

REFERENCES

1. Neogi T. Gout. N Engl J Med. 2011;364(5):443–452.
2. Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the standing committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis. 2006;65(10):1301–1311.
3. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65(10):1312–1324.
4. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatol Oxf Engl. 2007;46(8):1372–1374.
5. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res. 2012;64(10): 1431–1446.
6. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res. 2012;64(10):1447–1461.
7. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76(1):29–42.
8. Qaseem A, McLean RM, Starkey M, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Diagnosis of Acute Gout: a Clinical Practice Guideline from the American College of Physicians. Ann Intern Med. 2017;166(1):52–57.
9. Qaseem A, Harris RP, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Management of Acute and Recurrent Gout: a Clinical Practice Guideline from the American College of Physicians. Ann Intern Med. 2017;166(1):58–68.
10. Neogi T, Mikuls TR. To treat or not to treat (to target) in gout. Ann Intern Med. 2017;166(1):71–72.
11. Roddy E, Choi HK. Epidemiology of gout. Rheum Dis Clin North Am. 2014;40(2):155–175.
12. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007–2008. Arthritis Rheum. 2011;63(10):3136–3141.
13. Robinson PC, Horsburgh S. Gout: joints and beyond, epidemiology, clinical features, treatment and co-morbidities. Maturitas. 2014;78(4):245–251.
14. Shields GE, Beard SM. A systematic review of the economic and humanistic burden of gout. Pharmacoeconomics. 2015; 33(10):1029–1047.
15. Karis E, Crittenden DB, Pillinger MH. Hyperuricemia, gout, and related comorbidities: cause and effect on a two-way street. South Med J. 2014;107(4):235–241.
16. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation. 2007;116(8):894–900.
17. Chen JH, Lan JL, Cheng CF, et al. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. J Rheumatol. 2015;42(9):1694–1701.
18. Segal MS, Srinivas T, Mohandas R, et al. The effect of the addition of allopurinol on blood pressure control in African Americans treated with a thiazide-like diuretic. J Am Soc Hypertens. 2015;9(8):610–619.
19. Tsuruta Y, Kikuchi K, Tsuruta Y, et al. Febuxostat improves endothelial function in hemodialysis patients with hyperuricemia: a randomized controlled study. Hemodial Int. 2015;19(4):514–520.
20. Neogi T, Jansen TLTA, Dalbeth N, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheumatol Hoboken NJ. 2015;67(10):2557–2568.
21. Schumacher HR. Crystal-induced arthritis: an overview. Am J Med. 1996;100(2A):46S–52S.
22. Schumacher HR, Berger MF, Li-Yu J, et al. Efficacy and tolerability of celecoxib in the treatment of acute gouty arthritis: a randomized controlled trial. J Rheumatol. 2012;39(9):1859–1866.
23. DailyMed—COLCRYS—colchicine tablet. National Institutes of Health, U.S. Department of Health and Human Services. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=56c130d1-7581-4152-99a2-0014ee9366c0. Accessed August 31, 2017.
24. Ahern MJ, Reid C, Gordon TP, et al. Does colchicine work? The results of the first controlled study in acute gout. Aust N Z J Med. 1987;17(3):301–304.
25. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: twenty-four–hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum. 2010;62(4):1060–1068.
26. Rainer TH, Cheng CH, Janssens HJEM, et al. Oral Prednisolone in the treatment of acute gout: a pragmatic, multicenter, double-blind, randomized trial. Ann Intern Med. 2016;164(7):464–471.

27. Zhang YK, Yang H, Zhang JY, et al. Comparison of intramuscular compound betamethasone and oral diclofenac sodium in the treatment of acute attacks of gout. Int J Clin Pract. 2014;68(5):633–638.
28. Janssens HJEM, Janssen M, van de Lisdonk EH, et al. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet. 2008;371(9627):1854–1860.
29. Rai SK, Fung TT, Lu N, et al. The Dietary Approaches to Stop Hypertension (DASH) diet, Western diet, and risk of gout in men: prospective cohort study. BMJ. 2017;357:j1794.
30. Thurston MM, Phillips BB, Bourg CA. Safety and efficacy of allopurinol in chronic kidney disease. Ann Pharmacother. 2013;47(11):1507–1516.
31. Yang CY, Chen CH, Deng ST, et al. Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. JAMA Intern Med. 2015;175(9):1550–1557.
32. Stamp LK, O'Donnell JL, Zhang M, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. Arthritis Rheum. 2011;63(2):412–421.
33. DailyMed—ALLOPURINOL—allopurinol tablet. National Institutes of Health, U.S. Department of Health and Human Services. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=682dd8b8-fc6e-47c5-95b7-82d7ad96b750. Updated January 31, 2017. Accessed August 31, 2017.
34. Zineh I, Mummaneni P, Lyndly J, et al. Allopurinol pharmacogenetics: assessment of potential clinical usefulness. Pharmacogenomics. 2011;12(12):1741–1749.
35. Fam AG, Dunne SM, Iazzetta J, Paton TW. Efficacy and safety of desensitization to allopurinol following cutaneous reactions. Arthritis Rheum. 2001;44(1):231–238.
36. DailyMed—ULORIC—febuxostat tablet. National Institutes of Health, U.S. Department of Health and Human Services. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=54de10ef-fe5f-4930-b91d-6bbb04c664bd. Updated August 18, 2017. Accessed August 31, 2017.
37. Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353(23):2450–2461.
38. Uloric (febuxostat): drug safety communication—FDA to evaluate increased risk of heart-related death. U.S. Food and Drug Administration, U.S. Department of Health and Human Services. Available from: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm585281.htm. Updated November 20, 2017. Accessed November 20, 2017.
39. DailyMed—PROBENECID—probenecid tablet. National Institutes of Health, U.S. Department of Health and Human Services. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ab497fd8-00c3-4364-b003-b39d21fbdf38. Updated April 29, 2017. Accessed August 31, 2017.
40. Takahashi S, Moriwaki Y, Yamamoto T, et al. Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism. Ann Rheum Dis. 2003;62(6):572–575.
41. DailyMed—ZURAMPIC—lesinurad tablet. National Institutes of Health, U.S. Department of Health and Human Services; [; cited 2017 August 31]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=92d614a3-760d-492c-930d-22f91ff016b1. Updated January 8, 2016. Accessed August 31, 2017.
42. Saag KG, Fitz-Patrick D, Kopicko J, et al. Lesinurad combined with allopurinol: a randomized, double-blind, placebo-controlled study in gout patients with an inadequate response to standard-of-care allopurinol (a US-based study). Arthritis Rheumatol. 2017;69(1):203–212.
43. Dalbeth N, Jones G, Terkeltaub R, et al. Lesinurad, a selective uric acid reabsorption in-hibitor, in combination with febuxostat in patients with tophaceous gout: findings of a phase III clinical trial. Arthritis Rheumatol. 2017;69(9):1903–1913.
44. Perez-Ruiz F, Sundy JS, Miner JN, et al. Lesinurad in combination with allopurinol: results of a phase 2, randomised, double-blind study in patients with gout with an inadequate response to allopurinol. Ann Rheum Dis. 2016;75(6):1074–1080.
45. Prescribing Information for DUZALLO. U.S. Food and Drug Administration, U.S. Department of Health and Human Services. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209203s000lbl.pdf. Accessed August 31, 2017.
46. Shahid H, Singh JA. Investigational drugs for hyperuricemia. Expert Opin Investig Drugs. 2015;24(8):1013–1030.
47. Sundy JS, Becker MA, Baraf HSB, et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: results of a phase II randomized study. Arthritis Rheum. 2008;58(9):2882–2891.

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60 Musculoskeletal Disorders

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LEARNING OBJECTIVES

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

LO

1. Describe the pathophysiologic principles of tissue injury and inflammation.
2. Identify the desired therapeutic outcomes for a patient with musculoskeletal injury or pain.
3. Identify the factors that guide selection of an analgesic or counterirritant for a particular patient.
4. Recommend appropriate nonpharmacologic and pharmacologic therapy for a patient with musculoskeletal injury or pain.
5. Design a patient education plan, including nonpharmacologic therapy and preventative strategies.
6. Develop a monitoring plan to assess treatment of a patient with a musculoskeletal disorder.

INTRODUCTION

The musculoskeletal system consists of muscles, bones, joints, tendons, and ligaments. Disorders related to the musculoskeletal system often are classified by etiology. Acute soft-tissue injuries include strains and sprains of muscles and ligaments.[1] Repeated movements in sports, exercise, work, or activities of daily living can lead to repetitive strain injury, where cumulative damage occurs to the muscles, ligaments, or tendons.[2] Although tendonitis and bursitis can arise from acute injury, more commonly these conditions occur as a result of chronic stress.[2,3] Other forms of chronic musculoskeletal pain, such as pain from rheumatoid arthritis (see Chapter 57) or osteoarthritis (see Chapter 58), are discussed elsewhere in this textbook.

EPIDEMIOLOGY AND ETIOLOGY

Musculoskeletal disorders are commonly self-treated, so true estimates of the incidence of both acute and chronic injury are difficult to obtain. In the United States, over 65 million musculoskeletal injuries occur each year, with 62% of episodes treated in ambulatory care offices.[4] These disorders account for a large portion of medical care expenditures and are a leading cause of work absenteeism and disability, resulting in a substantial economic burden from lost productivity and lost wages.

Some musculoskeletal disorders arise from workplace injuries, including those induced by trauma or an acute overexertion and those induced by repetition and cumulative trauma.[4] The most common sites of injury include the upper extremities (eg, hand, shoulder, and wrist), back, and lower extremity (eg, ankle, knee).

In older adults, musculoskeletal injuries may not be related to work but to daily life. Half of all musculoskeletal injuries occur in the home with falls being the most common cause for those aged 65 and older.[4] In children and adolescents, fractures are more common than muscle and tendon injuries because growth spurts cause bones to weaken while the muscle–tendon unit tightens.[2]

Muscle injuries comprise the majority of sports-related injuries, and roughly half are related to overuse.[4,5] The ankle is the most common site of sports injury.[6] Activities that require rapid acceleration or pivoting at high speeds, such as basketball and soccer, pose the greatest risk of muscle sprain and acute injury.[5,7]

Overuse musculoskeletal injury is the phrase used to describe disorders arising from repetitive motion.[5] This injury is common in activities such as running, particularly during periods of increased intensity or duration of training. It also can occur in the workplace with repeated, unvaried motion.[8]

PATHOPHYSIOLOGY

Skeletal muscle consists of muscle fibers linked together by connective tissue. Tendons and ligaments are composed of collagenous fibers that have a restricted capability to stretch. Tendons connect muscle to bone, whereas ligaments connect bone to bone.

Muscle Strains and Sprains

A sprain is an overstretching of supporting ligaments that results in a partial or complete tear of the ligament.[1] Although a strain also arises from an overstretching of the muscle–tendon unit, it is marked by damage to the muscle fibers or tendon without tearing of the ligament. The key difference is that a sprain involves damage to ligaments, whereas a strain involves damage primarily to muscle.

Overloading the muscle and connective tissue results in complete or partial tears of the skeletal muscle, tendons, or ligaments.[7,9] This usually occurs when the muscle is activated in an *eccentric contraction*, defined as a contraction in which the muscle is being lengthened.[9] Examples of this type of contraction include putting down a large, heavy object or lowering oneself from a chin-up bar. Small tears can occur in the muscle because it is lengthening while also trying to contract to support the load. This leads to rupture of blood vessels at the site of the injury, resulting in formation of a hematoma.[7,9] During the inflammatory stage, macrophages remove necrotic fibers. Activated neutrophils then release growth factors that activate myocytes for regeneration. Finally, capillaries grow into the area, and muscle fibers regenerate during the repair and remodeling phases of healing.

LO 1

Bursitis and Tendonitis

Bursitis is an inflammation of the bursa, the fluid-filled sac near the joint where the tendons and muscles pass over the bone.[3] Overuse of a joint can result in an inflamed bursa. Bursitis causes stiffness and pain because the bursa serves to reduce friction within the joint space.

Tendonitis (or *tendinitis*) refers to inflammation of the tendon that follows incomplete tendon degeneration.[2] Repetitive overuse of a tendon can cause cellular changes in the tissues. Specifically, collagenous tendon tissue is replaced with tissue that lacks the organized collagen arrangement of a normal tendon. Many patients diagnosed with chronic tendonitis may not have inflammation but instead have **tendinosis**, a condition marked by these degenerative changes. As a result of the cellular changes, the tendon progressively loses elasticity and its ability to handle stress or weight. This makes the tendon vulnerable to rupture or inflammation.

Inflammation and Peripheral Pain Sensation

LO 1

Inflammation is a common pathway in soft-tissue injury of musculoskeletal disorders. Inflammatory processes lead to two outcomes: swelling and pain. They are considered to be a necessary part of the remodeling process because inflammatory cells remove damaged tissue.[10,11] However, inflammation also contributes to continued pain and swelling that limits range of motion.

The initial injury exposes membrane phospholipids to phospholipase A_2, leading to the formation of arachidonic acid.[11] Next, arachidonic acid is transformed by cyclooxygenase (COX) to thromboxanes and prostaglandins (PGs), including prostaglandin E_2 (PGE_2). PGE_2 is the most potent inflammatory mediator; it increases vascular permeability, leading to redness, warmth, and swelling of the affected area. The increased permeability also increases proteolysis, or the breakdown of proteins in the tissue.

Neutrophils, lymphocytes, and monocytes are attracted to the area, and monocytes are converted to macrophages, which then stimulate additional PG production.[11] Phagocytic cells release cytokines, including interleukins, interferon, and tumor necrosis factor.

In addition to increasing vascular permeability, PGs also induce pain by sensitizing pain receptors to other substances such as bradykinin. Bradykinin, PGs, leukotrienes, and other inflammatory mediators lower the pain threshold through peripheral pain sensitization.[12] These substances make nerve endings more excitable, and the nerve fibers are more reactive to serotonin, heat, and mechanical stimuli. The increased sensitization in the damaged tissue causes tenderness, soreness, **hyperalgesia**, and production of additional PGs. In a cyclic fashion, the PGs then sensitize the nerves to bradykinin action.

Without interruption, the neurochemicals ultimately lead to a firing of the unmyelinated or thinly myelinated afferent neurons. This sends messages along the pain pathway in the periphery and communicates the pain message to the central nervous system (CNS). Interruption of this cycle may occur via the effects of anti-inflammatory agents such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).

Nerve receptors, or **nociceptors**, release substance P and other peptides when they are activated.[12] Substance P mediates the production and release of inflammatory mediators and acts as a potent vasodilator. This receptor activation also increases the sensitivity of nociceptors to painful stimuli. Capsaicin relieves pain by stimulating the release of substance P from sensory nerve fibers, ultimately depleting stores of substance P.[13]

CLINICAL PRESENTATION AND DIAGNOSIS

See next page for information on the clinical presentation and diagnosis of musculoskeletal disorders.

TREATMENT

Desired Outcomes

LO 2

KEY CONCEPT The primary goals of treating musculoskeletal disorders are to: (a) relieve pain, (b) maintain functionality, and (c) prevent or minimize overuse injury. This is accomplished by decreasing the severity and duration of pain, shortening the recovery period, and preventing the acute injury from becoming an overuse injury. If these goals are achieved, functional limitations are decreased. Ideally, a patient should be able to continue to perform activities of daily living and maintain normal functions. Children ideally should be able to maintain usual play activities and sports schedules.

Further goals include a return to usual activity, prevention of future injury, and allowing for full emotional recovery. It is also important to minimize the potential for adverse events from nonpharmacologic and pharmacologic therapies.

General Approach to Treatment

LO 4

Treatment of musculoskeletal injury involves three phases: (a) nonpharmacologic therapy of an acute injury (eg, using the rest, ice, compression, and elevation [RICE] principle); (b) pain relief using oral or topical agents; and (c) lifestyle and behavioral modifications for rehabilitation and to prevent recurrent injury, overuse injury, or disability (**Figure 60–1**).

The approach to treatment for low back pain with nonpharmacologic and pharmacologic therapies is stratified by duration of pain. In acute or subacute low back pain, nonpharmacologic therapy (eg, superficial heat) is preferred, whereas for chronic low back pain pharmacologic therapy may be warranted after failure of nonpharmacologic measures.

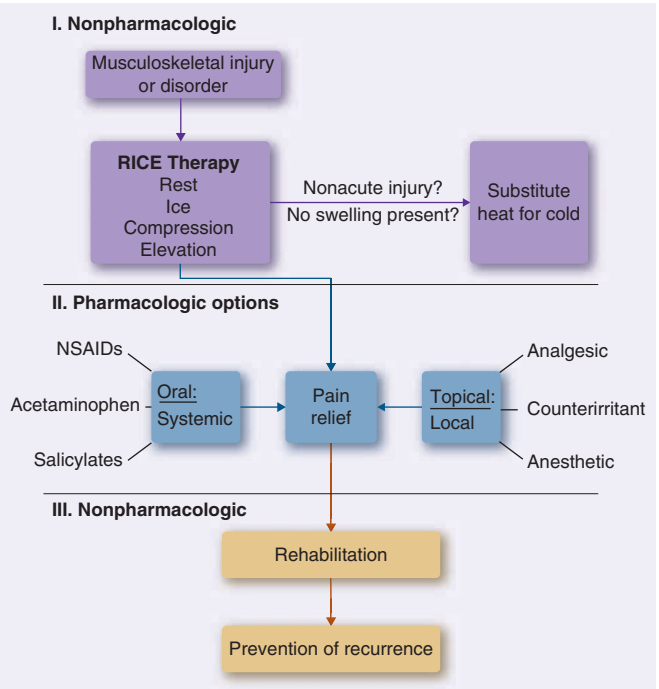

FIGURE 60–1. Treatment plan for musculoskeletal injury or disorder.

Clinical Presentation and Diagnosis of Musculoskeletal Disorders

General[2,3,5]

- Clinical presentation varies based on etiology of the disorder.
- Repetitive strain or overuse injuries may have a gradual onset.
- Disorders due to acute injury may be associated with other signs of injury such as abrasion.

Signs and Symptoms of Acute Soft-Tissue Injury (Strains, Sprains)[1,6]

- Discomfort ranging from tenderness to pain may occur at rest or with motion
- Swelling and inflammation of the affected area
- Bruising
- Loss of motion
- Mechanical instability

Signs and Symptoms of Repetitive Strain or Overuse Injury (Tendonitis, Bursitis)[2,3,5,14]

- Pain and stiffness that occur either at rest or with motion
- Localized tenderness on palpation
- Mild swelling of the affected area
- Decreased range of motion
- Muscle atrophy

Low Back Pain[15,16]

- Low back pain is often chronic, but other cases may present acutely.
- Pain is often nonspecific and may be accompanied by stiffness upon waking.
- Lifting, twisting, or bending may worsen pain.
- In some cases, pain may radiate to the hip or thigh.

Other Diagnostic Tests and Assessments[6]

- *Radiograph (x-ray)*: Evaluates bony structures to rule out fracture, malalignment, or joint erosion as the primary cause of pain.
- *MRI*: Soft-tissue imaging to evaluate for tendon or ligament tears.
- *Ultrasound*: Superficial soft-tissue imaging to evaluate for tears in tendons or ligaments. Ultrasound does not penetrate bone, so it is of limited usefulness for assessing tendons or ligaments deep within joints.
- *Electromyogram*: Evaluates electrical activity in muscles and may be used when low back pain is accompanied by leg pain or sciatica to rule out other causes of the pain.
- *Pain scale*: Patient self-rating on a pain scale. For example, a numeric pain scale with zero (no pain) to 10 (worst possible pain) or a visual analog scale. Used to assess pain both at rest and with movement. Determined at baseline and to assess response to therapy.

LO 6

Acute pain typically improves within 1 to 5 days of therapy. Further evaluation may be warranted if acute pain persists longer than 7 to 10 days with treatment, symptoms worsen or subside and then return, or there are signs of a more serious condition.[6,9,17,18] Some warning signs of more serious conditions that may warrant immediate emergency care include joint deformity, dislocation, immobility, or paralysis. Some red flags specifically for low back pain include fracture, infection, urinary or bowel incontinence, or foot drop syndrome.[15,16]

LO 3

In children and adolescents, treatment practices are similar to the approach in adults with a focus on nonpharmacologic therapy and oral analgesics. Children younger than 2 years, older adults, and pregnant women also may need special care.[19]

Patient Encounter 1, Part 1

A 48-year-old man presents with right wrist pain. He was playing flag football with his friends earlier today and twisted his wrist when he fell. The pain occurs at rest and is worsened with pressure or weight on the wrist and with rotation or movement. There is moderate swelling and bruising of the right wrist. Abrasions across his hand and wrist are noted.

What information is suggestive of a musculoskeletal disorder?

What is your assessment of the patient's wrist pain?

What additional information do you need to formulate a treatment plan?

Nonpharmacologic Therapy: RICE

LO 4

KEY CONCEPT The cornerstone of nonpharmacologic therapy for acute injury in the first 24 to 72 hours is known by the acronym RICE: rest, ice, compression, and elevation.[7,9,18,20] These four methods initially minimize bleeding from broken blood vessels followed by anti-inflammatory and analgesic actions to allow for appropriate healing at the site of injury. See Table 60–1.

Rest eases pressure on the affected area, promotes pain control during the acute inflammatory phase (the first 1–5 days after injury), and prevents additional injury to the affected area.[7,9,20] During acute injury, the ability of muscles and tendons to stretch is limited. Movement in the injured tissue can cause further retraction of the ruptured muscle and increase the size of the gap in the muscle to be healed. For simple injuries, immobilization should not exceed 1 week, with low impact, isometric, and passive stretching or exercise modalities started 3 to 4 days after injury while minimizing pain.[9,20-22] Mobilization too early after injury predisposes a patient to further injury, but prolonged inactivity can lengthen recovery times and delay healing. Longer immobilization may sometimes be warranted for more severe injuries (eg, extensive muscle tears or fractures) and may require additional support devices (eg, crutches).

The benefits of cryotherapy (modalities that act to lower tissue temperatures) following acute musculoskeletal injury are well documented.[7,10,23] Cold causes vasoconstriction, assisting in prevention of a large hematoma and providing analgesia by slowing nerve impulses. Immediately after injury, ice also helps to reduce metabolic rate and oxygen demand, thereby reducing tissue damage from hypoxia.[7,9,23] Types of cryotherapy include

Table 60–1

RICE Therapy[6,7,9,18,21-23]

Therapy	General Guidelines	Therapeutic Benefit
*R*est	Rest the affected area	Analgesia
	Use supports such as slings and crutches as necessary	Anti-inflammatory
	Employ during the acute inflammatory phase, 1–5 days after injury	Prevent further injury
*I*ce	Cool the affected area by submersion in cool water (13°C [55°F]) or by application of crushed ice in a plastic bag covered with a thin cloth	Analgesia Anti-inflammatory
	Cool the affected area for 15–20 minutes; repeat every 2 hours for the first 48 hours	
*C*ompression	Compress the affected area with an elastic bandage or support	Anti-inflammatory
	Begin wrapping the bandage at the point most distal to the injury (eg, at the toes for an ankle injury); bind firmly but not tightly	Adjunctive analgesia
	If the area distal to the injury (eg, fingers, toes) throbs or turns cold or blue, the bandage is too tight and should be loosened	
*E*levation	Elevate the area (especially the extremities) above heart level	Anti-inflammatory

(1) crushed ice (preferred over large ice pieces to provide more even cooling), (2) single-use cold packs, or (3) reusable ice packs. Patients should wrap the injured surface with a thin moist towel and then apply the ice therapy to the injured site for no longer than 20 minutes. Applying ice directly to the affected area or for longer than recommended can cause tissue damage, and any ice application should be stopped if the area becomes white or blue.[23] Recommend ice application every other 20 minutes for approximately 2 hours, followed by 2 hours of no cryotherapy. This process should then be repeated for at least the first 48 hours after injury.[18,23] If swelling is present, cryotherapy can be continued throughout the recovery process, but the duration may be shortened as pain and swelling is lessened.[21,23] Alternatively, soaking the area for 20 minutes in a cool bath (13°C [55°F]) provides effective cooling.[7,23] For small areas, direct ice massage for 15 to 20 minutes can cool the area and add relief.[23] However, there is little evidence for the effectiveness of cryotherapy in relieving low back pain, regardless of presentation.[24]

LO 4 KEY CONCEPT Heat should not be applied during the acute injury phase (when edema is present) because it promotes swelling and inflammation.[23] After the acute inflammatory phase, many patients find that heat decreases pain and eases muscle stiffness. A heating pad, heat wrap, or warm bath can be used as long as no edema is present and no swelling develops after heat is applied. Application time should not exceed 20 minutes to minimize tissue injury.[23] Patients should avoid sleeping with or sitting or lying on heating pads because this can result in burns. Low-level heat, such as that supplied by therapeutic heat wraps (eg, ThermaCare), may provide a safer means of heat application. However, the risk of burns increases with age, and older adults should be cautioned about this risk.

In the presence of acute or subacute low back pain, superficial heat application provides effective pain relief and reduces disability after 4 to 5 days of application.[24] For chronic low back pain, there is insufficient evidence to support the effectiveness of superficial heat for reduction of pain or disability (Table 60–2).

Compression and elevation are important steps in the initial treatment of an acute injury. Compression, achieved by wrapping the area with an elastic bandage, massage, or intermittent pressure devices, also reduces the size of the developing hematoma and swelling.[25] Preventing hematoma formation is important because a large hematoma can limit mobility and range of motion. Alternating compression with cryotherapy provides more swelling reduction than use of either method alone.[25] Elevating the injured area is most critical within the first 24 to 48 hours, but elevation should continue as long as swelling is present. Elevation, ideally above the heart level, decreases blood flow and reduces fluid accumulation at the injured site.[7,9]

Pharmacologic Therapy

LO 3 KEY CONCEPT There are two main approaches to pharmacologic intervention for pain relief: oral (systemic) and topical agents. In many cases, musculoskeletal disorders are self-treated with over-the-counter (OTC) oral or topical agents. The choice between systemic or topical options is often guided by patient preference. The extent of musculoskeletal pain also guides treatment choice. KEY CONCEPT Localized pain may be treated effectively with local topical therapy, whereas generalized pain is best treated with systemic agents. Factors such as alcohol use, liver function, renal function, allergies, age, and comorbid conditions should be considered when choosing among therapeutic options.

▶ *Oral Analgesics*

Nonopioid analgesics, including acetaminophen, aspirin, and NSAIDs, are used commonly for musculoskeletal disorders. These agents all provide analgesia, but aspirin and NSAIDs also work peripherally by inhibiting the enzyme COX

Table 60–2

Treatment for Low Back Pain[24]

Low Back Pain Type by Duration	Acute (< 4 weeks) or Subacute (4 to 12 weeks)	Chronic (> 12 weeks)
Nonpharmacologic therapy[a]	Superficial heat application, spinal manipulation, massage, acupuncture, exercise	Exercise, multidisciplinary rehabilitation, acupuncture, massage, psychological stress reduction, spinal manipulation
Pharmacologic therapy	NSAIDs or muscle relaxants	NSAIDs, duloxetine[b], tramadol[b], opioids[b]

[a]Evidence supporting use ranges from low to moderate.

[b]Refer to Chapter 34 (Pain Management) for further drug review.

to decrease production of PGE_2, the principal mediator of acute inflammation.[12,21] Although the mechanism of action of acetaminophen is less clear, it appears that acetaminophen acts as a weak inhibitor of PG production via COX-2 inhibition and exerts only a mild anti-inflammatory effect.[13,26]

LO 4 **Acetaminophen** KEY CONCEPT Acetaminophen is the drug of choice for mild-to-moderate regional musculoskeletal pain without inflammation.[13,27] However, acetaminophen does not provide adequate analgesia for patients with any low back pain.[24] Comparative trials between acetaminophen and oral NSAIDs demonstrate equivalent analgesia in some situations, but NSAIDs may be preferred in others. Therefore, if adequate analgesia is not achieved with acetaminophen, switching to an NSAID is a reasonable alternative. Acetaminophen offers the advantage of less gastrointestinal (GI) toxicity than NSAIDs. Although tolerability of acetaminophen is high at therapeutic doses, hepatotoxicity has been reported after overdose and at therapeutic doses, especially in combination with other factors.[13,26] Patients should not exceed 4 g/day of acetaminophen to minimize the risk of liver injury. Acetaminophen should be used with caution in patients who have liver disease or consume alcohol because of the risk of hepatotoxicity. Due to concern over liver injury, many nonprescription products are now labeled with a maximum recommended dose of 3 g/day. In addition, oral prescription combination products are limited by the US Food and Drug Administration (FDA) to 325 mg acetaminophen per dosage unit.[28] Acetaminophen can be used safely in infants, children, adolescents, and older adults.

LO 5 LO 3 LO 3

LO 4 **Salicylates** KEY CONCEPT Aspirin is not more effective than acetaminophen, and it is not recommended for initial treatment of acute musculoskeletal pain because its adverse effects may be more common and severe.[13] Gastric irritation is more common with aspirin, and bleeding risk is increased because aspirin irreversibly inhibits platelet aggregation. Patients with aspirin-induced asthma should avoid aspirin and other salicylates. Due to the risk of Reye syndrome, aspirin should be avoided in persons younger than age 19 during episodes of fever-causing illnesses.

LO 3

Some salicylates are specifically marketed for musculoskeletal back pain, such as magnesium salicylate. However, use of salicylates is not supported given the limited evidence showing benefit in treating acute pain.[29] Magnesium salicylate should be used with caution in patients with renal impairment due to risk of hypermagnesemia and should be avoided in patients 19 years old and younger due to risk of Reye syndrome.[30]

LO 3 LO 3

NSAIDs Oral NSAIDs are used commonly for musculoskeletal pain because of their availability without a prescription and anti-inflammatory effects.[12,27] KEY CONCEPT NSAIDs are a preferred choice over acetaminophen in musculoskeletal disorders in which inflammation is the primary problem.[27] As a result, NSAIDs are particularly beneficial for chronic overuse injury, in which inflammation is central to the pain and loss of motion.[21] Although NSAIDs may be helpful in relieving pain and inflammation in tendonitis, many tendinopathies are not associated with inflammation. Therefore, use of acetaminophen may relieve pain adequately.[2] For patients with low back pain, NSAIDs are first-line pharmacotherapy given the evidence demonstrating efficacy.[24] There has been some debate that early NSAID use in severe injuries such as fractures or extensive muscle tears may impede healing by reducing collagen formation, causing further chronic instability.[21,31] However, use of NSAIDs for less severe injury has shown beneficial effects in the recovery and healing process.[21]

LO 4

The analgesic effects of NSAIDs are attributed to inhibition of the COX-2 enzyme, whereas the negative GI effects are due to inhibition of COX-1.[13,27] Patients taking oral anticoagulants, those with a history of peptic ulcer disease, or others at high risk for GI complications may be considered candidates for a COX-2 inhibitor (eg, celecoxib) or a combination of a nonselective NSAID with a gastroprotective agent such as a proton pump inhibitor (see Chapter 58). Combination of any NSAID, including COX-2 inhibitors, with alcohol can increase GI adverse effects.[13]

LO 3

Both nonselective NSAIDs and COX-2 inhibitors are associated with nephrotoxicity.[13,21] Furthermore, NSAIDs, including selective COX-2 inhibitors, may increase the risk of myocardial infarction. See Chapter 58 (Osteoarthritis) for discussion of the relative risks of nonselective NSAIDs and COX-2 inhibitors, treatment options based on an individual patient's cardiovascular and GI risk profile, and maximum dosing recommendations. Refer to the drug package labeling for children and adolescents to ensure correct dosing and safe use. For example, ibuprofen is approved for use in infants 6 months and older, whereas naproxen is approved for individuals age 12 years and older.

LO 3

▶ *Topical (External) Analgesics*

Topically (or externally) applied drugs that exert a local analgesic, anesthetic, or antipruritic effect by either suppressing cutaneous sensory receptors or by stimulating these receptors in a counterirritant fashion.[13] These medications are applied directly to the affected area to create high local concentrations of the drug and exert action locally in the nerves or tissues. Negligible systemic concentrations are achieved with intact skin, minimizing systemic adverse effects.[13] Formulations include gel, cream, lotion, patch, liquid, liniment, or aerosol spray. Topical delivery should not be confused with transdermal delivery, in which drug absorption into the bloodstream produces a systemic effect. Musculoskeletal disorders often are treated with topical (not transdermal) medications.

After application, the topical medication penetrates the skin to the soft tissue and peripheral nerves.[13] Topical analgesics suppress the sensitization of pain receptors at the site, thereby reducing pain and burning. Examples include topical NSAIDs and local anesthetics. In contrast, *counterirritant* products are external analgesics that stimulate cutaneous sensory receptors, producing a burning, warming, or cooling sensation that masks the underlying pain. In effect, the irritation or inflammation caused by the counterirritant distracts from the underlying pain.

External analgesics are useful adjuvants to nonpharmacologic therapy and systemic analgesic therapy to provide additional relief. These agents are also an option in patients who cannot tolerate systemic analgesics. Because these products are not in pill form and many are available without a prescription, they may be overused or misused. Clinicians should advise patients to read and follow directions on the labels of OTC products.

Topical NSAIDs In acute soft-tissue injury such as strains and sprains, efficacy of topical NSAIDs is superior to that of placebo and similar to that of oral NSAIDs.[32] Tissue concentrations of topical NSAIDs are high enough to produce anti-inflammatory effects, but systemic concentrations after application remain low.

Diclofenac is the only topical NSAID commercially available in the United States.[13] Topical diclofenac solution (Pennsaid) and gel (Voltaren) are only indicated for treatment of osteoarthritis (see Chapter 58).[33-35] The diclofenac patch (Flector Patch) is indicated specifically for topical treatment of acute pain from minor sprains and strains in adults.[36] One patch is applied to

the most painful area twice daily to intact skin only.[13,36] Patients should be instructed to wash hands before and after application, discard the patch after use, avoid wearing the patch while bathing or showering, and to tape the patch in place if it begins to peel off.

Theoretically, the risk of serious GI adverse events should be less than with oral NSAIDs, but long-term studies evaluating these events are lacking.[21] Like oral NSAIDs, topical NSAIDs should be used with caution in patients with a history of GI bleeding or ulcer.[13] Use of topical NSAIDs with oral NSAIDs is not recommended given the potential for increased systemic adverse effects. See Chapter 58 (Osteoarthritis) for further review of NSAID-related adverse effects. Studies comparing topical NSAIDs with other topical products, including counterirritants, are also needed. Local cutaneous adverse reactions (eg, erythema, rash, pruritus, and irritation) are reported and may be due in part to the vehicle used.[13]

LO 3

Local Anesthetics Nonprescription topical anesthetics such as lidocaine and benzocaine are available in many types of products. Local anesthetics decrease discharges in superficial somatic nerves and cause numbness on the skin surface but do not penetrate deeper structures such as muscle where the pain often lies.[37] Although these topical anesthetics are not effective in direct treatment of musculoskeletal pain, they are helpful when abrasion accompanies the injury. Anesthetics are often formulated in combination with an antibiotic for OTC use; the anesthetic provides soothing relief to the abrasion site while the antibiotic promotes healing of abrasions and prevents soft-tissue infection.

Prescription topical anesthetic agents are not approved for the treatment of acute musculoskeletal pain.[13] Agents include topical lidocaine patch (Lidoderm) and heated lidocaine/tetracaine patch (Synera). The patches deliver lidocaine to local tissues to reduce neuronal impulse, induce an anesthetic effect, and reduce inflammation. The heated lidocaine/tetracaine patch provides a similar mechanism of action but also is formulated with an oxygen-activated heating component to enhance local anesthetic delivery. These agents may be considered for off-label treatment of musculoskeletal and low back pain when other first-line or approved therapies have not provided adequate pain relief.

LO 4

Counterirritants Counterirritants are indicated for the temporary relief of minor aches and pains related to muscles and joints.[17] These symptoms may be associated with arthritis, strains, or sprains. Many are available as combination products with ingredients from different counterirritant groups. Active ingredients in marketed products sometimes change; clinicians should be aware of the current ingredients before recommending a product. These products are applied multiple times a day (ranging from 3 to 4 applications daily) for up to 7 days; if pain relief is not achieved by that time, the patient should follow-up with the provider to further evaluate the acute musculoskeletal pain.

LO 4

Nonprescription counterirritants are categorized by the FDA into four groups (groups A through D) based on their primary actions (Table 60–3).[17] They produce a feeling of redness, cooling, warmth, or irritation that diverts sensation from the pain. Because these irritant effects are central to the beneficial

Table 60–3

Nonprescription Counterirritant External Analgesics[17]

Group and Effect	Agents and Concentration	Example Products (If Applicable)	Comments
Group A			
Rubefacients: Produce redness	Allyl isothiocyanate 0.5%–5%		Mustard derivative; pungent odor; avoid inhalation
	Ammonia water 1%–2.5%		More concentrated solutions are highly caustic; avoid inhalation
	Methyl salicylate 10%–60%	BenGay Ultra Strength,[a] Flexall Plus,[a] Icy Hot Stick[a]	Caution in aspirin sensitivity May produce systemic concentrations May increase INR with warfarin Use in adults and children > 12 years old
Group B			
Produce cooling	Camphor 3%–11% Menthol 1.25%–16%	JointFlex BenGay Patch, Icy Hot Patch, Mineral Ice[c]	Medicinal odor Sensation of heat follows cooling Mild anesthetic effects at low concentrations Use in adults and children > 12 years old[d]
Group C			
Produce vasodilation	Methyl nicotinate 0.25%–1%	Arth Arrest[b]	May produce systemic vasodilation Use in adults and children > 2 years old
Group D			
Irritate without redness	Capsaicin 0.025%–0.25% Capsicum oleoresin 0.025%–0.25%	Capzasin-HP, Zostrix	Must use regularly Burning effect subsides with regular use Use in adults only (ages > 18 years old)

[a]Combination products that also contain menthol and/or camphor.

[b]Combination product that also contains capsaicin.

[c]May be used in adults and children age 2 years old and older.

[d]Federal Register recommends to avoid in children less than 2 years old.

INR, international normalized ratio.

Table 60–4

Patient Education for Counterirritants[17]

Apply up to three to four times daily to affected area.
Only for external use on the skin; do not ingest.
Do not apply to broken or damaged skin or cover large areas.
Wash hands immediately after application.
Avoid contact with the eyes and mouth.
Do not use with heating pads or other methods of heat application, because burning or blistering can occur.
Do not wrap or bandage the area tightly after application.
Discontinue product if excessive skin irritation or rash occurs.
Consult a physician if:
- Symptoms worsen
- Symptoms persist for more than 7 days[a] for acute pain
- Symptoms resolve but then recur

[a]Capsaicin is used for chronic pain, and efficacy is evaluated after 2 weeks.

actions, counterirritants should not be combined with topical anesthetics or topical analgesics. KEY CONCEPT Patient education on proper use of counterirritants is essential to therapeutic success (Table 60–4).[17] LO 5

Rubefacients (group A) are counterirritants that produce redness on application. Evidence from clinical trials and a systematic review showed rubefacients to be ineffective for relieving acute pain from strains, sprains, and sports injuries, and for chronic musculoskeletal pain.[29] However, topical rubefacients containing salicylates (eg, methyl salicylate) are still used commonly if a patient does not tolerate or has contraindications to other therapy or prefers an alternative route of administration for acute pain.

Application of methyl salicylate can lead to systemic effects similar to aspirin therapy, especially if the product is applied liberally.[38] Repeated application and occlusion with a wrap or bandage also can increase systemic concentrations. Salicylate-containing products should be used with caution in patients in whom systemic salicylates are contraindicated, such as patients with severe asthma or aspirin allergy.[38] Topical salicylates have been reported to increase prothrombin time in patients on warfarin and should be used with caution in patients on oral anticoagulants. Methyl salicylate, including oil of wintergreen, is a common source of pediatric poisonings.[39,40] LO 3

The group B counterirritants menthol and camphor exert a sensation of cooling through direct action on sensory nerve endings, followed by a sensation of warmth.[38,40] The agents cause a burning sensation by stimulating cutaneous nociceptors.[40] For topical analgesic use, menthol is available in creams, lotions, ointment, and patches. The patches can be trimmed to fit the affected area. Despite limits on the concentration of available products, camphor can be toxic to children even in small amounts, posing a seizure risk.[41]

The group C counterirritants methyl nicotinate and histamine dihydrochloride produce vasodilation.[17] Methyl nicotinate produces PG-mediated vasodilation.[42] NSAIDs and aspirin block the production of PGs and decrease methyl nicotinate–induced vasodilation. Application over a large area has been reported to cause systemic symptoms and syncope, possibly due to vasodilation and a decrease in blood pressure.[43] Patients should be educated to apply only scant amounts to the affected area. LO 5

The primary counterirritant in group D is capsaicin, a natural substance found in red chili peppers.[13,40] Capsaicin stimulates the release of substance P from local sensory nerve fibers, depleting substance P stores over time. A period of reduced sensitivity to painful stimuli follows, and transmission of pain impulses to the CNS is reduced.

As with other counterirritants, capsaicin and its derivatives (capsicum and capsicum oleoresin) exert a warming or burning sensation.[13,40] With repeated application, desensitization occurs, and the burning sensation subsides within the first 1 to 2 weeks. Pain relief is usually noted within 2 to 6 weeks.[13] After discontinuation, resensitization occurs gradually over several weeks for autonomic nerves and 4 to 5 months for sensory nerves.[40]

Because of the lag time between initiation and effect, capsaicin is not used for treatment of acute pain from injury. Topical capsaicin is used for chronic pain from musculoskeletal and neuropathic disorders. Capsaicin preparations have been studied for treatment of pain from diabetic neuropathy, osteoarthritis, postherpetic neuralgia, and other disorders.[13] It is often used as an adjuvant to systemic analgesics in these chronic pain conditions. LO 4

Although systemic adverse effects to capsaicin are rare, local adverse effects are expected and common.[13,40] Patient education regarding consistent use of capsaicin products is essential to achieving desired outcomes. Product should be applied in a thin layer and rubbed into the skin thoroughly until little remains on the surface. KEY CONCEPT Patients using capsaicin should be advised to apply it regularly and consistently three to four times daily and that full effect may take 2 weeks or longer. Patients should be assured that the burning effects will diminish with repeated application. Adherence to therapy is essential because the burning sensation persists if applications are less frequent than recommended. Because the burning sensation is enhanced with heat, patients should avoid hot showers or baths immediately before or after application. Wearing nitrile gloves during application and washing hands immediately after application can decrease the potential for unintended contact with eyes or mucous membranes. Dried product residue has been reported to cause respiratory effects on inhalation (eg, coughing), and caution should be used in patients with asthma or other respiratory illnesses. Transient increases in blood pressure have been noted upon initial application, so it is important to evaluate the patient's cardiovascular status before initiation.[40] LO 5 LO 3

▶ *Oral Muscle Relaxants*

Oral muscle relaxants are a useful adjunct to therapy when pain is worsened by muscle spasm.[13] Antispasmodic agents are preferred over antispastic agents for musculoskeletal pain because antispasmodics exert their effect directly on skeletal muscle fibers, polysynaptic reflexes, and/or descending facilitatory systems; whereas antispastic agents mostly target upper motor neuron conditions. Examples of antispasmodic agents include baclofen, tizanidine, carisoprodol, metaxalone, and cyclobenzaprine. Muscle relaxants decrease spasm and stiffness associated with either acute or chronic musculoskeletal disorders. For low back pain, a systematic review demonstrated that muscle relaxants provide significant acute or subacute pain relief but are not effective in treating chronic low back pain.[24,44] These agents should be used with caution because they all may cause sedation, especially in combination with alcohol or opioid analgesics. Many produce anticholinergic effects, such as xerostomia and blurred vision, and have potential for abuse; therefore, patient-specific factors should be reviewed before recommending muscle relaxants. Sudden discontinuation should be avoided because it may lead to withdrawal symptoms. LO 3

▶ *Opioid Analgesics*

Opioid analgesics may be considered in acute pain management if nonopioid analgesics are already optimized and the patient is still experiencing moderate to severe pain.[21,27] Opioids may be used in combination with nonopioids such as acetaminophen or NSAIDs, but not to exceed the recommended daily dose of the respective nonopioid agent(s). Opioids are not recommended as initial therapy for acute or subacute low back pain, given the low level of evidence of effectiveness in reducing pain. Patients presenting with chronic low back pain, having inadequate response to NSAIDs, duloxetine, or tramadol, may benefit from opioid medications.[24] Given the concern for abuse potential and adverse events with opioids, a full patient medical history is recommended before prescribing. See Chapter 34 (Pain Management) for more information on use of duloxetine, tramadol, and opioids.

▶ *Complementary and Alternative Medicine for Pain Relief*

Various complementary and alternative modalities are available for patients seeking additional or alternative treatments for pain relief.[13] Integrative practices include manipulation therapy, acupuncture, massage therapy, yoga, electrical stimulating currents, low-power laser, hyperbaric oxygen therapy, and ultrasound therapy.[7,9,10,13]

Massage therapy, spinal manipulation, and acupuncture have shown potential benefit in relieving acute or subacute low back pain.[24] Acupuncture and cognitive behavioral therapy have demonstrated moderate benefit in reducing chronic low back pain, whereas massage therapy and spinal manipulation have shown minimal benefit.

Dietary supplements that have been shown to potentially reduce pain and/or inflammation include devil's claw, willow bark extract, aspen or goldenrod, marijuana, and turmeric.[13] Given the mechanisms of action and metabolism of these supplements, it is highly recommended to review potential adverse events, drug interactions, and a patient's current medical history before recommending any of these supplements.[45] Overall evidence of benefit may be limited or conflicting, and patients should be educated on the benefits and risks of these therapies before initiation as additional treatment.[45]

Lifestyle and Behavioral Modifications

After treatment of an acute injury, repetitive strain injury, or low back pain with nonpharmacologic and pharmacologic therapy, the final phase of therapy is rehabilitation and prevention of future injury. For most injuries, prolonged immobilization can lengthen the recovery time by causing wasting of the healthy muscle fibers and increased scarring.[9,21] Rehabilitation starts with decreasing inflammation, then increasing range of motion and flexibility via stretching exercises. The patient should warm the muscle first with light activity or moderate heat. Warmth produces relaxation and increases elasticity. Next, the patient may start general strengthening exercises. The focus of the rehabilitation may not be the injured muscle itself but nearby muscles to assist with stability. End goals of rehabilitation are specific to each patient and may range from return to activities of daily living to a rigorous sports schedule.

After rehabilitation, the patient should be educated about behavior changes to prevent reinjury.[21] The strength and flexibility exercises learned in the rehabilitation phase should be continued. For overuse injury, correction of biomechanical abnormalities with proper footwear and changes in technique may correct misalignments and imbalances.[2,5] Repetitive trauma can be decreased with proper training (eg, a gradual increase in mileage in a running plan).

In the workplace, repetitive motion can be decreased through proper ergonomic design and diversification of job tasks.[8] In pain of the back or lower extremity, weight loss in overweight or obese patients can help to prevent reinjury or repetitive strain injuries.[3,16]

OUTCOME EVALUATION

LO 6

- Use a pain scale to monitor treatment interventions to ensure that pain relief is achieved. Ask the patient to rate pain on a scale of zero (no pain) to 10 (worst possible pain) both at rest and with movement. Compare the results with baseline pain assessment to monitor the response to therapy. In pediatric patients, use a visual pain scale with facial expressions depicting various degrees of pain.

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH/PSH: Appendectomy 10 years ago

SH: Smokes 2 to 3 cigarettes per week socially; drinks 2 to 3 beers Friday and Saturday

Meds: Multivitamin one tablet by mouth daily, fish oil 1000 mg daily

Allergies: Sulfa drugs (rash)

Intolerances: None

Preferences: No preference to topical or oral medications at this time

Diagnostic Tests: Radiographs of right wrist show no evidence of fracture

Pain (numerical rating scale): 5 out of 10

What are your treatment goals and desired outcomes?

What nonpharmacologic and pharmacologic treatment options are available? Are there treatment options that should be avoided? If so, which options and why?

Patient Encounter 1, Part 3: Creating a Care Plan

Based on the information presented, create a care plan to treat this patient's wrist injury. Your plan should include the following:

(a) The goals of therapy and desired outcomes

(b) A patient-specific therapeutic plan, including nonpharmacologic therapy

(c) A plan to monitor the outcome of therapy to determine whether goals of therapy have been met and adverse effects avoided

Patient Encounter 2

A 26-year-old woman presents with left ankle pain. Upon questioning, you find she is an avid runner for the past 4 years, running several marathons, and trains by running at least 6 continuous miles daily every morning. She reports gradual onset of pain over the last few months. When she wakes in the morning, she has minimal pain after resting overnight, but the pain begins to intensify during the middle of her morning run and lasts throughout the day. She denies any swelling. She reports a decreased range of motion compared to her right ankle. She has no significant past medical history and only takes a daily prenatal multivitamin.

Given this information, what is your assessment of the patient's ankle pain? What is the likely etiology of the pain?

What nonpharmacologic and pharmacologic treatment options should be considered?

Based on the information presented, create a care plan for this patient's ankle injury. Your plan should include the following:

(a) The goals of therapy and desired outcomes

(b) A patient-specific therapeutic plan, including nonpharmacologic therapy

(c) A monitoring plan to determine whether goals of therapy have been met and adverse effects avoided

- Assess range of motion at baseline and after treatment by comparing movement with the unaffected limb and functionality before the injury. Assess functionality by asking patients if they are able to perform activities of daily living or participate in exercise as desired.
- If pain from acute injury does not decrease greatly within 7 to 10 days, further diagnostic evaluation is warranted.
- In patients with chronic low back pain, periodically assess the patient for new signs and symptoms that may warrant further workup.
- Assess adherence to recommended treatments for therapeutic benefit. For all products except capsaicin, assess for acute pain relief within 7 days. For topical capsaicin, assess chronic pain control in 2 weeks.
- Assess medication adverse effects on a regular basis. When NSAIDs and aspirin are used, ask about GI tolerability, bruising, and bleeding. Inquire about local adverse effects, such as burning, when topical counterirritants are used for treatment. When oral muscle relaxants are used, inquire about anticholinergic effects such as xerostomia and blurred vision. Refer to Chapter 34 (Pain Management) for opioid side effects.
- Evaluate adherence to preventative rehabilitation measures such as proper footwear, warm-up before activity, strength training, and proper lifting technique.

Patient Care Process

Collect Information:

- Establish the timing of injury (if applicable), duration, type and degree of pain, and exacerbating factors. Ask about interference with usual activities or range of motion.
- Ask the patient about exacerbating or alleviating factors. Inquire if the patient has tried any successful or unsuccessful nonpharmacologic or pharmacologic treatments for the current complaint or for this condition in the past.
- Obtain a complete medication history, including prescription and nonprescription drugs and dietary supplement use. Gather patient history, including social history and alcohol use. Inquire about drug allergies and chronic health problems such as asthma. Collect physical assessment and laboratory data when available.
- Inquire about patient preference for systemic (oral) or local (topical) therapy including acceptability of topical medication with frequent application and/or a medicinal odor. Identify the patient's goals, beliefs, lifestyle habits, and socioeconomic factors relevant to development of care plan.

Assess the Information:

- Assess the efficacy, safety, and patient adherence of any nonprescription or prescription medications currently being used for the condition and consider alignment with patient preferences for therapy.
- Based on review of symptoms and timing, assess whether empirical care or diagnostic evaluation is appropriate and whether pharmacologic therapy is warranted.

Develop a Care Plan:

- Develop goals of therapy in collaboration with the patient.
- Determine if referral to another health care provider on the team is warranted based on the symptoms provided.
- Recommend nonpharmacologic and pharmacologic therapy appropriate for the specific patient (Tables 60–1, 60-2, and 60–3; Figure 60–1).

Implement the Care Plan:

- Educate the patient on nonpharmacologic therapy for the presenting pain type when appropriate (Tables 60–1 and 60–2).
- Educate on proper use of oral or topical agents selected (Table 60–4). If a counterirritant is recommended, counsel patients on the irritant effect of the product and recommend washing hands immediately after use and to avoid heating pads. For patients using a capsaicin product, emphasize adherence.
- Coordinate any referrals, when applicable.

Follow-up: Monitor and Evaluate:

- If pain is from an acute injury, assess effectiveness within 7 to 10 days. For chronic pain treated with capsaicin, begin to assess pain control in 2 weeks.
- Evaluate for adherence, adverse effects (systemic or local), and drug interactions.

Patient Encounter 3

A 67-year-old man presents with left shoulder pain. He states he was at his daughter's house yesterday and tripped on one of his grandson's toys. As he fell, his weight was placed on his left arm and shoulder. He reports decreased range of motion compared to his right shoulder and mild swelling.

PMH/PSH: Hypertension, dyslipidemia

SH: Nonsmoker, 1 glass of wine on holidays

Meds: Lisinopril 10 mg one tablet orally daily, atorvastatin 10 mg one tablet orally daily, aspirin 81 mg one tablet orally daily, multivitamin one tablet orally daily

Allergies: NKDA

Intolerances: NSAIDs, stomach upset

Preferences: Prefers topical medications

Vital signs: BP 160/92 today

Diagnostic Tests: None

Pain (numerical rating scale): 3 out of 10. Pain worsens to 4 out of 10 with weight or lifting.

Given this information, what is your assessment of the patient's shoulder pain? What is the likely etiology of the pain?

What nonpharmacologic and pharmacologic treatment options should be considered?

Based on the information presented, create a care plan for this patient's shoulder injury. Your plan should include:

(a) Goals of therapy and desired outcomes

(b) Patient-specific therapeutic plan, including nonpharmacologic therapy

(c) A plan to monitor the outcome of therapy to determine whether goals of therapy have been met and adverse effects avoided

Abbreviations Introduced in This Chapter

CNS	Central nervous system
COX	Cyclooxygenase
FDA	Food and Drug Administration
GI	Gastrointestinal
NSAIDs	Nonsteroidal anti-inflammatory drugs
OTC	Over-the-counter
PG	Prostaglandin
RICE	Rest, ice, compression, and elevation

REFERENCES

1. Aziz F, Doty CI. Orthopedic emergencies. In: Stone CK, Humphries RL, eds. CURRENT Diagnosis & Treatment: Emergency Medicine, 8th ed. New York: McGraw-Hill Education; 2017. Chapter 28.
2. Rodenberg RE, Bowman E, Ravindran R. Overuse injuries. Prim Care. 2013;40:453–473.
3. Yamada E, Thomas DC. Common musculoskeletal diagnoses of upper and lower extremities in older patients. Mt Sinai J Med. 2011;78:546–557.
4. Weinstein SI, Yelin EH, Watkins-Castillo SI. The Big Picture: The Burden of Musculoskeletal Diseases in the United States (BMUS), 3rd ed. Rosemont(IL): United States Bone and Joint Initiative; ©2014. Available from: http://www.boneandjointburden.org. Accessed July 10, 2017.
5. Paterno MV, Taylor-Haas JA, Myer GD, Hewett TE. Prevention of overuse sports injuries in the young athlete. Orthop Clin North Am. 2013;44:553–564.
6. Doperak J, Anderson K. Acute musculoskeletal complaints. In: South-Paul JE, Matheny SC, Lewis EL, eds. CURRENT Diagnosis & Treatment: Family Medicine, 4th ed. New York: McGraw-Hill Education; 2015. Chapter 38.
7. Delos D, Maak TG, Rodeo SA. Muscle injuries in athletes: enhancing recovery through scientific understanding and novel therapies. Sports Health. 2013;5:346–352.
8. Keyserling WM. Occupational ergonomics: promoting safety and health through workplace design. In: Levy BS, Wegman DH, Baron SL, Sokas RK, eds. Occupational and Environmental Health: Recognizing and Preventing Disease and Injury, 6th ed. New York: Oxford University Press, Inc.; 2011. Chapter 27.
9. Järvinen TA, Järvinen M, Kalimo H. Regeneration of injured skeletal muscle after the injury. Muscles Ligaments Tendons J. 2013;3:337–345.
10. Prentice WE. Using therapeutic modalities to affect the healing process. In: Prentice WE, Quillen WS, Underwood F, eds. Therapeutic Modalities in Rehabilitation, 4th ed. New York: McGraw-Hill Education; 2011. Chapter 2.
11. Widmaier EP, Raff H, Strang KT. Vander's Human Physiology: The Mechanism of Body Function, 14th ed. New York: McGraw Hill; 2016.
12. Rathmell JP, Fields HL. Pain: pathophysiology and management. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 19th ed. New York: McGraw-Hill Education; 2014. Chapter 18.
13. Gammaitoni AR, Galer BS. Analgesic pharmacology. In: Staats PS, Wallace MS, eds. Pain Medicine and Management: Just the Facts. New York: McGraw Hill Education; 2015. pp. 87–151.
14. Khodaee M. Common superficial bursitis. Am Fam Physician. 2017;95:224–231.
15. Casazza BA. Diagnosis and treatment of acute low back pain. Am Fam Physician. 2012;85(4):343–350.
16. Herndon CM, Zoberi KS, Gardner BJ. Common questions about chronic low back pain. Am Fam Physician. 2015;91(10): 708–714.
17. Food and Drug Administration. External analgesic drug products for over-the-counter human use: tentative final monograph. Fed Regist. 1983;48:5851–5869.
18. Tripp AM. Treating Acute Sports and Exercise Injuries in the First 24 to 72 hours [Internet]. Sports-health™: Veritashealth.com. Available from: https://www.sports-health.com/treatment/treating-acutesports-and-exercise-injuries-first-24-72-hours. Updated July 10, 2014. Accessed August 10, 2017.
19. Houghton PE. The role of therapeutic modalities in wound healing. In: Prentice WE, Quillen WS, Underwood F, eds. Therapeutic Modalities in Rehabilitation, 4th ed. New York City: McGraw-Hill Education; 2011. Chapter 3.
20. Barroso GC, Thiele ES. Muscle injuries in athletes. Rev Bras Ortop. 2011;46:354–358.
21. Griffin LY, Aboulafia AJ, Andras LM, et al. General orthopaedics. In: Armstrong A, Hubbard M, eds. Essentials of Musculoskeletal Care, 5th ed. Rosemont (IL): American Academy of Orthopaedic Surgeons; 2016. Section 1.
22. Luke A, Ma CB. Sports medicine & outpatient orthopedics. In: Papadakis MA, McPhee SJ, Rabow MW, eds. CURRENT Medical Diagnosis & Treatment 2017. New York: McGraw-Hill Education; 2017. Chapter 41.

23. Prentice WE. Cryotherapy and thermotherapy. In: Prentice WE, Quillen WS, Underwood F, eds. Therapeutic Modalities in Rehabilitation, 4th ed. New York: McGraw-Hill Education; 2011. Chapter 9.
24. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive treatment for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:514–530.
25. Hooker DN. Intermittent compression devices. In: Prentice WE, Quillen WS, Underwood F, eds. Therapeutic Modalities in Rehabilitation, 4th ed. New York: McGraw-Hill Education; 2011. Chapter 15.
26. Graham GG, Davies MJ, Day RO, et al. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacology. 2013;21:201–232.
27. Blondell RD, Azadfard M, Wisniewski AM. Pharmacologic therapy for acute pain. Am Fam Physician. 2013;87:766–772.
28. FDA drug safety communication. Prescription acetaminophen products to be limited to 325 mg per dosage unit; boxed warning will highlight potential for severe liver failure. U.S. Food and Drug Administration. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm239821.htm. Updated July 31, 2017. Accessed August 10, 2017.
29. Derry S, Matthews PR, Wiffen PJ, Moore RA. Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2014;(11):Cd007403.
30. Doans extra strength (magnesium salicylate tablet). Somerville (NJ): Dr. Reddy's Laboratories Inc., 2016. Package insert. NDC 55741-224-24.
31. van den Bekerom MP, Sjer A, Somford MP, Bulstra GH, Struijs PA, Kerkhoffs GM. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating acute ankle sprains in adults: benefits outweigh adverse events. Knee Surg Sports Traumatol Arthrosc. 2015;23:2390–2399.
32. Derry S, Moore RA, Gaskell H, McIntyre M, Wiffen PJ. Topical NSAIDs for acute musculoskeletal pain in adults. Cochrane Database Syst Rev. 2015:Cd007402.
33. Pennsaid (diclofenac sodium topical solution 2%). Lake Forest (IL): Horizon Pharma Inc.; 2016. Package insert. NDC 75987-040-05.
34. Pennsaid (diclofenac sodium topical solution 1.5%). Hazelwood (MO): STAT RX USA LLC; 2010. Package insert. NDC 16590-453-33.
35. Voltaren Gel (diclofenac sodium topical gel 1%). Malvern (PA): Endo Pharmaceuticals Inc.; 2016. Package insert. NDCs 63481-684-03, 63481-684-05, 63481-684-47, 63481-684-83.
36. Flector Patch (diclofenac epolamine patch 1.3%). New York City (NY): Pfizer, Inc.; 2017. Package insert. NDC 60793-411-30.
37. Kumar M, Chawla R, Goyal M. Topical anesthesia. J Anaesthesiol Clin Pharmacol. 2015;31:450–456.
38. Brayfield A, ed. Martindale: The Complete Drug Reference. London: Pharmaceutical Press. ©1933-2017. Available from: http://www.medicinescomplete.com/. Accessed August 10, 2017.
39. Anderson A, McConville A, Fanthorpe L, Davis J. Salicylate poisoning potential of topical pain relief agents: from age old remedies to engineered smart patches. Medicines. 2017;4:48–60.
40. Barkin RL. The pharmacology of topical analgesics. Postgrad Med. 2013;125:7–18.
41. MacKinney TG, Soti KR, Shrestha P, Basnyat B. Camphor: an herbal medicine causing grand mal seizures. BMJ Case Rep. 2015;2015.
42. Koprowski R, Wilczynski S, Wrobel Z, Blonska-Fajfrowska B. Dynamic thermal imaging analysis in the effectiveness evaluation of warming and cooling formulations. Comput Biol Med. 2014;54:129–136.
43. Fergusson DA. Systemic symptoms associated with a rubefacient. BMJ. 1988;297:1339.
44. Abdel Shaheed C, Maher CG, Williams KA, McLachlan AJ. Efficacy and tolerability of muscle relaxants for low back pain: systematic review and meta-analysis. Eur J Pain. 2017;21(2):228–237.
45. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. JAMA Intern Med. 2013;173:355–361.

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61 Glaucoma

Mikael D. Jones

LEARNING OBJECTIVES

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

LO

1. Identify risk factors for the development of primary open-angle glaucoma (POAG) and acute angle-closure glaucoma.
2. Recommend a frequency for glaucoma screening based on patient-specific risk factors.
3. Compare and contrast the pathophysiologic mechanisms responsible for open-angle glaucoma and acute angle-closure glaucoma.
4. Outline the clinical presentation of chronic open-angle glaucoma and acute angle-closure glaucoma.
5. List the goals of managing patients with POAG suspect, POAG, and acute angle-closure glaucoma.
6. Choose the most appropriate therapy based on patient-specific data for open-angle glaucoma, glaucoma suspect, and acute angle-closure glaucoma.
7. Develop a monitoring plan for patients on specific pharmacologic regimens.
8. Counsel patients about glaucoma, drug therapy options, ophthalmic administration techniques, and the importance of adherence to the prescribed regimen.

INTRODUCTION

Glaucoma refers to a spectrum of ophthalmic disorders characterized by neuropathy of the optic nerve and loss of retinal ganglion cells, which typically leads to permanent deterioration of the visual field (peripheral vision) initially and potentially total vision loss (including central vision). It is often, but not always, eye pressure related.[1-3] Table 61–1 describes the general classification of glaucoma. *Glaucoma Suspects* are patients with a higher than average risk of developing glaucoma because of the presence of certain clinical findings, risk factors, family history, or racial background. Glaucoma suspects can be further classified as open-angle glaucoma suspects or angle-closure glaucoma suspects.

Primary Open-Angle Glaucoma (POAG) and Primary Angle-Closure Glaucoma (PACG) represent the most common types of glaucoma and therefore are the focus of this chapter. PACG can present clinically as acute angle-closure crisis (AACC). AACC is the sudden obstruction of the trabecular meshwork, which leads to a rapid increases in IOP resulting in pressure-induced optic neuropathy if untreated.[1-4] KEY CONCEPT In contrast, patients with POAG typically have a slow, insidious loss of vision which is often asymptomatic until the latter stage of the disease process. This is contrasted by the course of AACC, which can lead to rapid and painful vision loss that develops over hours to days.

EPIDEMIOLOGY AND ETIOLOGY

LO 1

It is estimated that almost 65 million people had glaucoma in 2013, making it the second leading cause of blindness after cataracts. By 2040 this number may increase to greater than 110 million people worldwide.[5] In North America it is estimated that almost 3 million people are affected by POAG, and by 2040 this number will increase to 4.2 million.[5] The prevalence varies with race and ethnicity, and it is three to five times more prevalent in African Americans than white Americans.[6] The prevalence of POAG increases with age and is rarely seen in patients younger than 40 years.[6,7] The prevalence of POAG suspects is difficult to estimate at this time, but it is expected that 3.5% to 4.5% of white and Hispanic patients older than 40 years have ocular hypertension.[2]

Approximately 20 million people were estimated to have angle-closure glaucoma in 2013, and this is projected to increase to 32 million people by 2040.[5] The prevalence of angle-closure glaucoma is lower than POAG and varies significantly by race and ethnicity. The prevalence is lower in patients of European ancestry (0.4%) but higher in patients of Asian ancestry (1.2%).[5] PACG is also more prevalent with increasing age and among females.[4]

PATHOPHYSIOLOGY

The pathophysiology of glaucomatous neurodegeneration has not been completely elucidated, but appears to be caused by both IOP-dependent and IOP-independent factors. Elevated IOP is clearly associated with damage and eventual death of optic nerves; however, optic neuropathy can occur in patients without elevated IOP which indicates the presence of independent factors that contribute to ganglion cell death.[8,9] The key to understanding the pathophysiology and treatment of glaucoma relies on an understanding of aqueous humor dynamics, IOP, and optic nerve anatomy and physiology.

Aqueous Humor and Intraocular Pressure

Intraocular pressure (IOP) maintains the curvature of the cornea which is important for the refractive properties of the eye.[10] The distribution of IOP in the general population is 10 to 21 mm Hg (1.3–2.8 kPa) and is slightly skewed toward higher values. However, caution should be used in assigning this as the "normal range" for IOP because some patients may have

Table 61–1

Glaucoma Classifications[3,4]

Classification	Description
Primary glaucoma	Glaucoma that cannot be attributed to a preexisting ocular or systemic disease
Secondary glaucoma	Glaucoma that can be attributed to preexisting ocular or systemic disease. Examples include pigment dispersion syndrome, neovascular glaucoma, and pseudoexfoliative syndrome.
Open-angle glaucoma	Glaucoma characterized by normal anterior-chamber angles and glaucomatous changes of the optic disc. Can be further classified as primary or secondary.
Angle-closure glaucoma	Glaucoma characterized by the obstruction of the anterior chamber angle resulting in either intermittent or progressive elevated IOP with subsequent damage to the optic nerve. Can be further classified as primary or secondary.

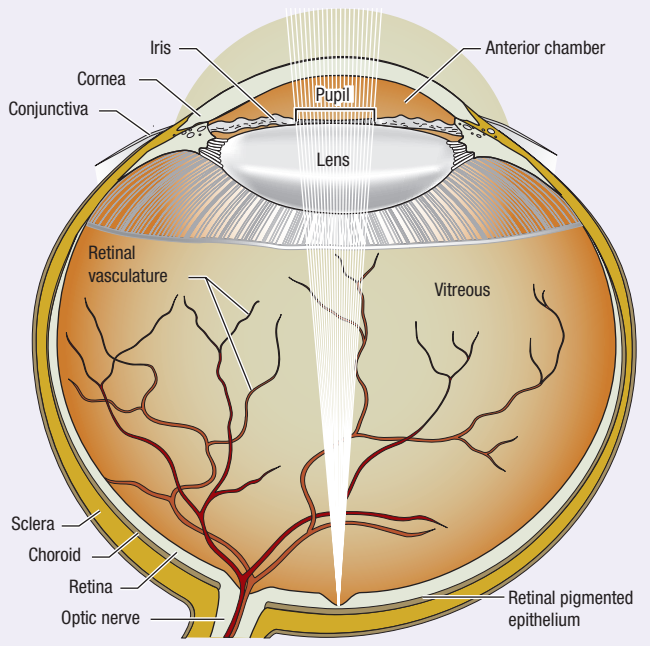

FIGURE 61–1. Anatomy of the eye. (From Fiscella RG, Lesar TS, Owaidhah OA, et al. Glaucoma In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017: Figure 94–1; with permission.)

optic neuropathy in the "normal range" while for other patients optic neuropathy may be absent at higher IOPs. Elevated IOP is generally considered greater than 21 mm Hg (2.8 kPa).[11]

Aqueous humor is an optically neutral fluid that provides oxygen and nutrition to the avascular lens and cornea. IOP is dependent on the balance between aqueous humor production and outflow from the anterior segment (Figures 61–1 and 61–2). The anterior segment of the eye is separated by the iris into the posterior and anterior chambers. The ciliary body is a ring-like structure that surrounds and supports the lens. It also produces aqueous humor through the diffusion and ultrafiltration of plasma. The nonpigmented epithelium of the ciliary body secretes the aqueous humor into the posterior chamber. Aqueous humor production can be modified pharmacologically through the α- and β-adrenoceptors, carbonic anhydrase, and sodium and potassium adenosine triphosphatase of the nonpigmented ciliary epithelium.[12,13]

After secretion, the aqueous humor flows from the posterior chamber through the pupil into the anterior chamber. From the

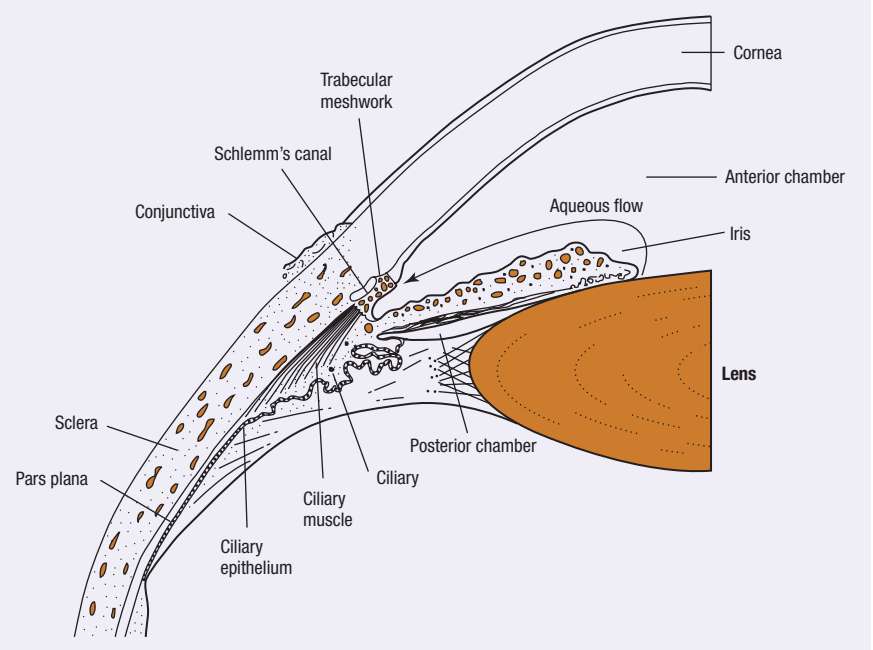

FIGURE 61–2. Anterior chamber of the eye and aqueous humor flow. (From Fiscella RG, Lesar TS, Owaidhah OA, et al. Glaucoma In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017: Figure 94–2; with permission.)

anterior chamber, approximately 80% of aqueous humor then exits through the trabecular meshwork while the remaining 20% exits through the uveoscleral pathway.[12,13]

The trabecular meshwork is a lattice of connective tissue that surrounds peripheral edge of the anterior chamber located in the inside intersection of the edge of the cornea and the iris insertion. The size of the trabecular meshwork can be altered by the contraction or the relaxation of the ciliary muscle. Stimulation of muscarinic receptors on the ciliary muscle causes contraction, which in turn causes the pores of the trabecular meshwork to open, increasing aqueous humor outflow into Schlemm canal and the episcleral venous system.[12] The contraction can also be decreased by inhibiting Rho Kinases which are involved in the regulation of the contractile tone of the trabecular meshwork tissue.[13]

In the uveoscleral pathway, aqueous humor exits the anterior chamber through the iris root and through spaces in the ciliary muscles, which then drain into the suprachoroidal space. Uveoscleral outflow can be pharmacologically modulated by adrenoceptors, prostanoid receptors, and prostamide receptors.[10,14]

Optic Nerve

In the posterior segment of the eye, retinal ganglion cells are responsible for transmitting visual signaling from the retina to the brain. The axons of the retinal ganglion cells converge at the retinal nerve fiber layer to form the optic nerve. The optic nerve head (also called the optic disc) is the portion of the optic nerve that is visible on funduscopic examination. The optic nerve head is vertically oval and pink to pale yellow with a depression in the center of the optic nerve, called a physiologic cup, which is formed as the axons converge and exit the eye as a bundle through the **lamina cribrosa** (**Figure 61–3**). The optic nerve synapses at the lateral **geniculate nucleus** in the brain.[8,9,15,16]

Pathophysiology of Open-Angle Glaucoma

LO 3

In patients with POAG, the cause of elevated IOP is not obvious, as obstruction in aqueous humor outflow is not clinically discernible. Possible causes of this increased IOP may be related to an increase in outflow resistance in the trabecular meshwork.[8,9,13,15]

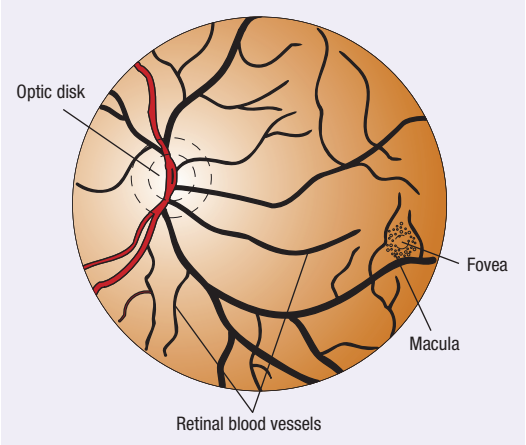

FIGURE 61–3. Normal fundus of the eye and optic disk and cup. (From Fiscella RG, Lesar TS, Owaidhah OA, et al. Glaucoma In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017: Figure 94–3; with permission.)

LO 3

Glaucomatous optic neuropathy may also occur independent of increased IOP. Pressure independent causes of optic neuropathy include abnormal ocular perfusion, oxidative stress, and inflammation.[8,9,11,15]

Regardless of the underlying cause, elevated IOP initiates several detrimental changes to glial cells, the lamina cribrosa, and retinal ganglion cells. The increase in IOP can lead to alterations in retinal blood flow and axonal transport of neurotrophic factors, resulting in cellular stress of the retinal ganglion cells. This stress activates the glial cells in a manner that leads to inappropriate remodeling of the extracellular matrix. Elevated IOP deforms the lamina cribrosa, which places mechanical strain on the retinal ganglion cells. Chronic elevation of IOP ultimately causes the retinal ganglion cells to undergo apoptosis.[8,9,15,17,18]

Current glaucoma therapies fail to target IOP-independent glaucoma pathophysiologic factors. However, IOP reduction may still be beneficial, as the rate of visual field progression is decreased in many patients who exhibit IOP reduction via medical or surgical modalities.[3,8]

Pathophysiology of Angle-Closure Glaucoma

LO 3

PACG involves a mechanical obstruction of aqueous humor outflow through the trabecular meshwork by the peripheral iris. Two major mechanisms of trabecular meshwork obstruction by the peripheral iris include pupillary block and an abnormality of the iris called *iris plateau*. Pupillary block is the more common mechanism of obstruction and results from a complete or functional apposition of the central iris to the anterior lens and is associated with mid-dilation of the pupil. The trapped aqueous humor in the posterior chamber increases pressure behind the iris, causing the peripheral iris to bow forward and obstruct the trabecular meshwork. Plateau iris refers to an anterior displacement of the peripheral iris caused by anteriorly positioned ciliary processes. In this configuration, the peripheral iris bunches as the eye dilates. Both of these mechanisms result in the occlusion of aqueous humor outflow, causing IOP elevation at extreme levels that can lead to vision loss in hours to days.[4,8,19] The degree of iridotrabecular contact (angle closure) can be assessed by visualizing the anatomy of the iridocorneal angle by an examination technique called **gonioscopy**.

Patient Encounter Part 1

LN, a 65-year-old Hispanic female with a history of asthma and hypertension, presents to your clinic for her yearly checkup. She states that she is concerned about losing her eyesight because her older sister has started losing her vision from glaucoma. She denies any changes in her vision.

Meds: Budesonide 160 mcg/formoterol 4.5 mcg meter dose inhaler two inhalations twice daily, Albuterol HFA MDI 1-2 puffs every 4 to 6 hours as needed, and Ramipril 5 mg orally twice daily.

Based on the patient's medical and family history, what risk factors does this patient have for glaucoma?

What objective assessments should be gathered in order to fully evaluate her risk factors for glaucoma?

How often would you recommend that this patient receive a comprehensive eye evaluation?

Table 61–2

Recommended Frequency of Comprehensive Adult Medical Eye Evaluation[21]

Age (Years)	With Risk Factors for Glaucoma	No Known Risk Factors for Ocular Disease
65 or above	1–2 years	1–2 years
55–64	1–2 years	1–3 years
40–54	1–3 years	2–4 years
Under 40	1–2 years	5–10 years

Data from Feder RS, Olsen TW, Prum BE, Jr., et al. Comprehensive Adult Medical Eye Evaluation Preferred Practice Pattern® Guidelines. Ophthalmol. 2016;123(1):P209–P236.

Table 61–3

Risk Factors for Glaucoma[3,4]

POAG	PACG
Elevated IOP	Advancing age
African or Hispanic descent	Asian or Eskimo ethnicity
Family history of glaucoma	Female sex
Older age	Hyperopia
Thinner CCT	Shallow anterior chamber
Type 2 diabetes	Family history of angle-closure glaucoma
Low ocular perfusion pressures	
Myopia	

CCT, central corneal thickness; IOP, intraocular pressure; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma.

CLINICAL PRESENTATION AND DIAGNOSIS

Risk Factor Evaluation

For POAG, only 4% to 8% of patients may progress to legal blindness. Vision loss does not occur until there has been significant loss of the retinal ganglion cells. It may take 13 to 16 years for a patient to go blind from glaucoma. A patient's quality of life may not be affected until significant visual field loss is present and the patient can no longer perform the activities of daily living.[20] KEY CONCEPT Practitioners can play an important role in eye care by assessing patients for risk factors and referring to an eye care specialist for appropriate screening and evaluation. Risk factor evaluation is essential in determining the frequency of comprehensive eye examinations for patients (Table 61–2).[21] Glaucoma risk factors are also useful in deciding when to start therapy and determining the sequence of pharmacotherapeutic or surgical treatment modalities.[2-4] Table 61–3 lists the major risk factors associated with POAG and PACG.

LO 4

The development of PACG is associated with several anatomical risk factors that lead to shallow anterior chambers. PACG patients may have a thick, anteriorly displaced lens that results from continued growth of the lens and/or cataractous changes. The anterior chamber depth is typically shallower in many individuals with PACG, which predisposes these eyes to anatomically narrower iridocorneal inlets that are a set-up for developing critically narrow angles more susceptible to closure (from an enlarging cataractous lens or other insults).[4,19]

Patients with PACG are characterized by at least 180 degrees of iridotrabecular contact, elevated IOP, and ophthalmic examination characteristic of glaucomatous changes. Recurrent attacks or a prolonged acute attack can lead to the development of peripheral anterior synechia, which partially obstructs the flow of aqueous humor through the trabecular meshwork.[4,19]

TREATMENT

Primary Open-Angle Glaucoma

► *Desired Outcomes and Goals*

LO 5

KEY CONCEPT The goals of therapy are to prevent further loss of visual function; minimize adverse effects of therapy and impact on the patient's vision, general health, and quality of life; maintain IOP at or below a pressure at which further optic nerve damage

Clinical Presentation and Diagnosis of POAG

General

- Adult onset (usually > 40 years of age)
- Patients may be unaware that they have glaucoma and may be diagnosed during routine eye evaluation
- POAG is usually bilateral with asymmetric disease progression

Symptoms

- Patients with severe disease progression may report loss of peripheral vision ("tunnel vision") and may describe the presence of paracentral, nasal, and arcuate scotoma (blind spots) in their field of vision

Signs

Ophthalmoscopic examination may reveal:

- Optic nerve head (optic disc) cupping
- Large cup-to-disc ratio
- Diffuse thinning, focal narrowing, or notching of the optic nerve head rim
- Splinter hemorrhages
- Optic nerve head/nerve fiber layer changes occur before visual field changes can be detected

Diagnostic Tests

- Gonioscopy—anterior-chamber angles are to be open.
- Applanation tonometry—elevated IOP (> 21 mm Hg [2.8 kPa]) may be present. However, patient can have signs of optic neuropathy without elevated IOP.
- Pachymetry—measures central corneal thickness. Thin corneas (< 540 µm) are considered a glaucoma risk factor.
- Automated static threshold perimetry—evaluates visual fields. Can detect defects in the visual field before a patient may notice.
- Other diagnostic tests—scanning laser polarimetry, confocal scanning laser ophthalmoscopy, and optical coherence tomography.

is unlikely to occur; and educate and involve the patient in the management of their disease. KEY CONCEPT Current therapy is directed at altering the flow and production of aqueous humor, which is the major determinant of IOP.

▶ General Approach

KEY CONCEPT Because POAG is a chronic, often asymptomatic condition, the decision of when and how to treat patients is difficult, as the treatment modalities are often expensive and have potential adverse effects or complications. Currently lowering IOP is the best method to reduce the risk of visual field loss.[1,22] The clinician should evaluate the potential effectiveness, toxicity, and the likelihood of patient adherence for each therapeutic modality. The ideal therapeutic regimen should have maximal effectiveness and patient tolerance to achieve the desired therapeutic response. The American Academy of Ophthalmology (AAO) publishes Preferred Practice Patterns for POAG and POAG Suspect.[2,3]

Before the selection of a therapeutic modality, the target IOP should be determined for each patient. The target IOP ideally represents an IOP range that will slow the progression of optic neuropathy and not simply obtain an IOP in the range of 10 to 21 mm Hg (1.3–2.8 kPa). Currently, the initial target IOP is an estimate, but it should be modified based on the progression of the disease at each follow-up visit (treatment is individualized).

LO 6 KEY CONCEPT The AAO recommends an initial target IOP to be set at least 25% lower than the patient's baseline IOP. The target IOP can be set lower (30%–50% of baseline IOP) for patients who already have severe disease, risk factors for disease progression, or have normal-tension glaucoma (NTG).[3,23] Risk factors for progression include high IOP, older age, hemorrhage of the optic disc, large cup-to-disc ratio, thinner CCT (central corneal thickness), and established glaucomatous progression (velocity of disease progression is nonlinear).

LO 6 Initial IOP control can be achieved by medical, laser, surgical, or combination of these therapies. The AAO guidelines[3] do not provide a specific recommendation on which therapeutic modality should be selected first, but patients in the early stages

LO 6 of glaucoma should receive treatment. In general, medical and laser trabeculoplasty are preferred as early treatment options over surgical as surgical interventions are not without potential intraoperative or postoperative complications.[22] The ophthalmologist will individualize therapy based on the risk and benefits for a specific patient. Table 61–4 describes nonpharmacologic treatment modalities for POAG.[3]

LO 6 Medical treatment is the most commonly selected therapeutic modality. A well-tolerated ocular antihypertensive, at the lowest concentration, should be selected as the initial mediation (Table 61–5). The ocular hypotensive lipids are preferred first-line agents since they are the most effective at lowering at IOP of both peak and trough measurements by at least 25% of baseline IOP.[24-28] Additionally, these agents lack systemic side effects and are dosed once-daily. If monotherapy alone lowers IOP but does not reach target pressure or there is evidence of progression, then combination therapy or switching to another agent is appropriate. The addition of a second agent from another class generally has an additive effect

LO 6 on IOP reduction. The ocular hypotensive lipids, timolol, carbonic anhydrase inhibitors, or brimonidine are reasonable choices for addition as a second agent.[3,8,11] Combination eye-drops reduce the number of drops that need to be administered. Increasing the concentration or dose frequency can also be tried when possible. Adverse effects can be caused by an eye drop's therapeutic agent or inactive excipients, such as preservatives. Benzalkonium chloride is a common eye drop preservative that has been associated with superficial punctate keratitis, corneal erosion, and conjunctival allergy. Intolerances to preservatives can be resolved by changing to a preservative-free eye drop.[29] Figure 61–4 presents an algorithm to select and optimize POAG treatment.

A uniocular trial can be used to assess the safety and effectiveness of a topical medication before initiation in both eyes; however, uniocular drug trials do not always predict the IOP response of the second eye. Ideally, the effectiveness of a medication should be assessed independently using baseline IOP measurements.

Table 61–4

Select Nonpharmacologic Treatment Options for POAG[3,4,14]

Treatment Option	Description
Laser trabeculoplasty	Laser energy aimed at trabecular meshwork Improves aqueous humor outflow
Trabeculectomy	Surgical removal of a portion of the trabecular meshwork Improves aqueous humor outflow Mitomycin C and fluorouracil are used to decrease scarring
Cyclodestructive surgery	Trans-scleral laser reduces rate of aqueous humor production Reserved for patients who have failed other options
Aqueous shunts	Drainage device that redirects the outflow of aqueous humor through a small tube into an outlet chamber placed underneath the conjunctiva

▶ Treatment Considerations for POAG Suspects

LO 6 POAG suspects should be considered for topical medication therapy if they are at high risk for developing POAG or have a high IOP in which glaucomatous nerve damage is likely to occur. POAG suspects that develop evidence of glaucomatous damage or visual field defect have developed POAG and should be treated accordingly.[2] The Ocular Hypertension Treatment Study (OHTS) demonstrated that a 20% decrease in IOP can reduce the progression from ocular hypertension to POAG over a 5-year period. The incidence of progression to POAG in the treatment (4.4%) and control (9.5%) groups was small, which underscores the importance of selecting patients at high risk of progressing

LO 6 to POAG.[30] When medical therapy is indicated, a well-tolerated agent should be selected and optimized following the POAG treatment algorithm (Figure 61–4). The benefit of therapy should be reassessed in patients who may require third- or fourth-line agents to control IOP. Surgical or laser intervention are not indicated in the treatment of glaucoma suspects.[2]

Primary Angle-Closure Glaucoma

▶ Desired Outcomes and Goals

LO 5 Therapeutic modalities for PACG are targeted at decreasing IOP. The goals of therapy are to preserve visual function by controlling the elevation in IOP, prevent damage to the optic nerve, and manage or prevent an acute attack of angle closure.[4]

▶ General Approach

LO 6 KEY CONCEPT Acute angle-closure crisis is a medical emergency and requires urgent laser or surgical intervention. The treatment of choice for PACG is peripheral laser iridotomy. Laser iridotomy

TABLE 61–5

Pharmacologic Treatment Options for Primary Open Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
β-Adrenergic Blocking Agents						
Betaxolol	Relative β_1-selective	Generic	Solution	0.5	One drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	One drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	One drop twice a day	
Levobunolol	Nonselective	Betagan	Solution	0.25, 0.5	One drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	One drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol	Solution	0.25, 0.5	One drop every day—one to two times a day	
		Timoptic-XE	Gelling solution	0.25, 0.5	One drop every day[a]	
Adrenergic Agonists						
Nonspecific Adrenergic Agent						
Dipivefrin[b]	Epinephrine prodrug	Propine	Solution	0.1	One drop twice a day	Increased aqueous humor outflow
α_2-Adrenergic Agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5 (U.D.), 1	One drop two to three times a day	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only brimonidine has primary indication
Brimonidine		Alphagan P	Solution	0.2 (generic) 0.15 (brand/generic), 0.1	One drop two to three times a day	
Cholinergic Agonists Direct Acting						
Carbachol[b]	Irreversible	Carboptic, Isopto Carbachol	Solution	1.5, 3	One drop two to three times a day	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Irreversible	Isopto Carpine, Pilocar	Solution	0.5, 1, 2, 4, 6	One drop two to three times a day One drop four times a day	
		Pilopine HS[b]	Gel	4	Every 24 hours at bedtime	
Cholinesterase Inhibitors						
Echothiophate[b]		Phospholine Iodide	Solution	0.125	Once or twice a day	
Carbonic Anhydrase Inhibitors						
Topical						
Brinzolamide	All carbonic anhydrase inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt Generic	Solution	2	Two to three times a day	

(*Continued*)

TABLE 61–5

Pharmacologic Treatment Options for Primary Open Angle Glaucoma (*Continued*)

Drug	Pharmacologic Properties	Common Brand Names	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action
Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125-250 mg two to four times a day	
			Injection	500 mg/vial	250-500 mg	
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25-50 mg two to three times a day	
Prostaglandin Analogs						
Latanoprost	Prostanoid agonist	Xalatan	Solution	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Bimatoprost	Prostamide agonist	Lumigan	Solution	0.01, 0.03	One drop every night	
Travoprost	Prostanoid agonist	Travatan Z	Solution	0.004	One drop every night	
Tafluprost	Prostanoid agonist	Zioptan	Preservative free solution	0.0015	One drop every night	
Combinations						
Timolol–dorzolamide		Cosopt Generic	Solution	Timolol 0.5 dorzolamide 2	One drop twice daily	Reduce aqueous production
Timolol–brimonidine		Combigan	Solution	Timolol 0.5 brimonidine 0.2	One drop twice daily	Reduce aqueous production and increase uveoscleral outflow
Brinzolamide–brimonidine		Simbrinza		Brinzolamide 1 brimonidine 0.2	One drop three times daily	Reduce aqueous production and increase uveoscleral outflow
Timolol-latanoprost[c]		Xalacom	Solution	Timolol 0.5 latanoprost 0.005	One drop every night	All reduce aqueous production and increase uveoscleral outflow
Timolo-travoprost[c]		Duotrav	Solution	Timolol 0.5 travoprost 0.004	One drop every night	
Timolol-bimatoprost[c]		Ganfort	Solution	Timolol 0.5 Bimatoprost 0.03	One drop every night	

[a]Use of eyelid closure (ELC) technique for 5 minutes will increase the drug availability and reduce potential for local and systemic side effects.

[b]Often used as fourth-line agents; limited or no commerical availability.

[c]Not available in the United States.

Adapted from Fiscella RG, Lesar TS, Owaidhah OA, et al. Glaucoma In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017: Table 94–4; with permission.

uses laser energy to cut a hole into the iris to alleviate the aqueous humor buildup behind the iris, resulting in reversal of appositional angle closure. Patients currently experiencing an acute angle-closure crisis should receive medical therapy to lower IOP, reduce pain, and reverse corneal edema before the iridotomy. IOP should first be lowered with topical β-blockers, topical α-agonist, prostaglandin $F_{2\alpha}$ analog, systemic carbonic anhydrase inhibitors, or hyperosmotic agents. Once the IOP has been controlled, miotics (ie, pilocarpine) can be used to break the pupillary block. A topical IOP-lowering agent should be continued to control IOP until laser iridotomy can be performed. Corneal indentation with a cotton-tipped applicator or gonioscopic lens may break pupillary block. If laser iridotomy cannot be performed, then surgical incisional iridectomy is used. Incisional iridectomy is the surgical removal of a small portion of the peripheral iris to allow flow of aqueous humor trapped in the posterior chamber to migrate to the anterior chamber (bypassing the normal flow pattern through the pupil). Topical corticosteroid may be employed to decrease inflammation postoperatively. The fellow eye is at high risk to develop an acute attack and should receive prophylactic iridotomy within a reasonable interval of time. Lens extraction surgery may be another treatment modality as it increases the anterior chamber depth. PACG patients may require chronic medical therapy if the patient has PACG

Clinical Presentation and Diagnosis of Acute Angle-Closure Crisis

General
- Medical emergency due to high risk of vision loss
- Unilateral in presentation, but fellow eye is at risk

Symptoms
- Ocular pain
- Red eye
- Blurry vision
- Halos around lights
- Systemic symptoms may develop
  - Nausea/vomiting
  - Abdominal pain
  - Headache
  - Diaphoresis

Signs
- Cloudy cornea caused by corneal edema
- Conjunctival hyperemia
- Pupil semidilated and fixed to light
- Eye will be harder on palpation through closed eye

Diagnostic Tests
- Gonioscopy—anterior-chamber angles will be closed. Peripheral anterior synechiae may be present.
- Applanation tonometry—elevated IOP (> 21 mm Hg [2.8 kPa], but when symptoms are present, IOP may be > 30 mm Hg [4.0 kPa])
- Slit-lamp biomicroscopy—reveals shallow anterior-chamber depth. Signs of previous attacks include peripheral anterior synechiae, iris atrophy, and pupillary dysfunction

superimposed on preexisting POAG or if synechia formation causes reduced outflow with a continued increase in IOP.[4,8,19]

Pharmacologic Therapy

▶ *Ocular Hypotensive Lipids*

LO 6

The ocular hypotensive lipids in typical ophthalmology practice are considered first-line agents along with β-blockers because of their superior efficacy and safety profiles. Many clinicians may choose to use the ocular hypotensive lipids as first line, especially in patients who have an initial requirement to lower IOP by greater than 25%.[27,28,31,32] All four of the available agents currently have an FDA indication for both POAG and ocular hypertension. Latanoprost and travoprost have dosing aids that help patients administer each medication. Travoprost and tafluprost are available as benzalkonium chloride–free solutions.

Latanoprost, travoprost, tafluprost are analogs of prostaglandin $F_{2\alpha}$ and are agonists of the prostanoid FP receptor, which appears to lower IOP by increasing aqueous humor outflow through the uveoscleral pathway. Bimatoprost is a prostamide analog and appears to lower IOP by activating prostamide receptors in the uveoscleral pathway and possibly through increasing outflow through the trabecular meshwork. The exact mechanism of how uveoscleral outflow is increased is still unclear, but stimulation of prostanoid FP receptors and prostamide receptors in the ciliary body cause remodeling of the extracellular matrix, making it more permeable to aqueous humor, thus increasing aqueous humor outflow through the ciliary muscles.[31,33,34]

The ocular hypotensive lipids are administered once daily at bedtime and should not be increased to twice daily, as this may decrease effectiveness. The ocular hypotensive lipids can provide a consistent reduction in IOP over a 24-hour period.[32] For patients nonresponsive to latanoprost, switching to IOP goal, presumably because of the proposed difference in the site of action of each drug.[35,36]

The ocular hypotensive lipids are well tolerated and rarely cause systemic side effects (headache has been reported). Local effects include conjunctival hyperemia, stinging on instillation, increase in iris pigmentation, deepening of the upper eyelid sulcus, hypertrichosis, and darkening of the eyelashes. Increases in iris pigmentation occur most commonly in patients with multicolored irides on long-term prostaglandin analog therapy. The mechanism of this effect is by its action on melanocytes of the iris, in which the irides become darker because of increased production of melanin in the iris.[29] Increased iris pigmentation appears to be only a cosmetic effect but may affect your product selection, especially when choosing monocular therapy. Conjunctival hyperemia or engorgement of conjunctival blood vessels is a common adverse effect caused by a vasodilatory effect on scleral blood vessels. It is most prominent early in therapy and usually subsides over time. Although generally a benign adverse effect, patients may have a concern if it affects their cosmetic appearance.[29,31]

The ocular hypotensive lipids should be used with caution in patients, since they may worsen anterior uveitis and herpetic keratitis. Cystoid macular edema has been reported during treatment with the ocular hypotensive lipids; therefore, use caution in patients with intraocular inflammation, aphakic patients, pseudophakic patients with a history of intraoperative complications (eg, torn posterior lens capsule), or in patients with risk factors for macular edema.[29]

LO 8

Patients prescribed ocular hypotensive lipids should be counseled on potential adverse effects and appropriate administration. Patients receiving latanoprost or tafluprost should be instructed to refrigerate unopened medication. Once open latanoprost can be stored at room temperature for 6 weeks. Tafluprost single-use containers can be stored at room temperature for up to 28 days.

▶ *β-Adrenergic Antagonists*

LO 6

Topical β-adrenergic antagonists (β-blockers) are now considered a second-line agent after the prostaglandin analogues for the treatment of POAG unless contraindications are present.[3,8] Topical β-blockers decrease IOP by reducing the formation of aqueous humor made by the ciliary body, which results in a 20% to 35% reduction in IOP.[27,28,31,32] Timolol, levobunolol, metipranolol, and carteolol are nonselective for β_1- and β_2-adrenergic receptors, whereas betaxolol has β_1-selective properties.[31,32] Betaxolol reduces IOP to a lesser extent than the nonselective β-blockers,

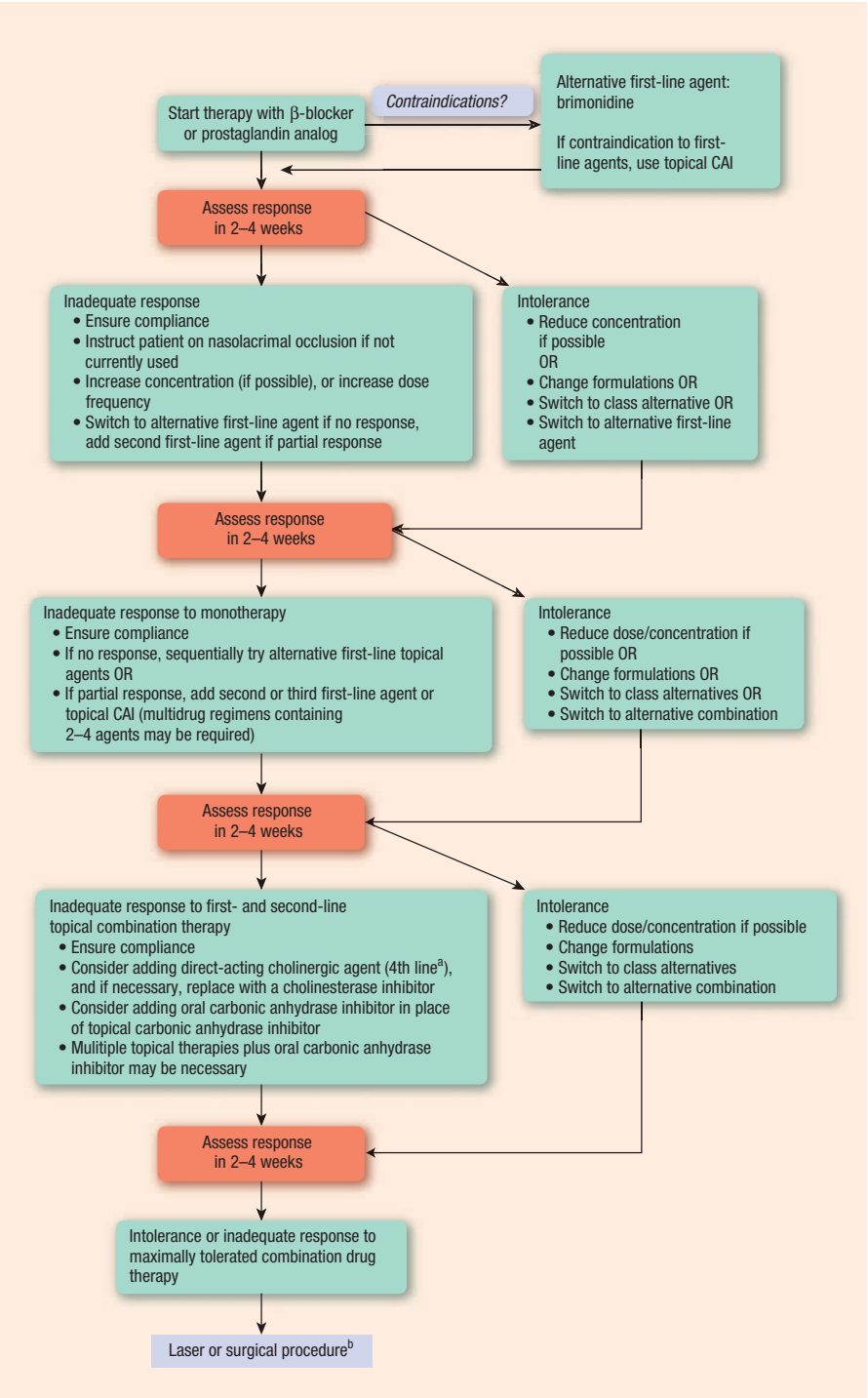

FIGURE 61–4. Algorithm for the pharmacotherapy of open-angle glaucoma. [a]Fourth-line agents not commonly used any longer or commercially unavailable. [b]Most clinicians believe the laser procedure should be performed earlier (eg, after three-drug maximum, poorly adherent patient). (CAI, carbonic anhydrase inhibitor.) (From Fiscella RG, Lesar TS, Owaidhah OA, et al. Glaucoma In: Dipiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017: Figure 94–4; with permission.)

but part of its efficacy may be related to a neuroprotective mechanism independent of IOP reduction.[37]

LO 6

Topical β-blockers are typically administered twice daily. A gel-forming solution of timolol (Timoptic-XE) can be administered once daily. Tachyphylaxis may occur in 20% to 50% of patients on monotherapy with a β-blocker, resulting in the need for a different agent or combination therapy. Patients on concurrent systemic β-blockers may experience less IOP reduction than patients on only topical β-blockers.[31,32]

β-Blockers can cause significant systemic adverse effects through nasolacrimal drainage and subsequent systemic absorption in the mucus membranes in the nasal-pharyngeal cavity. This route bypasses first-pass hepatic metabolism resulting in pharmacologically significant serum drug concentrations.[38]

Bronchospasm is the most common pulmonary effect of topical β-blockers. Pulmonary edema, status asthmaticus, and respiratory arrest have been reported with β-blockers as well. Cardiovascular effects include bradycardia, hypotension, and congestive heart failure exacerbation. As with systemic β-blockers, topical β-blockers have also been reported to cause depression and hyperlipidemia and mask symptoms of hypoglycemia. The β_1-selective properties of betaxolol may cause less exacerbation of pulmonary disease. Despite the intrinsic sympathomimetic activity demonstrated by carteolol, this does not translate to a clinically significant decrease in pulmonary or cardiovascular adverse effects. Topical β-blockers are generally contraindicated in patients with asthma, chronic obstructive pulmonary disease (COPD), sinus bradycardia, second- or third-degree heart block, cardiac failure, and hypersensitivity to the product.[29,32,38]

Stinging of the eyes upon instillation is the most common adverse effect. Other local adverse effects include conjunctivitis, keratitis, dry eyes, and **uveitis**.[29,31]

LO 8 Patients prescribed topical β-blockers should be counseled on the nasolacrimal occlusion technique to decrease systemic absorption.

▶ α_2-Adrenergic Agonists

LO 6 Brimonidine and apraclonidine are α_2-adrenergic agonists that decrease IOP by reducing aqueous humor production. Brimonidine has a higher selectivity to the α_2-receptor than apraclonidine and has a dual mechanism of action by increasing uveoscleral outflow.[31,32] LO 6 Apraclonidine is often used for the prevention and treatment of postsurgical IOP elevations and is no longer commonly used for long-term treatment of POAG because of tachyphylaxis and high rate of blepharoconjunctivitis. Brimonidine lowers IOP by 14% to 25%. Peak IOP-lowering effect is similar to that of timolol, but the trough IOP-lowering effect is less than that of timolol.[26,27] Brimonidine may exhibit a neuroprotective effect and has been shown to delay visual field progression compared with timolol but there is insufficient evidence it prevents retinal ganglion cell death.[39]

LO 6 Brimonidine is typically used as an adjunctive agent in combination with other agents and is usually administered every 8 hours. A 12-hour dosing schedule may be employed when used in combination therapy. Brimonidine-purite 0.1% and 0.15% solution (Alphagan-P) has similar efficacy compared with the brimonidine 0.2% solution, because the purite solution's higher pH allows for more drug to penetrate the cornea.[31,32] Brimonidine cause both local and systemic effects. Local effects include blepharoconjunctivitis, conjunctivitis, and ocular allergy. Systemic effects include headache, dry mouth, and fatigue.[29,31,32]

The frequency of dosing and local adverse effects may lead to nonadherence in some patients. LO 8 Patients prescribed brimonidine should be counseled on the nasolacrimal occlusion technique to reduce systemic adverse effects and to improve efficacy.[31,32]

▶ Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors decrease aqueous humor production by inhibition of the carbonic anhydrase isoenzyme II located in the ciliary body. In the eye, carbonic anhydrase catalyzes the conversion of H_2O and CO_2 to HCO_3^- and H^+, which is a significant step in aqueous humor production. Carbonic anhydrase inhibitors are available in systemic and topical preparations.[31,32]

LO 6 **Topical Carbonic Anhydrase Inhibitors** Dorzolamide and brinzolamide are the only topical carbonic anhydrase inhibitors available on the market. Both medications are administered every 8 hours and are used as adjunctive therapy or as monotherapy for patients who cannot tolerate first-line therapies. Nasolacrimal occlusion may allow for an every-12-hour dosing interval. They lower peak and trough IOP by 17% to 20%.[27,28,31,32]

Local side effects include burning, stinging, itching, foreign body sensation, dry eyes, and conjunctivitis. Brinzolamide may have fewer incidences of these side effects since the drug is in a neutral pH solution. Dorzolamide has been reported to cause irreversible corneal decompensation. Taste abnormalities have been reported with each agent. Both topical carbonic anhydrase inhibitors are sulfonamides and are contraindicated in patients with history of sulfonamide hypersensitivity.[29,31,32]

LO 6 **Systemic Carbonic Anhydrase Inhibitors** There are three systemic carbonic anhydrase inhibitors: acetazolamide, dichlorphenamide, and methazolamide. These agents effectively lower IOP by 20% to 30% but are reserved as third-line to fourth-line agents because of their significant adverse effects. They are typically used as bridge therapy from maximal medical therapy to laser or surgical intervention or to control IOP in the perioperative period following a laser or surgical ocular procedure. The systemic carbonic anhydrase inhibitors can also be used to lower IOP in acute angle-closure glaucoma. Acetazolamide has an IV formulation that can be used in patients who are experiencing nausea due to the angle-closure attack. Acetazolamide and methazolamide are the best tolerated of the three agents.[4,31,32]

The systemic carbonic anhydrase inhibitors are associated with significant adverse effects that include paresthesias of the hands and feet, nausea, vomiting, and weight loss. Patients can develop systemic acidosis, hypokalemia, hyponatremia, and nephrolithiasis due to the inhibition of renal carbonic anhydrase. Sulfonamide allergy, renal failure, hepatic insufficiency, COPD, and decreased serum potassium and sodium levels are all contraindications of systemic carbonic anhydrase inhibitor therapy. Blood dyscrasias from bone marrow suppression have been reported and include agranulocytosis, aplastic anemia, neutropenia, and thrombocytopenia.[31,32]

▶ Cholinergic Agents

Cholinergic agents (also called parasympathomimetics or miotics) were the first class of agents to treat glaucoma. The class can be divided into direct-acting cholinergic agents and indirect-acting cholinergic agents.

LO 6 **Direct-Acting Cholinergic Agents** Pilocarpine directly stimulates the muscarinic (M_3) receptors of the ciliary body, which causes contraction of the ciliary muscle. This results in the widening of spaces in the trabecular meshwork, which causes an increase in aqueous humor outflow and reduces IOP by 20% to 30%.

Patient Encounter Part 2

LN was referred to an ophthalmologist for a comprehensive eye evaluation. The ophthalmology report reveals the patient has an IOP (as assessed by applanation tonometry) of 22 mm Hg (2.9 kPa) in the right eye and 24 mm Hg (3.2 kPa) in the left eye. Gonioscopic examination reveals open anterior angles in both eyes. Ophthalmoscopy reveals cupping of the optic discs in both eyes. Visual field examination reveals a nerve fiber bundle defect consistent with glaucoma in the right eye.

What is your assessment of this patient's glaucoma type?

What pharmacologic and nonpharmacologic treatment modalities are available for this patient?

Pilocarpine requires administration four times daily, since the IOP-lowering effect lasts only 6 hours. Pilocarpine is available in 1%, 2%, and 4% concentrations. Higher concentrations may be needed for patients with dark irides to obtain adequate IOP reduction. A pilocarpine 4% gel is available and allows for once-daily dosing at bedtime.[31] Pilocarpine is considered a fourth-line agent for POAG. In the treatment of PACG, it is important to delay use until IOP has been controlled, because pilocarpine could worsen angle closure by causing anterior displacement of the lens. Once IOP is controlled, pilocarpine can be given to break pupillary block by instilling one drop applied twice in an hour.

The adverse effects of pilocarpine are caused by the induction of miosis. The contraction of the ciliary muscle causes the lens to displace forward, which can lead to accommodation spasm and myopia, and can lead to brow ache. Pupillary constriction can also affect night vision. Pilocarpine should be avoided in patients with severe myopia as it increases the risk of developing retinal detachment. Systemic effects may occur at higher concentrations and include nausea, vomiting and diarrhea, and bradycardia.[29]

Carbachol stimulates the same muscarinic receptor as pilocarpine and also inhibits acetylcholinesterase, the enzyme that metabolizes acetylcholine. Carbachol is more potent than pilocarpine, but it causes more accommodation spasm and brow ache and may also cause anterior uveitis. Other reported side effects include corneal clouding, persistent bullous keratopathy, and retinal detachment. Carbachol is rarely used today because of the side effect profile.[29,31]

Indirect-Acting Cholinergic Agents Echothiophate iodide and demecarium bromide inhibit acetylcholinesterase. Inhibition of this enzyme increases the availability of acetylcholine at the nerve junction, thus increasing the stimulation of the muscarinic (M_3) receptors of the ciliary body. These products are given twice daily and have similar efficacy to pilocarpine in the degree of IOP reduction. The side effect profile is similar to that of pilocarpine; however, they can deplete systemic cholinesterases and pseudocholinesterases and may cause the formation of cataracts. These agents should be discontinued at least 1 week before general surgical procedures. Succinylcholine and some local anesthetics are metabolized by pseudocholinesterases; therefore, depletion of this enzyme by echothiophate or demecarium may lead to toxic effects. These agents are typically used when other topical agents have failed and are limited to patients who have had their lenses removed or who have artificial lenses.[31]

▶ *Hyperosmotics*

Glycerin, isosorbide, and mannitol are hyperosmotic agents that increase the osmolality of blood. These agents create an osmotic gradient that draws water from the vitreous humor, thus decreasing IOP. The resulting dehydration of the vitreous humor may cause posterior movement of the lens, which then causes the anterior chamber to deepen, thus opening the anterior angle. If the patient is not vomiting, glycerin (1–1.5 g/kg of a 50%) solution and isosorbide (1.5–2 g/kg) can be given orally. Isosorbide is preferred in patients with diabetes because it is not metabolized into glucose. If the patient has nausea or vomiting, mannitol (20%) can be given IV at a dose of 1 to 2 g/kg over 45 minutes. The hyperosmotic agents are rapid acting, reaching peak effect in 30 to 60 minutes. Headache and thirst are common complaints. Patients who are already dehydrated are at risk of developing CNS dehydration, which can lead to coma. These agents should be used with caution in patients with renal or cardiovascular disease, as extracellular water is increased.[32,40]

Nonselective Adrenergic Agonists Epinephrine and its prodrug, dipivefrin, are rarely used for the treatment of glaucoma and are considered last-line agents because of their systemic side effect profile. Dipivefrin increases the corneal penetration. Once it is absorbed through the cornea, it is enzymatically cleaved to epinephrine. Epinephrine has α- and β-agonist activity and is thought to increase the outflow of aqueous humor through the trabecular meshwork and the uveoscleral pathway. Both products are instilled twice daily and reduce IOP by 15% to 25%. Local adverse effects include mydriasis, conjunctival hyperemia, and ocular irritation. Aphakic patients should not use these medications because they cause a reversible cystoid macular edema. Epinephrine and dipivefrin should not be used in patients with narrow angles since these agents can cause acute angle closure. Systemic side effects include palpitations, increased blood pressure, and arrhythmia, and therefore, these drugs should be used with caution in patients with cardiovascular disease, cerebrovascular disease, and hyperthyroidism. Using the nasolacrimal technique may decrease systemic effects.[31]

SPECIAL CONSIDERATIONS: DRUG-INDUCED GLAUCOMAS

Medications have the potential to cause or exacerbate both POAG and PACG; however, PACG is more likely to be exacerbated by medications than POAG. The use of medications with anticholinergic or sympathomimetic properties can precipitate angle closure. Medications with anticholinergic properties include first-generation antihistamines, tricyclic antidepressants, and antipsychotics. Medications with sympathomimetic properties include phenylephrine and pseudoephedrine. PACG patients who have been treated with laser iridotomy can usually use these agents without causing an exacerbation. Sulfa-based drugs, such as topiramate, acetazolamide, and hydrochlorothiazide, cause swelling of the ciliary body, which causes an anterior displacement of the lens, resulting in a decrease in anterior-chamber depth. Patients with open or closed anterior angles can experience elevated IOP from these drugs. Controlled POAG is rarely exacerbated by anticholinergics and sympathomimetics unless the patient is concomitantly at risk for angle closure. For uncontrolled or untreated POAG, the risk–benefit ratio should be considered before employing these agents. POAG can be exacerbated by any administrated form of corticosteroids. Corticosteroids increase IOP by causing obstruction of the trabecular meshwork with extracellular material. The increase in IOP appears to increase with potency and intraocular penetration. Ophthalmic corticosteroid preparations carry the highest risk of increasing IOP. However, all administrated routes have been shown to raise IOP in some patients. The onset and extent of IOP elevation is dependent on the specific corticosteroid, dose, route, and frequency. Generally, corticosteroid-induced IOP elevation typically occurs within a few weeks of beginning steroid therapy. In most cases, the IOP lowers

Patient Encounter Part 3

The practitioner and LN agree to start medication therapy.

Develop a patient-specific care plan.

Address the patient's (a) drug-related needs, (b) goals of therapy, (c) potential pharmacologic therapies, and (d) plan for follow-up of therapy.

List the monitoring parameters for effectiveness and safety for the chosen therapy.

Explain how you would counsel the patient on the chosen therapy, including the administration of an ophthalmic preparation.

spontaneously to the baseline within a few weeks to months upon stopping the steroid. In rare instances, the IOP remains elevated. Some patients exhibit clinically significant and dangerously high IOP as a result of steroid use.[41]

OUTCOME EVALUATION

Primary Open-Angle Glaucoma

LO 7 Evaluate patients 2 to 4 weeks after the initiation or alteration of medical therapy. The clinician should elicit the status of ocular health since the last visit, systemic medical history, medication history, and presence of local and ocular adverse effects of medications. IOP measurement, visual acuity assessment, and slit-lamp biomicroscopy at every POAG follow-up visit are necessary. The frequency of visual fields and optic nerve evaluation depends on whether IOP is controlled, the length of time IOP has been controlled, and whether there is progression of the disease. Patients who are at target IOP and have no disease progression should have optic nerve head evaluation and visual field testing every 6 to 12 months. Patients with disease progression and/or who are not at target IOP should receive follow-up evaluation every 1 to 6 months. Assess the patient's ability to use topical eye drops.[3] (See Application of Ophthalmic Solutions or Suspensions textbox.) Finally, evaluate the patient's adherence to their medical regimen. Nonadherence among patients on topical medical therapy ranges from 5% to 80%. Suspect nonadherence in patients who have visual field and optic nerve progression despite a low-IOP measurement, as patients may be more adherent to their medical regimen before their visit. Pharmacy refill histories may be useful in assessing adherence but do not confirm that the patient is actually taking the regimen as prescribed.[42] Specific patient factors related to the risk of nonadherence may include health literacy, medication cost, complicated medication regimens, adverse effects, and ethnicity.[43] Using adherence aids, prescribing the least complex regimen, and educating patients about their glaucoma are ways to reduce nonadherence.[44] Consider providing an eye drop instillation aid for patients that have dexterity and/or coordination problems.[45]

LO 7 KEY CONCEPT Target IOP should be revised based on the course of the disease and rate of progression. Adjust therapy if the patient fails to reach his or her target IOP. Patients who have achieved target IOP yet have progressive damage of the optic nerve or who have worsening of their visual fields should have further adjustment of their therapy. Evaluate these patients further for possible reasons of continued disease progression. Consider determining the diurnal pattern of IOP and looking for signs of poor ocular perfusion pressure. Establish a lower target IOP. Adjust therapy in patients who are intolerant, are nonadherent, or develop contraindications to their drug therapy regimen. Consider increasing the target IOP and reducing drug therapy for patients who have stable disease and who have maintained a low IOP; closely follow these patients to assess their response.[3]

Primary Angle-Closure Glaucoma

LO 7 Follow-up of acute angle-closure crisis occurs in the postoperative period. Evaluate the patency of the iridotomy and IOP in the postoperative period. Perform gonioscopy and optic nerve head evaluation if not already performed. Stable patients with PACG should be evaluated at least annually, specifically for the presence

LO 8 Application of Ophthalmic Solutions or Suspensions

1. Clean hands with soap and water.
2. Avoid touching the dropper tip with your fingers or against your eye to maintain sterility of product; shake dropper bottle if product is a suspension.
3. Tilt head back; pull down the lower eyelid with index finger.
4. Hold the dropper bottle with the other hand as close as possible without touching the eye. The dropper should be pointing toward the eye with remaining fingers bracing against the face.
5. Gently squeeze the bottle so that one drop is placed into the pocket.
6. Close your eye for 2 to 3 minutes to allow for the maximum corneal penetration of drug.
7. Use a tissue to wipe away any excess liquid.
8. Replace and retighten the cap to the dropper bottle.
9. Wait at least 5 minutes before instilling another ophthalmic drug preparation.
10. Application of some ophthalmic preparations (suspension and gels) may cause blurring of vision.

Patient Care Process

Collect Information:

- Obtain the patient's medical history. Inquire about previous and current medical problems with eyes.
- Obtain a complete medication history for use of prescription, nonprescription, and dietary supplements.
- Review the medical record for ophthalmologic examination findings (IOP, visual acuity, gonioscopy, visual fields, optic nerve evaluation, and so on).
- Interview the patient and review records to identify socioeconomic factors and health beliefs that affect access to medical care and medications.
- Have patient demonstrate or explain how they instill their ophthalmic medications.

Assess the Information:

- Determine whether the patient is experiencing difficulty with vision.
- Determine the patient's risk factors for glaucoma.
- Review patient's prescription, nonprescription, and natural product use; determine if the patient uses any medications that could exacerbate glaucoma or interact with any glaucoma medications.

(*Continued*)

Patient Care Process (*Continued*)

- Determine if the patient is experiencing ocular or systemic adverse effects from glaucoma medications.
- Based on ophthalmic examination findings, determine if patient has achieved their goal IOP and if there is evidence of disease progression.
- Determine if there are barriers to adherence with the use of eye drops such as low health literacy, or socioeconomic and physical limitations.

Develop a Care Plan:

- Select medication therapy that will likely achieve goal IOP with minimal adverse effects.
- Use combination glaucoma eye drops when possible to improve adherence.
- When possible, discontinue or minimize the use of medications that could increase IOP.

Implement the Care Plan:

- Educate patient about changes in ophthalmic medication regimen.
- Address patient concerns about glaucoma and its treatment.
- Educate patient on importance of medication adherence. Instruct patient on how to instill eye drops and have them demonstrate their technique.
- Educate the patient on potential adverse effects. Reinforce proper instillation technique as a strategy to minimize local and systemic adverse effects.

Follow-up: Monitor and Evaluate:

- Follow-up in 2 to 4 weeks to reassess patient for progression in glaucomatous damage, achievement of target IOP, adherence, and presence of adverse effects to medication therapy.
- Review interval medical history.
- Perform/Review ophthalmic examination findings.
- Once disease progression is controlled, follow-up interval can be extended.

of peripheral anterior synechia and optic neuropathy. Treat patients according to POAG guidelines if they have underlying POAG or areas of peripheral anterior synechia with the presence of optic neuropathy.[4]

Abbreviations Introduced in This Chapter

POAG	Primary open-angle glaucoma
PACG	Primary angle-closure glaucoma
IOP	Intraocular pressure
CCT	Central corneal thickness
NTG	Normal-tension glaucoma
AAO	American Academy of Ophthalmology

REFERENCES

1. Boland MV, Ervin AM, Friedman DS, et al. Comparative effectiveness of treatments for open-angle glaucoma: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013;158(4):271–279.
2. Prum BE, Jr., Lim MC, Mansberger SL, et al. Primary open-angle glaucoma suspect preferred practice pattern(®) guidelines. Ophthalmol. 2016;123(1):P112–P151.
3. Prum BE, Jr., Rosenberg LF, Gedde SJ, et al. Primary open-angle glaucoma preferred practice pattern(®) guidelines. Ophthalmol. 2016;123(1):P41–P111.
4. Prum BE, Jr., Herndon LW, Jr., Moroi SE, et al. Primary angle closure preferred practice pattern(®) guidelines. Ophthalmol. 2016;123(1):P1–P40.
5. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmol. 2014;121(11):2081–2090.
6. Friedman DS, Wolfs RC, O'Colmain BJ, et al; Eye Diseases Prevalence Research Group. Prevalence of open-angle glaucoma among adults in the united states. Arch Ophthalmol. 2004;122(4):532–538.
7. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the united states. Arch Ophthalmol. 2004;122(4):477–485.
8. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–1911.
9. Jonas JB, Aung T, Bourne RR, Bron AM, Ritch R, Panda-Jonas S. Glaucoma. Lancet. 2017;390(10108):2183–2193.
10. Civan MM, Macknight AD. The ins and outs of aqueous humour secretion. Exp Eye Res. 2004;78(3):625–631.
11. King A, Azuara-Blanco A, Tuulonen A. Glaucoma. BMJ. 2013;346:f3518.
12. Malihi M, Sit AJ. Aqueous humor dynamics and implications for clinical practice. Int Ophthalmol Clin. 2011;51(3):119–139.
13. Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. Clin Ophthalmol. 2014;8:883–890.
14. Llobet A, Gasull X, Gual A. Understanding trabecular meshwork physiology: a key to the control of intraocular pressure? News Physiol Sci. 2003;18:205–209.
15. Kwon YH, Fingert JH, Kuehn MH, Alward WL. Primary open-angle glaucoma. N Engl J Med. 2009;360(11):1113–1124.
16. De Moraes CG. Anatomy of the visual pathways. J Glaucoma. 2013;22(suppl 5):S2–S7.
17. Vohra R, Tsai JC, Kolko M. The role of inflammation in the pathogenesis of glaucoma. Surv Ophthalmol. 2013;58(4):311–320.
18. Ghaffarieh A, Levin LA. Optic nerve disease and axon pathophysiology. Int Rev Neurobiol. 2012;105:1–17.
19. Patel K, Patel S. Angle-closure glaucoma. Dis Mon. 2014;60(6):254–262.
20. Robin AL, Frick KD, Katz J, Budenz D, Tielsch JM. The ocular hypertension treatment study: intraocular pressure lowering prevents the development of glaucoma, but does that mean we should treat before the onset of disease? Arch Ophthalmol. 2004;122(3):376–378.

21. Feder RS, Olsen TW, Prum BE, Jr., et al. Comprehensive adult medical eye evaluation preferred practice pattern(®) guidelines. Ophthalmol. 2016;123(1):P209–P236.
22. Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: Meta-analysis of randomised controlled trials. BMJ. 2005; 331(7509):134.
23. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative normal-tension glaucoma study group. Am J Ophthalmol. 1998;126(4): 498–505.
24. Cheng JW, Cai JP, Wei RL. Meta-analysis of medical intervention for normal tension glaucoma. Ophthalmol. 2009;116(7):1243–1249.
25. Stewart WC, Konstas AG, Kruft B, Mathis HM, Stewart JA. Meta-analysis of 24-h intraocular pressure fluctuation studies and the efficacy of glaucoma medicines. J Ocul Pharmacol Ther. 2010;26(2):175–180.
26. Stewart WC, Konstas AG, Nelson LA, Kruft B. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines. Ophthalmol. 2008;115(7):1117–1122.e1.
27. van der Valk R, Webers CA, Lumley T, Hendrikse F, Prins MH, Schouten JS. A network meta-analysis combined direct and indirect comparisons between glaucoma drugs to rank effectiveness in lowering intraocular pressure. J Clin Epidemiol. 2009;62(12):1279–1283.
28. van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophthalmol. 2005;112(7):1177–1185.
29. Inoue K. Managing adverse effects of glaucoma medications. Clin Ophthalmol. 2014;8:903–913.
30. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):701–713; discussion 829–830.
31. Marquis RE, Whitson JT. Management of glaucoma: focus on pharmacological therapy. Drugs Aging. 2005;22(1):1–21.
32. Sambhara D, Aref AA. Glaucoma management: relative value and place in therapy of available drug treatments. Ther Adv Chronic Dis. 2014;5(1):30–43.
33. Swymer C, Neville MW. Tafluprost: the first preservative-free prostaglandin to treat open-angle glaucoma and ocular hypertension. Ann Pharmacother. 2012;46(11):1506–1510.
34. Krauss AH, Woodward DF. Update on the mechanism of action of bimatoprost: a review and discussion of new evidence. Surv Ophthalmol. 2004;49(suppl 1):S5–S11.
35. Bournias TE, Lee D, Gross R, Mattox C. Ocular hypotensive efficacy of bimatoprost when used as a replacement for latanoprost in the treatment of glaucoma and ocular hypertension. J Ocul Pharmacol Ther. 2003;19(3):193–203.
36. Gandolfi SA, Cimino L. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. Ophthalmol. 2003;110(3):609–614.
37. Chidlow G, Wood JP, Casson RJ. Pharmacological neuroprotection for glaucoma. Drugs. 2007;67(5):725–759.
38. Vander Zanden JA, Valuck RJ, Bunch CL, Perlman JI, Anderson C, Wortman GI. Systemic adverse effects of ophthalmic beta-blockers. Ann Pharmacother. 2001;35(12):1633–1637.
39. Sena DF, Lindsley K. Neuroprotection for treatment of glaucoma in adults. Cochrane Database Syst Rev. 2013;2:Cd006539.
40. Hoh ST, Aung T, Chew PT. Medical management of angle closure glaucoma. Semin Ophthalmol. 2002;17(2):79–83. Pubed PMID: 15513460.
41. Razeghinejad MR, Myers JS, Katz LJ. Iatrogenic glaucoma secondary to medications. Am J Med. 2011;124(1):20–25.
42. Olthoff CM, Schouten JS, van de Borne BW, Webers CA. Noncompliance with ocular hypotensive treatment in patients with glaucoma or ocular hypertension an evidence-based review. Ophthalmol. 2005;112(6):953–961.
43. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. Ophthalmol. 2009;116(11 suppl): S30–S36.
44. Gray TA, Orton LC, Henson D, Harper R, Waterman H. Interventions for improving adherence to ocular hypotensive therapy. Cochrane Database Syst Rev. 2009(2):CD006132.
45. Davies I, Williams AM, Muir KW. Aids for eye drop administration. Surv Ophthalmol. 2017;62(3):332–345.

62 Minor Ophthalmic and Otic Disorders

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LEARNING OBJECTIVES

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

1. Differentiate between the various ophthalmic disorders based on patient-specific information.
2. Choose an appropriate treatment regimen for an ophthalmic disorder.
3. Discuss the product differences that direct the selection of ophthalmic medications.
4. Assess when further treatment is required based on patient-specific information.
5. Recommend an ophthalmic monitoring plan given patient-specific information, a diagnosis, and a treatment regimen.
6. Educate patients about ophthalmic disease states and appropriate drug and nondrug therapies.
7. Review common otic disorders and appropriate drug and nondrug therapies.

This chapter provides an overview of common ophthalmic and otic disorders and their treatments. KEY CONCEPT Many ophthalmic disorders are benign or self-limited, but the clinician must be able to distinguish conditions that lead to serious morbidity, including blindness. Preserving both visual function and cosmetic appearance is the goal.[1] The clinician must understand when referral is appropriate and the proper time frame for follow-up, based on the patient-specific condition. Health care professionals should also be aware of common otic disorders that may be encountered.

OCULAR INJURIES

Etiology and Epidemiology

Ophthalmic problems encompass 3% of all emergency department visits.[2] Corneal abrasions are the most common eye injury in children. Scratches, objects, and aggressive eye rubbing may damage the cornea.[3] Health care practitioners must know the proper treatment for ocular emergencies and the time frame for follow-up in order to prevent further morbidity (Table 62–1).

CORNEAL ABRASIONS

Treatment

▶ *Desired Outcomes*

- Complete healing of the corneal abrasion with no scarring or vision impairment
- Prevent infection and pain
- Prevent corneal loss or corneal transplant

▶ *General Approach to Treatment*

The five layers of the cornea contain no blood vessels but are nourished by tears, oxygen, and aqueous humor. Minor corneal abrasions, also called corneal epithelial defects, heal quickly—typically within 24 hours.[4] Moderate abrasions take 24 to 72 hours to heal. Deep abrasions may scar the cornea. This rarely results in sufficient visual impairment to require corneal transplant. Patients should be instructed not to rub the eye if a corneal abrasion is present. Do not use eye patches to treat uncomplicated corneal abrasion.[3]

▶ *Corneal Abrasion Prevention*[3]

- Wear eye protection during sports
- Wear industrial safety lenses
- Carefully fit and place contact lenses

▶ *Pharmacologic Therapy*

LO 2 **Topical NSAIDs** Topical nonsteroidal anti-inflammatory drugs (NSAIDs) decrease pain from corneal abrasion. In a Cochrane review of nine trials (n = 637), topical NSAIDs were associated with a reduced need for oral analgesics. However, strong evidence was not available to support their use in the management of corneal abrasions.[4] Available ocular NSAIDs are diclofenac,

Table 62–1

Ophthalmic Emergencies: Time to Follow-Up by Ophthalmologist

Immediate Consult Required	Within 24 Hours
Foreign body in eye	Acute angle-closure glaucoma
Acute, painless loss of vision	Orbital cellulitis
Acute chemical burn	Blood in the eye (hyphema)
Blunt trauma to eye	Macular edema
	Retinal detachment
	Sudden congestive proptosis (bulging of eye forward)
	Corneal ulcer

Adapted from Handler JA, Ghezzi KT. General ophthalmologic examination. Emerg Med Clin North Am. 1995;13:521–538.

Clinical Presentation and Diagnosis of Corneal Abrasions[3]

Symptoms

- Photophobia
- Pain with eye or eyelid movement
- Foreign body sensation (or gritty feeling)
- Recent ocular trauma

Signs

- Excessive tearing
- Blepharospasm
- Blurred vision
- Conjunctival injection ("red eye")

Diagnostic Test

Use sterile fluorescein dye strips and visualize the cornea under a cobalt-blue filtered light; abrasions appear green; ensure that no foreign body remains in the eye or under eyelid.

ketorolac, nepafenac, and bromfenac. The usual dose for diclofenac and ketorolac is one drop four times daily; nepafenac is dosed one to three times daily, and bromfenac is dosed once or twice daily. Use topical NSAIDs with caution in patients with clotting disorders or those who are on systemic NSAIDs or warfarin therapy. Adverse effects typically include discomfort upon administration and conjunctival hyperemia or itching.[4]

LO3 **Topical Antibiotics** Infection slows the healing of a corneal abrasion; therefore, prophylactic antibiotics are often used. However, antibiotic-steroid ophthalmic products are not recommended as the steroid may slow healing of the abrasion. Patients should be asked if any contaminated matter could have entered the eye as this can lead to bacterial keratitis. Discontinue the use of contact lenses until the abrasion is healed and the antibiotic course complete. KEY CONCEPT In patients who do not wear contacts, antibiotics active against *Staphylococcus*, such as erythromycin ointment or trimethoprim-polymyxin B solution, are appropriate choices. In contact lens wearers, choose an ophthalmic antibiotic that covers *Pseudomonas aeruginosa*, like gentamicin or a fluoroquinolone.[3]

► *Outcome Evaluation*

LO5
1. Reevaluate patients in 24 hours.
2. If symptoms worsen, recheck for foreign bodies.
3. Refer to ophthalmologist if:[3]
   - Contact lens wearers
   - Decreased vision
   - Lack of improvement or worsening symptoms

OTHER OCULAR INJURIES: TREATMENT

Traumatic Injuries

Attempt to remove loose foreign bodies by gentle irrigation with artificial tears or sterile saline. If removal is successful, a topical broad-spectrum antibiotic, such as erythromycin, will prevent infection. If irrigation is unsuccessful, only ophthalmologists should complete mechanical removal of foreign objects. Protect the eye from further injury with a metal eye shield or a paper cup taped over the eye while awaiting the ophthalmologist.[2]

Splash Injuries and Chemical Exposure

LO6 LO4 Instruct patients to immediately irrigate the eye with water or saline continuously for at least 15 minutes before seeking a clinician. Irrigation dilutes and removes the chemical agent and is the best way to decrease ocular tissue damage. Patients should then seek immediate care from an ophthalmologist or emergency facility.[5]

Loss of Vision

LO1 A variety of disorders may lead to rapid, painless, monocular, or binocular vision loss. These include central retinal artery occlusion, acute narrow-angle glaucoma, trauma, and others.[6] The differential diagnosis is complex and should be undertaken by an emergency department or ophthalmologist.

CONJUNCTIVITIS

Etiology

Conjunctivitis, also known as red eye, is one of the most common ophthalmic complaints seen by clinicians. An inflamed conjunctiva is the most common cause of red eye.[7] Conjunctivitis cases are most commonly viral in nature. Both viral and bacterial conjunctivitis are highly contagious. The most common symptoms indicating bacterial conjunctivitis rather than viral are adherence of the eyelids upon waking and presence of mucopurulent discharge. The most common symptom differentiating allergic conjunctivitis from bacterial or viral is itching.[8] Use the differential diagnosis algorithm shown in Figure 62–1 to determine the proper treatment or need for referral.

BACTERIAL CONJUNCTIVITIS

Etiology and Pathophysiology

The primary causes of acute bacterial conjunctivitis (ABC) are gram-positive organisms, *Staphylococcus aureus, Streptococcus pneumoniae,* and gram-negative *Haemophilus influenzae.*[6] *S. aureus* is a more common cause in adults, while *S. pneumoniae* and *H. influenzae* are more common in children.[7] KEY CONCEPT The pathogens are rarely cultured unless the case is unresponsive to treatment.[6] Patients with bacterial conjunctivitis lasting 4 weeks or more should be referred to an ophthalmologist.[8]

Hyperacute bacterial conjunctivitis is associated with gonococcal (*Neisseria gonorrhoeae*) infections in sexually active patients. Prompt workup and treatment is required, as corneal perforation can occur.[6,7]

Treatment

► *Desired Outcomes*

- Complete resolution of the bacterial conjunctivitis
- Prevent adverse consequences of the infection
- Preserve functionality of the eye

► *General Approach to Treatment*

LO2 ABC may be treated with broad-spectrum antibiotics. Although the condition is usually self-limiting, antibiotic treatment decreases the spread of disease to others and prevents extraocular infection. Additionally, treatment may help decrease the risk of corneal ulceration or other complications that affect sight. Finally, treatment speeds recovery.[6,7]

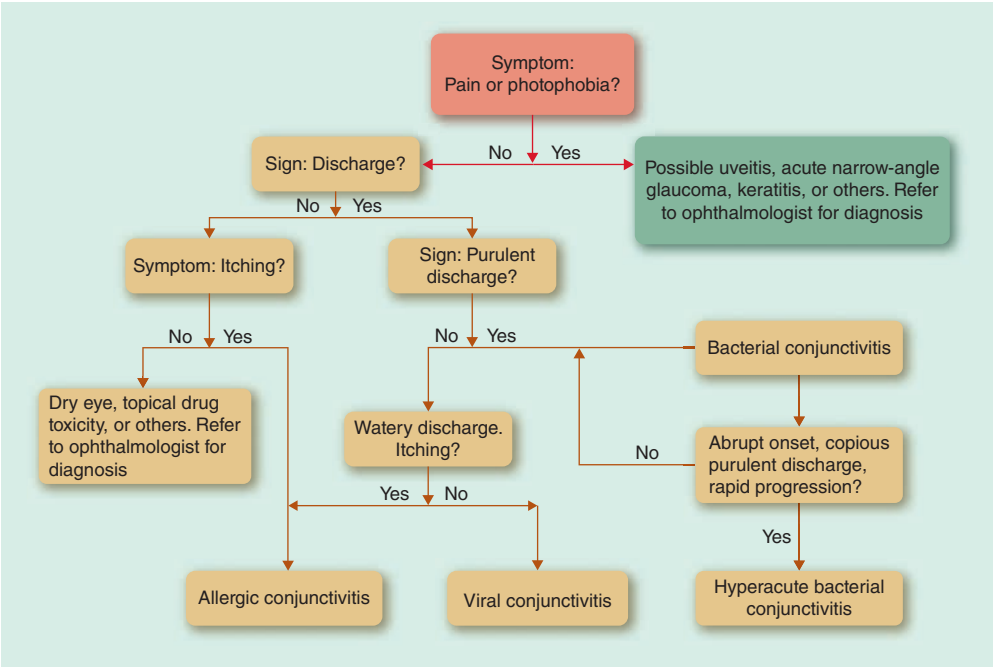

FIGURE 62–1. Differential diagnosis for red eye.

▶ *Pharmacologic Therapy*

LO 3

The choice of an antibiotic agent for ABC is largely empiric. The initial treatment needs to include *Staphylococcus* coverage, and cost and side-effect profile may be pertinent.[6] In general, ointments are a good dosage form for children. Adults may prefer drops because they do not interfere with vision.

Many broad-spectrum topical antibiotics are approved to treat ABC (Tables 62–2 and 62–3).

LO 2

- First-line treatments include polymyxin B/trimethoprim solution, polymyxin B with bacitracin ointment, or erythromycin ointment as these provide activity against *S. aureus*.
- The aminoglycosides (tobramycin and gentamicin) are alternatives but have incomplete gram-positive coverage and can cause corneal epithelial toxicity.[7]
- Sulfacetamide has significant resistance.

Table 62–2

Adult Bacterial Conjunctivitis Dosing Guidelines for Topical Ophthalmic Antibiotics

Azithromycin 1% solution	Days 1 and 2: 1 drop twice daily Days 3–7: 1 drop once daily
Ciprofloxacin 3.5 mg/mL solution	Days 1 and 2: 1–2 drops every 2 hours while awake Days 3–7: 1–2 drops every 4 hours while awake
Ciprofloxacin 0.3% ointment	Apply a ½ in (~1 cm) ribbon of ointment 3 times daily for 2 days, then twice daily for next 5 days
Erythromycin 0.5% ointment	Apply a ½ in (~1 cm) ribbon of ointment up to 6 times daily
Gatifloxacin 0.5% solution	Days 1 and 2: 1 drop every 2 hours while awake up to 8 times daily Days 3–7: 1 drop 4 times per day while awake
Gentamicin 0.3% solution	1–2 drops every 4 hours. In severe infections, may use up to 2 drops every hour
Gentamicin 0.3% ointment	Apply a ½ in (~1 cm) ribbon of ointment 2–3 times daily
Levofloxacin 0.5% solution	Days 1 and 2: 1–2 drops every 2 hours while awake, up to 8 times per day Days 3–7: 1–2 drops every 4 hours while awake, up to 4 times daily
Moxifloxacin 0.5% solution	1 drop 2 times a day for 7 days 1 drop 3 times a day for 7 days
Ofloxacin 0.3% solution	Days 1 and 2: 1–2 drops every 2–4 hours while awake Days 3–7: 1–2 drops 4 times daily
Polymyxin B with bacitracin ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours, or 2–3 times per day for 7–10 days
Polymyxin B/trimethoprim solution	1 drop every 3 hours for 7–10 days
Sulfacetamide 10% ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours and at bedtime
Sulfacetamide 10% solution	1–2 drops every 2–3 hours for 7–10 days
Sulfacetamide 10% ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours and at bedtime
Tobramycin 0.3% ointment	Mild-to-moderate infections: Apply a ½ in (~1 cm) ribbon of ointment 2–3 times daily. Severe infections: Apply every 3–4 hours
Tobramycin 0.3% solution	Mild-to-moderate infections: 1–2 drops every 2–4 hours Severe infections: initially, 2 drops every hour

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson (OH): Lexi-Comp, Inc.; 2017. Available from: http://online.lexi.com. Accessed: August 30, 2017.

Table 62–3

Pediatric Bacterial Conjunctivitis Dosing Guidelines for Topical Ophthalmic Antibiotics

Azithromycin 1% solution	Children 1 year of age or older: Days 1 and 2: 1 drop twice daily, 8–12 hours apart Days 3–7: 1 drop once daily
Ciprofloxacin 3.5 mg/mL solution	Children 1 year of age or older: Days 1 and 2: 1–2 drops every 2 hours while awake Days 3–7: 1–2 drops every 4 hours while awake
Ciprofloxacin 0.3% ointment	Children 2 years of age or older: Apply a ½ in (~1 cm) ribbon of ointment 3 times daily for 2 days, then twice daily for next 5 days
Erythromycin 0.5% ointment	Apply a ½ in (1 cm) ribbon of ointment up to 6 times daily
Gatifloxacin 0.3% solution	Children 1 year of age or older: Days 1 and 2: 1 drop every 2 hours while awake up to 8 times daily Days 3–7: 1 drop every 4 hours while awake
Gentamicin 0.3% solution	1–2 drops every 4 hours. In severe infections, may use up to 2 drops every hour
Gentamicin 0.3% ointment	Apply a ½ in (~1 cm) ribbon of ointment 2–3 times daily; up to every 3–4 hours
Levofloxacin 0.5% solution	Children 1 year of age or older: Days 1 and 2: 1–2 drops every 2 hours while awake, up to 8 times daily Days 3–7: 1–2 drops every 4 hours while awake, up to 4 times daily
Moxifloxacin 0.5% solution	Children 4 months of age or older: 1 drop 2 times per day for 7 days Children 1 year of age or older: 1 drop 3 times a day for 7 days
Ofloxacin 0.3% solution	Children 1 year of age or older: Days 1 and 2: 1–2 drops every 2–4 hours while awake Days 3–7: 1–2 drops 4 times daily
Polymyxin B with bacitracin ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours for 7–10 days
Polymyxin B/trimethoprim solution	Infants and children 2 months of age or older: 1 drop every 3 hours for 7–10 days
Sulfacetamide 10% ointment	Apply a ½ in (~1 cm) ribbon of ointment every 3–4 hours and at bedtime
Sulfacetamide 10% solution	1–2 drops every 2–3 hours for 7–10 days
Tobramycin 0.3% ointment	Infants and children 2 months of age or older: Mild-to-moderate infections: Apply an approximately ½ in (~1 cm) ribbon 2–3 times daily Severe infections: Apply every 3–4 hours
Tobramycin 0.3% solution	Infants and children 2 months of age or older: Mild-to-moderate infections: 1–2 drops every 4 hours Severe infections: initially, 2 drops every hour

Data from Lexi-Drugs Online™. Lexi-Comp Online™. Hudson (OH): Lexi-Comp, Inc.; 2017. Available from: http://online.lexi.com. Accessed: August 30, 2017.

Patient Encounter 1

This morning, a mother brings in her 13-year-old son who has been complaining of irritation, redness, and "goop" coming out of his right eye for the past 13 hours. He woke up terrified this morning because his right eye seemed glued shut. At first, the mother was concerned because his younger sister had "pink-eye" 2 weeks ago. A warm washcloth was used to ease the eye open, and upon examination, the right eye was red and revealed a whitish discharge, whereas the left eye was just red.

What is the probable diagnosis?

Please differentiate between bacterial, hyperacute bacterial, viral, and allergic causes based on physical assessment.

What organisms should be suspected, and what are reasonable treatment regimens?

If the child would have been diagnosed with viral conjunctivitis, what nonpharmacologic measures should be employed to prevent spreading?

- If infection recurs or is severe, use a topical fluoroquinolone.[7] Moxifloxacin has been shown to have similar efficacy when compared to polymyxin B ointment.[9]
- Treat hyperacute bacterial conjunctivitis with a single dose of intramuscular ceftriaxone in combination with topical antibiotics and refer the patient to an ophthalmologist.[7]
- If concurrent blepharitis is present, add a lid hygiene regimen to antibiotic treatment.[6]

Outcome Evaluation

LOS

Significant improvement of ABC should be seen within 1 week.[7]

VIRAL CONJUNCTIVITIS

Etiology

Viral conjunctivitis is commonly caused by adenovirus and is often called "pink-eye."[7] Adenovirus is easily spread through swimming pools, camps, and contaminated fingers and medical instruments.[8] Patients often present with an upper respiratory tract infection or recent exposure to viral conjunctivitis.[7] KEY CONCEPT Viral conjunctivitis is usually self-limiting, resolving within 2 weeks.[7]

Treatment

▶ *Desired Outcomes*

- Complete resolution of the viral conjunctivitis
- Prevent adverse consequences of the infection
- Avoid spreading infection to others

▶ *Nonpharmacologic Therapy*

KEY CONCEPT Nonpharmacologic measures are critical to prevent the spread of viral conjunctivitis. Cold compresses may relieve symptoms.[6,7] Patients should not share towels or other contaminated objects, should avoid close contact with other people, and avoid swimming for 2 weeks.[7,8] Current contact lenses in the infected eyes and their lens case should be discarded. Take care in the medical setting to thoroughly decontaminate instruments and wash hands.[7,8]

LO 6

▶ *Pharmacologic Therapy*

Patients may obtain further symptomatic relief by using artificial tears.[7,8] If artificial tear solutions sting, recommend a preservative-free formula.

LO 3

Topical antivirals are not used to treat adenovirus conjunctivitis. Topical antibiotics are unnecessary and should not be used for a viral infection and to help prevent the development of antibiotic resistance.[8]

LO 1

Patients with severe subepithelial infiltration may require a topical steroid. However, topical steroids may cause serious ocular complications, increase the period of viral shedding, and may worsen herpetic conjunctivitis, which has similar symptoms as viral conjunctivitis.[8] Only ophthalmologists should prescribe topical steroids.[7]

LO 4

Outcome Evaluation

Refer patients who do not see improvement within 7 to 10 days or with visual loss to an ophthalmologist to rule out herpetic and other infectious processes.[7,8]

ALLERGIC CONJUNCTIVITIS

Etiology and Clinical Presentation

LO 1

Ocular allergy is a broad term that includes several diseases with the hallmark symptom of itching, often accompanied by tearing, conjunctival swelling, photophobia, and stringy or sticky mucoid discharge.[10] Allergic conjunctivitis affects up to 40% of patients.[11] Seasonal ocular allergy is the most common type of allergic conjunctivitis. Often, the patient's history is positive for atopic conditions including allergic rhinitis, asthma, or eczema.[7] Perennial allergic conjunctivitis has similar but less severe symptoms and may not be tied to a specific time of year. Finally, **conjunctivitis medicamentosa** is a drug-induced form of allergic conjunctivitis caused by overuse of topical vasoconstricting agents and sometimes polypharmacy from use of multiple topical glaucoma eyedrops.[10]

LO 1

Pathophysiology

The conjunctiva of the eye is often the initial site of contact with an environmental allergen. Mast cell degranulation occurs, and the earliest mediator is histamine, which causes itching, redness, and swelling.[11] Leukotrienes and prostaglandins cause cellular infiltration and increased mucus secretion along with chemosis, resulting in conjunctival vasodilation.

Table 62–4

Mechanisms of Action of Ocular Allergy Drugs

Drug	Mechanisms
Azelastine	H_1-receptor antagonist
Cromolyn sodium	Mast cell stabilizer
Emedastine	H_1-receptor antagonist
Epinastine	H_1- and H_2-receptor antagonist, mast cell stabilizer
Ketorolac	Inhibitors prostaglandin synthesis
Ketotifen	H_1-receptor antagonist, mast cell stabilizer, eosinophil inhibitor
Lodoxamide	Mast cell stabilizer
Loteprednol	Corticosteroid
Nedocromil	Mast cell stabilizer, eosinophil inhibitor
Olopatadine	H_1-receptor antagonist, mast cell stabilizer
Pemirolast	Mast cell stabilizer

Adapted from McEvoy GK, ed. AHFS Drug Information 2014. Bethesda, MD: American Society of Health-System Pharmacists Inc., 2018.

Treatment of ocular allergy is aimed at slowing or stopping these processes. Antihistamines block the histamine receptors, prevent histamine release from the mast cells and stop eosinophil activity.[11] Mast cell stabilizers inhibit the degranulation of mast cells, preventing mediator release. Some topical agents have multiple mechanisms of action, combining antihistaminic, mast cell stabilization, and anti-inflammatory properties (Tables 62–4 and 62–5).[11]

Treatment

▶ *Desired Outcomes*

- Relief of current allergic symptoms
- Prevention of future allergic symptoms
- No adverse effects from treatment

▶ *Nonpharmacologic Therapy*

LO 2

The primary treatment for ocular allergy is removal and avoidance of the allergen.[7,8] For conjunctivitis medicamentosa, discontinue the offending medication. Patients should be instructed to avoid rubbing their eyes. Apply cold compresses several times daily to reduce redness and itching and to provide symptomatic relief.[10]

LO 6

▶ *Pharmacologic Therapy*

KEY CONCEPT Use a step-care approach for the treatment of allergic conjunctivitis.

LO 2

- Step 1: nonmedicated, artificial tears solution. The solution dilutes or removes the allergen, providing relief while lubricating the eye. The artificial tear solutions may be refrigerated to provide additional topical relief.[12] Solutions are applied two to four times daily as needed. Ointments may be used in the evenings to further moisturize the surface of the eye. Preservative-free formulations may be tried if other products sting or burn, or if the artificial tears need to be used frequently throughout the day.

LO 3

- Step 2: topical antihistamine or antihistamine/decongestant combination. The antihistamine/decongestant combination is more effective than either agent alone. Decongestants are vasoconstrictors that reduce redness and seem to have a small synergistic effect with the antihistamine. Topical

Table 62–5

Pediatric and Adult Dosing and Common Side Effects of Ocular Allergy Drugs

Drug	Dosing	Common Side Effects
Azelastine 0.05%	Children 3 years of age or older and adults: 1 drop in affected eye(s) twice daily	Ocular stinging, bitter taste, headache
Cromolyn sodium 4%	Children 4 years of age or older and adults: 1–2 drops in each eye 4–6 times daily	Ocular stinging
Emedastine 0.05%	Children 3 years of age or older and adults: 1 drop in affected eye up to 4 times daily	Ocular stinging, blurred vision, headache
Epinastine 0.05%	Children 3 years of age or older and adults: 1 drop in each eye twice daily	Ocular burning, ocular itching, cold symptoms
Ketorolac 0.5%	Children 3 years of age or older and adults: 1 drop 4 times a day	Ocular stinging, irritation
Ketotifen 0.025%	Children 3 years of age or older and adults: 1 drop in affected eye(s) twice daily	Red eyes, headache, rhinitis
Lodoxamide 0.1%	Children 2 years of age or older and adults: 1–2 drops in affected eye(s) 4 times daily, for up to 3 months	Ocular stinging, discomfort, foreign body sensation
Loteprednol 0.2%	Adults only: 1 drop in affected eye(s) 4 times daily	Elevated intraocular pressure, cataracts, secondary ocular infections, systemic side effects possible
Nedocromil 2%	Children 3 years of age or older and adults: 1–2 drops in each eye twice daily	Headache, ocular stinging, unpleasant taste, nasal congestion
Olopatadine 0.1%; 0.2%	Children 3 years of age or older and adults (0.1%): 1 drop in affected eye(s) 2 times daily with minimum 6- to 8-hour interval between doses Children 2 years of age or older: and adults (0.2%): 1 drop in affected eye(s) once daily	Headache, blurred vision, ocular stinging
Pemirolast 0.1%	Children 3 years of age or older and adults: 1–2 drops in affected eye(s) 4 times daily	Headache, cold symptoms

Adapted from McEvoy GK, ed. AHFS Drug Information 2014. Bethesda, MD: American Society of Health-System Pharmacists Inc., 2018.

Alomide (lodoxamide tromethamine) solution/drops 0.1%. Fort Worth (TX): Alcon Laboratories, Inc., 2003.

decongestants used in combination products include naphazoline and tetrahydrozoline. Topical decongestants burn and sting on instillation and commonly cause mydriasis, especially in patients with lighter-colored eyes. Topical decongestant use should be limited to less than 10 days to avoid rebound congestion.

LO 3
- Step 3: a mast cell stabilizer or a multiple-action (antihistamine-mast cell stabilizer) agent. Use mast cell stabilizers, including cromolyn or nedocromil, prophylactically throughout the allergy season-they are not used for acute relief of symptoms. Full response may take 4 to 6 weeks.

LO 4
- Step 4: short-term topical corticosteroids and immunotherapy.[10,11]

LO 3 Topical antihistamine-mast cell stabilizers are recommended before oral agents in step therapy due to the increased risk of systemic side effects with oral drugs. Topical antihistamines provide faster relief of ocular symptoms. Topical antihistamine-mast cell stabilizers include alcaftadine, bepotastine, emedastine, epinastine, ketotifen, and olopatadine. Topical NSAID ketorolac tromethamine is approved for ocular itching, though it is used less commonly than topical antihistamines.[11]

Outcome Evaluation

LO 5 Monitor patients for relief of symptoms. Ensure an adequate trial of each agent. Refer severe cases that do not respond to an ophthalmologist.

Patient Encounter 2

TS is a 63-year-old female who presents with eye complaints. She states her eyes are watering off and on and feel like they have sand in them. She has been wearing her glasses, rather than her usual contact lens use. She is able to look up at the light on the ceiling and denies eye pain or itching. She denies any discharge from the eye, except the feeling that they water occasionally. She states now that the spring temperatures have increased, she has recently turned on the fans in her apartment.

Past medical history:
- GERD
- Migraines
- Insomnia

Social history:
- Alcohol use: denies
- Tobacco: 1 pack per day
- Illicit drug use: denies

Medications:
- Amitriptyline 25 mg at bedtime
- Ibuprofen 400 mg PRN headaches
- Pantoprazole 40 mg Q AM

Which symptoms would distinguish dry eye from conjunctivitis?

Which environmental or medication risk factors may contribute to TS's dry eye?

What nonpharmacologic therapies should be recommended for this patient?

What pharmacologic therapies should be recommended for this patient?

Which dosage forms should be recommended for this patient?

How should the patient be monitored?

BACTERIAL KERATITIS

Epidemiology

Thirty thousand cases of microbial keratitis occur annually in the United States.[13] Microbial keratitis encompasses bacterial, fungal, and *Acanthamoeba* keratitis.[13] Only bacterial keratitis, the most common form, is discussed here.

Pathophysiology

Bacterial keratitis is a broad term for a bacterial infection of the cornea including corneal ulcers and corneal abscesses. The cornea in a healthy eye has natural resistance to infection, making bacterial keratitis rare. However, many factors may predispose a patient to bacterial infection by compromising the defense mechanisms of the eye (Table 62–6).[13]

The most common pathogens in bacterial keratitis are *Pseudomonas* (including *Pseudomonas aeruginosa*) and other gram-negative rods, *Staphylococci*, and *Streptococci*.[13] If the keratitis is related to the use of contacts, *Pseudomonas* and *Serratia marcescens* are the most common pathogens.[13] KEY CONCEPT Untreated bacterial keratitis can result in corneal scarring and potential loss of vision. Corneal perforation may occur which may require emergent corneal transplant, and the patient could lose the eye.[13] In virulent organisms, this destruction may occur within 24 hours.[13] Central corneal scarring may result in vision loss even after successful eradication of the organism.[13]

Table 62–6

Risk Factors for Bacterial Keratitis

Exogenous Factors	
	Contact lenses
	Loose sutures from ocular surgeries
	Previous corneal surgery
	Previous ocular or eyelid surgery
	Trauma, including foreign bodies, chemical and thermal injuries, and local irradiation
Ocular Surface Disease	
	Abnormal lid anatomy or function
	Misdirection of eyelashes
	Ocular infection (eg, conjunctivitis, blepharitis)
	Tear film deficiencies
Systemic Conditions	
	Atopic dermatitis
	Connective tissue disease
	Diabetes mellitus
	Gonococcal infection
	Immunocompromised
	Stevens-Johnson syndrome
	Substance abuse
	Vitamin A deficiency
Ocular Medications	
	Anesthetics
	Antimicrobials
	Contaminated ocular medications
	Glaucoma medications
	Preservatives
	Steroids
	Topical NSAIDs
Corneal Epithelial Abnormalities	
	Corneal epithelial edema
	Predisposition to recurrent erosion of the cornea
	Viral keratitis (eg, herpes simplex or zoster keratitis)

Data from American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Bacterial Keratitis [Internet]. San Francisco, CA: American Academy of Ophthalmology, 2013 [cited 2017 Aug 30]. Available from: www.aao.org/ppp.

Clinical Presentation and Diagnosis of Bacterial Keratitis[7,13]

General

The rate of progression of signs and symptoms varies depending on the infecting organism. A differential diagnosis for keratitis must include viral, fungal, and nematodal infections in addition to bacterial causes.

Symptoms

- Photophobia
- Rapid onset of ocular pain

Signs

- Red eye
- Conjunctival discharge
- Decreased vision

Laboratory Tests

Culture if keratitis is severe or sight-threatening, chronic or unresponsive to broad-spectrum antimicrobial therapy.

Treatment

▶ *Desired Outcomes*[13]

- Resolution of infection and corneal inflammation
- Reduced corneal pain
- Restored corneal integrity with minimal scarring
- Restored visual function

▶ *General Approach to Treatment*

LO 4 All cases of suspected bacterial keratitis require prompt ophthalmology consultation to prevent permanent vision loss.[7]

▶ *Pharmacologic Therapy*

LO 3 **Dosage Considerations** Topical antibiotic drops are preferred. Consider subconjunctival antibiotics if compliance is a concern. Systemic therapy is useful in cases of systemic infection (eg, gonorrhea) or if the sclera is infected. Reserve ointments for minor cases or adjunctive nighttime therapy.[13]

LO 2 **Drug Choice** Start topical broad-spectrum antibiotics empirically. Use a loading dose for severe keratitis (Table 62–7). Single-drug therapy with a fluoroquinolone is as effective as combination therapy. Resistance is seen with some fluoroquinolones, LO 4 choose moxifloxacin or gatifloxacin in severe keratitis cases.[13] Antibacterials should be continued until positive response, then tapered. Fortified antibiotic therapy is an option for severe or unresponsive cases, but may increase toxicity to the corned and surrounding tissues. Fortified antibiotics are compounded products that are a higher concentration than the commercially available formulations.

Table 62–7

Pharmacologic Therapies for Bacterial Keratitis

Organism	Drug
Unknown or multiple types of organisms	Cefazolin 50 mg/mL *and* tobramycin/gentamicin 9–14 mg/mL *or* Fluoroquinolones various strengths
Gram-positive cocci	Cefazolin 50 mg/mL *or* Vancomycin[a] 15–50 mg/mL *or* Bacitracin[a] 10,000 international unit *or* Moxifloxacin or gatifloxacin various strengths
Gram-negative rods	Tobramycin 9–14 mg/mL *or* Gentamicin 9–14 mg/mL *or* Ceftazidime 50 mg/mL *or* Fluoroquinolones various strengths
Gram-negative cocci	Ceftriaxone 50 mg/mL *or* Ceftazidime 50 mg/mL *or* Fluoroquinolones various strengths
Nontuberculous mycobacteria	Amikacin 20–40 mg/mL *or* Oral clarithromycin, adults: 500 mg every 12 hours Fluoroquinolones various strengths
Nocardia	Amikacin 20–40 mg/mL *or* Trimethoprim 16 mg/mL *and* sulfamethoxazole 80 mg/mL
Adult Topical Dosing	
Severe keratitis: loading dose every 5–15 minutes for the first hour, then every 15 minutes to 1 hour around the clock. Less severe keratitis may use less frequent dosing	

[a]Use for resistant *Enterococcus* and *Staphylococcus* species and penicillin allergy. Due to the absence of gram-negative activity, do not use vancomycin or bacitracin for single-agent empiric therapy in bacterial keratitis.

Data from American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Bacterial Keratitis [Internet]. San Francisco, CA: American Academy of Ophthalmology, 2013 [cited 2017 Aug 30]. Available from: www.aao.org/ppp.

LO 3 Topical corticosteroids are employed in some cases of bacterial keratitis. The suppression of inflammation may reduce corneal scarring. However, local immunosuppression, increased ocular pressure, and reappearance of the infection are disadvantages to their use. Topical steroids may be beneficial in bacterial keratitis if initiated early (within 72 hours of antibiotic therapy), but may lead to worse outcomes in keratitis caused by fungi or *Acanthamoeba*.[14]

Outcome Evaluation[13]

LO 5
- Symptomatic improvement is indicative of therapeutic efficacy.
- Adjust treatment based on culture and sensitivity reports.
- Modify the treatment regimen if the patient does not show improvement within 48 hours.
- Gram-negative keratitis will have increased inflammation in the first 24 to 48 hours, even on appropriate therapy.
- Taper therapy based on clinical response.
- Reculture if negative clinical response; discontinue antibiotics 12 to 24 hours before culturing for best results.
- Contact lenses–wearers should be educated about the increased risk of infection overnight and continuous wear and the importance of adherence to contact lens hygiene.

Table 62–8

Risk Factors for Dry Eye

Androgen deficiency
Antihistamine use
Connective-tissue disease
Estrogen replacement therapy
Female gender
Hematopoietic stem cell transplantation
Hepatitis C infection
LASIK and refractive excimer laser surgery
Low dietary intake of omega-3 fatty acids
Older age
Radiation therapy
Vitamin A deficiency

Data from American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome [Internet]. San Francisco, CA: American Academy of Ophthalmology, 2013 [cited 2017 Aug 30]. Available at: www.aao.org/ppp.

DRY EYE

Epidemiology and Etiology

Dry eye is a frequent cause of eye irritation. The lack of a single diagnostic test for the condition limits the available epidemiologic data. Reports of the prevalence of dry eye range from 5% to 30%, being more frequent in elderly patients.[15] The risk factors for dry eye are listed in Table 62–8. Dry eye that is left untreated can cause loss of vision, structural damage, an increased risk for infection, and compromised efficacy of ocular surgery.[16]

Pathophysiology

The surface of the eye and the tear-secreting glands work together as an integrated unit that refreshes the tear supply and clears away used tears. Dry eye may be caused by impaired tear secretion and/or increased tear evaporation.[16] It has been suggested that dry eye be called "dysfunctional tear syndrome," as all of the predisposing factors cause some disruption of the tear.[15]

Dysfunction may be caused by aging, systemic inflammatory diseases, a decrease in androgen hormones, surgery, ocular surface diseases, systemic diseases, or medications that affect the efferent cholinergic nerves. Dysfunctional tear film may result in an inflammatory response on the ocular surface called keratoconjunctivitis sicca.[16]

Environmental causes (Table 62–9) and an abnormal blink reflex are common causes of increased evaporative loss of tears and worsening of dry eye.[16]

Treatment

▶ *Desired Outcomes[16]*

- Relief of the symptoms of dry eye
- Maintain or improve visual acuity
- Prevention of long-term adverse effects from dry eye

▶ *General Approach to Treatment*

KEY CONCEPT Dry eye is a chronic condition. Symptoms can be improved with treatment, but unless dry eye is secondary to a disease, it is not usually curable. Because of this, patient education is important, and a periodic reassessment of the efficacy of the treatment is appropriate. If the patient is unresponsive to treatment, refer to an ophthalmologist for additional options. LO 6

Table 62–9

Associated Conditions That Cause or Worsen Dry Eye

Ocular Conditions	Environmental Factors
Blepharitis	Air travel
Eyelid malposition	Air conditioning or heating
Lagophthalmos	Contact lenses
Meibomian gland dysfunction	Exogenous irritants or allergens
Systemic Diseases	Prolonged use of computer or reading
Amyloidosis	Reduced humidity
Bell palsy	Smoke exposure
Epstein-Barr virus	Wind and/or use of fans
Graft-versus-host disease	**Local Trauma**
Hemochromatosis	Injury/scarring
Hepatitis C infection	Orbital surgery
Human immunodeficiency virus infection	Radiation
Lymphoma	**Medications**
Neuromuscular diseases	Anticholinergics
Ocular mucous membrane pemphigoid	Antidepressants
Parkinson disease	Antihistamines
Rosacea	Beta-blockers
Rheumatoid arthritis	Diuretics
Sarcoidosis	Hormone therapy
Scleroderma	Systemic retinoids
Sjögren syndrome	Frequent administration of ophthalmic medication
Stevens-Johnson syndrome	
Systemic lupus erythematosus	

Data from American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome [Internet]. San Francisco, CA: American Academy of Ophthalmology, 2013 [cited 2017 Aug 30]. Available at: www.aao.org/ppp.

If the dry eye is secondary to a systemic disease, the disease should be managed by the appropriate medical specialist.[16]

► *Nonpharmacologic Therapy*

LO 6 Behavioral and environmental modifications may significantly improve dry eye, especially in mild cases. Patients should be counseled to increase their frequency of blinking, use eyelid hygiene and warm compresses, and stop smoking. Reduce air drafts and consider adding a humidifier in low-humidity areas. Schedule regular breaks from computer work, other electronic screens, or reading. These activities promote decreased blinking and can increase dry eye symptoms. Lower the computer screen to below eye level to decrease lid aperture. Evaluate medication profile and therapeutically substitute medications that do not exacerbate dry eye. Spectacle side shields or goggles may reduce tear evaporation.[15,16]

LO 4 If pharmacologic and other therapies are not sufficient, punctal occlusion or lateral tarsorrhaphy may be an option for more severe cases.[15,16] Punctal occlusion is the plugging of the punctal drainage sites with collagen or silicone plugs. Lateral tarsorrhaphy sutures portions of the lid margins together to decrease evaporative tear loss.

► *Pharmacologic Therapy*

LO 2 The mainstay of treatment for dry eye is artificial tears. Artificial tears augment the tear film topically by increasing viscosity and provide symptom relief. If a patient uses artificial tears more than four times daily, or develops an allergy to ophthalmic preservatives, recommend a preservative-free formulation.

LO 1 Clinical Presentation and Diagnosis of Dry Eye[15,16]

General

Many other ocular diseases have similar symptoms. Patients with suggestive symptoms without signs should be placed on a treatment trial. Repeated observations may be required for a clinical diagnosis.

Symptoms

- Dry or foreign body sensation
- Mild itching
- Burning or stinging
- Photophobia
- Ocular irritation or soreness
- Blurry vision and/or variable vision
- Contact lens intolerance
- Diurnal fluctuation or symptoms worsening later in the day

Signs

- Redness
- Mucus discharge
- Increased blink frequency
- Intermittent tearing

Other Diagnostic Tests

- The tear break-up time test assesses the stability of precorneal tear film. Break-up times of less than 10 seconds are considered abnormal.
- Ocular surface dye staining assesses the ocular surface and will show blotchy areas in the dry eye.
- Schirmer test evaluates aqueous tear production but is not diagnostic. Results of 5 mm or less are considered abnormal.
- Assess corneal sensation if trigeminal nerve dysfunction is suspected.
- Consider an autoimmune disorder if significant dry eyes, other signs and symptoms, or family history are present.

Artificial tears are available in gel, ointment, and emulsion forms that provide a longer duration of relief. Ointment use is appropriate at bedtime as it may cause blurry vision.[15]

LO 2 Preliminary data suggest dietary or supplemental intake of omega-3 fatty acids may be beneficial.[7,15,16] Omega-3 fatty acids may block the production of inflammatory cytokines and proinflammatory mediators.[15]

LO 3 Anti-inflammatory agents may be used in conjunction with artificial tears. The first approved agent was cyclosporine emulsion. Cyclosporine emulsion increases tear production in some patients. Fifteen minutes should elapse after instillation of cyclosporine before artificial tears are instilled.[17] Cyclosporine emulsion may require several months for full results, so it should not be used for acute relief.

An additional treatment for the signs and symptoms of dry eye is twice daily lifitegrast 5% ophthalmic solution. Lifitegrast is a lymphocyte function associated antigen-1 (LFA-1) antagonist. LFA-1 is a protein that interacts with an intracellular adhesion

molecule (ICAM-1). ICAM-1 may be overexpressed in patients with dry eye disease and can promote inflammation of the ocular surface. By blocking the interaction of LFA-1 to ICAM-1, lifitegrast may reduce ocular surface inflammation. The duration of therapy in clinical trials was 12 weeks. The most common adverse effects of lifitegrast include eye irritation, distortion of taste, and reduced visual acuity.[18,19] Use of topical corticosteroids for short periods (2 weeks) may suppress inflammation and ocular irritation symptoms, but should be used with caution[16] (Table 62–10).

LO 2

Outcome Evaluation[16]

- Monitor patient for relief of symptoms and ocular damage.
- Periodically reassess the patient's compliance with therapy and understanding of the disease.
- Cyclosporine therapy may take up to 3 months for full improvement.

Table 62–10

Pharmacologic Therapies for Dry Eye

Drug	Dosing
Cyclosporine ophthalmic emulsion 0.05%	1 drop in each eye twice daily
Lifitegrast 5% ophthalmic solution	1 drop in each eye twice daily
Loteprednol etabonate suspension 0.5%	1–2 drop(s) in affected eye(s) 4 times daily; short-term use only
Cevimeline capsule	30 mg orally 3 times daily

Adapted from American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Dry Eye Syndrome [Internet]. San Francisco, CA: American Academy of Ophthalmology, 2013 [cited 2017 Aug 30]. Available at: www.aao.org/ppp.

Adapted from McEvoy GK, ed. AHFS Drug Information 2014. Bethesda, MD: American Society of Health-System Pharmacists Inc., 2018.

Patient Care Process: Dry Eye

Collect Information:

- Collect relevant information about medical history of dry eye.
- Collect information about the patient's signs and symptoms related to dry eye.
- Collect relevant information about the patient's behaviors, such as smoking, and environmental risk factors for dry eye.
- Collect an updated medication list including prescription medications, nonprescription medications, herbal products, and dietary supplements.

Assess the Information:

- Assess the patient's signs and symptoms of dry eye for potential need for referral.
- Assess the patient's reported behaviors and environmental risk factors for potential intervention.
- Assess each medication in the patient's medication list for appropriateness and risk of exacerbation of dry eye.

Develop a Care Plan:

- Address the patient's risk factors for dry eye, including potential nonpharmacologic interventions related to smoking and other environmental risk factors.
- Address the patient's medication-related problems and optimize the patient's medication therapy by recommending alternatives to medications that can exacerbate symptoms of dry eye.
- Determine an appropriate care plan based on the patient's frequency of symptoms. The care plan may include treatment options such as over-the-counter formulations of artificial tears, omega-3 fatty acids, or prescription therapies such as cyclosporine or lifitegrast.
- Plan to counsel the patient on appropriate use of ophthalmic solutions that may be utilized as part of the recommended therapy for dry eye.

Implement the Care Plan:

- Engage the patient in discussion about his/her risk factors for dry eye, including potential nonpharmacologic interventions related to smoking and other environmental risk factors.
- Recommend alternatives to medications that can exacerbate symptoms of dry eye.
- Initiate an appropriate care plan based on the patient's frequency of symptoms. The care plan may include treatment options such as over-the-counter formulations of artificial tears, omega-3 fatty acids, or prescription therapies such as cyclosporine or lifitegrast.
- Counsel the patient on appropriate use of ophthalmic solutions with the steps below:
  - Wash hands before and after instilling medication(s) into the eye.
  - Contact lenses should be removed prior to instilling eye medication, and the patient should wait 10 minutes before reinserting contact lenses.
  - Do not touch the tip of the container with anything.
  - Use of nasolacrimal occlusion decreases systemic absorption up to 60% and may increase ocular bioavailability of the drug. After instilling the eye drop, the patient should close the eye and press a finger gently against the nasolacrimal duct (tear duct) for 2 to 3 minutes.[20]
  - Contribute to the coordination of care by referring the patient to an ophthalmologist if self-care is not appropriate.

Follow-up: Monitor and Evaluate:

- Monitor patient for relief of symptoms and ocular damage.
- Assess adherence and recommend alternative formulations of artificial tears if necessary.
- Periodically reassess the patient's compliance with therapy and understanding of the disease.

- If a patient presents with vision loss, moderate or severe pain, corneal ulceration, or a lack of response to therapy, refer the patient to an ophthalmologist for prompt evaluation.

DRUG-INDUCED OCULAR DISORDERS

Many systemic medications can cause ocular adverse effects. Patients presenting with ocular complaints should have their medication profile evaluated.

OTIC DISORDERS

OTITIS EXTERNA

Epidemiology and Etiology

KEY CONCEPT Acute otitis externa (AOE), or what is commonly referred to as swimmer's ear, is an infection of the external auditory canal which potentially involves diffuse inflammation that may extend distally to the pinna and proximally to the tympanic membrane.[21,22] Otitis externa has a lifetime prevalence of approximately 10% and can be considered chronic rather than acute if it lasts 3 months or longer.[21]

A diffuse acute otitis media is diagnosed by a rapid onset, generally within 48 hours, in the past 3 weeks of symptoms and signs of inflammation such as intense or disproportionate tenderness of the tragus, pinna, or both.[22] Patients with a nonintact tympanic membrane, tympanostomy tube, diabetes, immunocompromised state, or prior radiotherapy are at risk for more serious infections and are not treated the same as an uncomplicated AOE.

Pathophysiology

In North America, the vast majority of AOE cases are bacterial caused by pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[21,22] Otitis externa can be polymicrobial, and it should be treated with topical antibiotics if uncomplicated.[22]

Otitis externa can be caused by a variety of different factors such as water exposure, self-cleaning, soapy deposits, alkaline eardrops, dermatologic conditions, trauma, sweating, allergies, genetics, climate, and stress.[22]

Treatment

▶ *Desired Outcomes*

- Relief of the symptoms of otitis externa
- Prevention of long-term adverse effects from otitis externa

▶ *General Approach to Treatment/Nonpharmacologic Therapy*

LO 7 Removing obstructing cerumen; using acidifying ear drops shortly before swimming, after swimming, at bedtime, or all three; drying the ear canal with a hair dryer; using ear plugs while swimming; and avoiding trauma to the external auditory canal are recommended by the guidelines as therapy options for preventing otitis externa.[22]

▶ *Pharmacologic Therapy*

An otitis externa in a patient with a perforated tympanic membrane needs to be treated with medications that are not ototoxic as compared to an uncomplicated case. There are not significant differences in efficacy of the topical agents; therefore, patient and provider preferences, cost, adherence, and adverse effects are priority.[22] Refer to Table 62–11 for common otic preparations.

LO 7

Table 62–11

Pharmacologic Therapies for Otitis Externa

Drug	Considerations
Acetic acid 2.0% solution (Acetic acid otic)	Pain and irritation, may be less effective beyond a week of treatment; not with perforated tympanic membrane
Acetic acid 2.0%, hydrocortisone 1.0 (Acetasol HC)	Pain and irritation; not with perforated tympanic membrane
Ciprofloxacin 0.2%, hydrocortisone 1.0% (Cipro HC)	Twice daily adequate
Ciprofloxacin 0.3%, dexamethasone 0.1% (Ciprodex)	Twice daily adequate
Neomycin, polymyxin B, hydrocortisone (Cortisporin Otic)	Ototoxic; four times daily; not with perforated tympanic membrane
Ofloxacin 0.3% (Floxin Otic)	Twice daily adequate, potentially daily

Adapted from Schaefer P, Baugh RF. Acute otitis externa: An update. Am Fam Physician. 2012 Dec 1;86(11):1055–1061.

Data from Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical practice guideline: acute otitis externa. Otolaryngol Head Neck Surg. 2014 Feb;150(1 suppl):S1–S24.

Cortisporin (bacitracin, neomycin, polymyxin B, hydrocortisone) is typically used first in patients with an intact tympanic membrane. Ofloxacin and ciprofloxacin/dexamethasone (Ciprodex) are used with a perforated tympanic membrane or if it cannot be visualized. A total of 7 to 10 days of topical therapy is recommended.[22] Also, pain is very common with otitis media, and it needs to be managed accordingly. Anesthetic otic drops are not recommended for pain management. If there is no improvement with the drops within 48 to 72 hours, then the diagnosis of otitis externa should be reviewed.

LO 7

Patient Encounter 3

NL, a 25-year-old white female, presents with an irritation to her left ear that started about 24 hours ago. She has recently started swimming at a local pool for exercise.

PMH: Hypertension

PE:

BP 142/82, P 68, R 14, Ht. 5'6" (168 cm), Wt. 132 lbs (60 kg)

Medications:

Lisinopril 10 mg daily

Multivitamin daily

Does NL have any potential risk factors for acute otitis externa?

What pharmacologic options are available?

What nonpharmacologic therapies could NL do to decrease the likelihood of this happening again?

Outcome Evaluation

- Monitor patient for relief of symptoms and otic damage.

CERUMEN IMPACTION

Epidemiology and Etiology

One of the most common reasons for patients seeking care for auditory problems is obstruction of the ear. Ear canal obstruction is most commonly caused by cerumen. Twelve million people in the United States annually seek care for cerumen impaction, 8 million cerumen removal procedures occur annually, and "… one in 10 children, 1 in 20 adults and more than one-third of the geriatric and developmentally delayed populations…" have excessive or impacted cerumen.[23]

Pathophysiology

Obstruction can lead to more serious problems including hearing loss, tinnitus, fullness, itching, otalgia, discharge, odor, and cough. Hearing loss can range from 5 to 40 dB depending on the degree of occlusion of the canal with cerumen.[23] Cerumen impaction can also prevent a provider from viewing the external auditory canal and/or tympanic membrane and performing auditory diagnostic tests that are vital components of any physical examination. Common symptoms include pain, itching, sensation of fullness, tinnitus, odor, drainage, and cough.

Treatment

▶ *Desired Outcomes*

- Relief of the symptoms of Cerumen impaction

▶ *General Approach to Treatment*

Prevention of cerumen impaction includes education in proper ear hygiene. Proper ear hygiene does not include using cotton-tipped swabs to clean ears. Cotton-tipped swabs have been implicated in increasing cerumen impaction.[23] Alcohol or hydrogen peroxide drops or irrigation, topical earwax-softening agents, and irrigation are all potential options for secondary prevention of impacted cerumen.[23]

Only patients who are symptomatic should receive treatment.[1] Patients with cerumen that prevent assessment of the ear should also be treated. Treatment for cerumen impaction may include cerumenolytic agents, irrigation, or manual removal.[23] Cerumenolytics work by thinning the cerumen to decrease the need for irrigation and manual removal. All cerumenolytic agents have been shown to be equally efficacious including water. The different cerumenolytic agents available include water-based, oil-based, and nonwater- and nonoil-based. Water-based agents work by breaking up the cerumen while oil-based preparations soften without breaking up the cerumen. Irrigation uses a jet of warm water to flush out the cerumen. A curette, probe, hook, forceps, or suction may be used for manual removal. All treatment regimens have been shown to be efficacious and none are preferred over another.

Side effects, although rare, can occur with treatment for cerumen impaction. Some side effects include tympanic membrane perforation, ear canal laceration, infection of the ear, bleeding, or hearing loss. The number of side effects from cerumen impaction treatment that occur in the United States is around 8000 yearly.[23]

Outcome Evaluation

- Monitor patient for relief of symptoms from excess cerumen.

Abbreviations Introduced in This Chapter

ABC	Acute bacterial conjunctivitis
AOE	Acute otitis externa
ICAM	Intracellular adhesion molecule
LFA	Lymphocyte function associated antigen
NSAID	Nonsteroidal anti-inflammatory drug

REFERENCES

1. Handler JA, Ghezzi KT. General ophthalmologic examination. Emerg Med Clin North Am. 1995;13:521–538.
2. Babineau MR, Sanchez LD. Ophthalmologic procedures in the emergency department. Emerg Med Clin N Am. 2008:26:17–34.
3. Wipperman JL, Dorsch JN. Evaluation and management of corneal abrasions. Am Fam Physician. 2013;87:114–120.
4. Wakai A, Lawrenson JG, Lawrenson AL, et al. Topical non-steroidal anti-inflammatory drugs for analgesia in traumatic corneal abrasions. Cochrane Database Syst Rev. 2017;5:CD009781.
5. Rodrigues Z. Irrigation of the eye after alkaline and acidic burns. Emerg Nurse. 2009;17(8):26–29.
6. Goold L, Durkin S, Crompton J. Sudden loss of vision—History and examination. Aust Fam Physician. 2009;38:764–767.
7. Cronau H, Kankanala RR, Mauger T. Diagnosis and management of red eye in primary care. Am Fam Physician. 2010;81(2): 137–144; patient handout 145.
8. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013;310:1721–1729.
9. Williams L, Malhotra Y, Murante B, et al. A single-blinded randomized clinical trial comparing polymyxin B-trimethoprim and moxifloxacin for treatment of acute conjunctivitis in children. J Pediatr. 2013;162(4):857–861.
10. Bielory L. Ocular allergy. Mt Sinai J Med. 2011;78:740–758.
11. O'Brien TP. Allergic conjunctivitis: an update on diagnosis and management. Curr Opin Allergy Clin Immuno. 2013;13:543–549.
12. Bilkhu PS, Wolffsohn JS, Naroo SA, Robertson L, Kennedy R. Effectiveness of nonpharmacologic treatments for acute seasonal allergic conjunctivitis. Ophthalmology. 2014;121(1):72–78.
13. American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Bacterial Keratitis. San Francisco, CA: American Academy of Ophthalmology, 2013. Available from: https://www.aao.org/preferred-practice-pattern/bacterial-keratitis-ppp–2013. Accessed August 30, 2017.
14. Ray KJ, Srinivasan M, Mascarenhas J, et al. Early addition of topical corticosteroids in the treatment of bacterial keratitis. JAMA Ophthalmol. 2014;132(6):737–741.
15. Jackson WB. Management of dysfunctional tear syndrome: a Canadian consensus. Can J Ophthalmol. 2009;44:385–394.
16. American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology, 2013. Available from: https://www.aao.org/preferred-practice-pattern/dry-eye-syndrome-ppp–2013. Accessed August 30, 2017.
17. Restasis (cyclosporine) emulsion [package insert]. Irvine, CA: Allergan, Inc., 2013.

18. Perez VL, Pflugfelder SC, Zhang S, Shojaei A, Hague R. Lifitegrast, a novel integrin antagonist for treatment of dry eye disease. Ocul Surf. 2016;14:207.
19. Donnenfeld ED, Karpecki PM, Majmudar P, et al. Safety of lifitegrast ophthalmic solution 5.0% in patients with dry eye disease: a 1-year, multicenter, randomized, placebo-controlled study. Cornea. 2016;35:741.
20. Zimmerman TJ, Kooner KS, Kandarakis AS, Ziegler LP. Improving the therapeutic index of topically applied ocular drugs. Arch Ophthalmol. 1984;102:551–553.
21. Schaefer P, Baugh RF. Acute otitis externa: an update. Am Fam Physician. 2012 Dec 1;86(11):1055–1061.
22. Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical practice guideline: acute otitis externa. Otolaryngol Head Neck Surg. 2014 Feb;150(suppl 1):S1–S24.
23. Schwartz SR, Magit AE, Rosenfeld RM, et al. Clinical Practice Guideline (Update): Earwax (Cerumen Impaction). Otolaryngol Head and Neck Surg. 2017;156(IS)S1–S29.

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63 Allergic Rhinitis

Hanna Phan and Michael Daines

LEARNING OBJECTIVES

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

LO

1. Describe the basic pathophysiology of allergic rhinitis (AR).
2. Define mild versus moderate/severe AR, persistent versus episodic, and differentiate between seasonal, perennial, and episodic AR.
3. Differentiate the categories of pharmacotherapy choices for treatment of AR based on mechanism, efficacy on symptom type (eg, ocular, nasal congestion), and side effect profile.
4. Identify situations in which a referral to an allergy specialist is needed.
5. Describe an approach for treatment and monitoring for treatment of mild and moderate–severe AR based on patient specific factors.
6. Identify the differences in approach to the treatment of AR for children, pregnant women, and the elderly compared with the routine approach in adults.

INTRODUCTION

Rhinitis is inflammation of the lining of the nose and contiguous parts of the upper respiratory tract.[1–4] Allergy is only one of numerous causes of rhinitis.[1–5] The most common causes of nonallergic rhinitis (NAR) are shown in Table 63–1.[1-5] Some patients suffer concurrently from both allergic rhinitis (AR) and one or more types of NAR. This is sometimes called mixed rhinitis (MR).[1,3] AR will be emphasized in this chapter, but some mention will be made of NAR. Because ocular symptoms (eg, itching and/or redness of eyes, tearing) frequently occur in association with AR, some sources use the term allergic rhinoconjunctivitis. This acknowledges involvement of the bulbar and palpebral conjunctivae in the allergic process.

KEY CONCEPT AR is an allergen-induced, immunoglobulin E (IgE)-mediated inflammatory condition of the lining of the nose and upper respiratory tract.[1,6–9] This pathophysiologic feature differentiates AR from NAR. AR has traditionally been categorized as either seasonal or perennial.[7,8] Seasonal allergic rhinitis (SAR) is attributed to inhaled allergens (aeroallergens) that have a seasonal variation. These allergens are usually encountered outdoors and are most often grass, tree, or weed pollens and substances from molds and fungi. Length of seasonal exposure depends on geographic location and climatic conditions.[7,8] Perennial allergic rhinitis (PAR) is attributed to aeroallergens that are present in the patient's environment year-round and are usually encountered indoors. Common perennial allergens are the house dust mite, indoor molds and fungi, insects (especially cockroaches), and companion animals (pets).[7,8] Some patients are affected by AR year-round, but have seasonal exacerbations. These people are probably allergic to both seasonal and perennial aeroallergens. Other patients have only episodic manifestations. These people are probably allergic to aeroallergens that are only episodically encountered (eg, cat at a friend's house).[7,8]

LO 2

Because these traditional categories of seasonal and perennial AR are imperfect and help little with therapeutic management decisions, another system for categorizing AR has been suggested by guidelines.[8,9,10] This alternative system categorizes the manifestations by a combination of frequency and severity. There are two divisions of frequency: intermittent and persistent. Intermittent frequency is defined as AR manifestations occurring less often than 4 days per week or for fewer than 4 consecutive weeks. Persistent frequency is defined as AR manifestations occurring for 4 or more days per week *and* for 4 or more consecutive weeks. Severity is categorized as either mild or moderate–severe based on presence of the following symptoms: sleep disturbance, impairment of daily activity (including leisure and/or sports), impairment of work/school, and troublesome symptoms. Mild manifestations are those of which none of the listed symptoms are present. Moderate–severe severity includes those patients with manifestations of AR with at least one of the listed symptoms present. Additionally, AR impact on comorbidities such as asthma and sinus disease which can also be considered when evaluating a patient's AR severity. See Table 63–2 for a summary of these categories of AR.

EPIDEMIOLOGY AND ETIOLOGY

AR affects up to 40% of adults and 25% of children in the United States.[8,9] The direct health care expenditures of AR in the United States were estimated to be between 2 to 5 billion dollars, annually.[8] Indirectly, as much as 4 billion dollars in work and school loss has been reported annually.[8]

Etiology of AR is multifaceted, both genetic and environmental in nature. Some studies have suggested that in addition to possible genetic predisposition, inadequate environmental exposure (eg, to animals) in early life may increase risk for AR.[11] The major risk factors for AR are: a family history of atopy (AR, asthma, eczema or food allergies); elevated serum IgE levels (especially before the age of 6 years); higher socioeconomic class; positive skin test results; exposure to particulate air pollution; maternal smoking;

Table 63–1

Types of Rhinitis

Allergic (see Table 63–2 for details)

Nonallergic

Vasomotor (also known as perennial nonallergic, idiopathic, and autonomic rhinitis) (triggered by irritants, cold air, exercise/running, or unidentified factors)
Food/meal related (gustatory)
Infectious
NARES (nonallergic rhinitis with eosinophilia syndrome)
Occupational (caused by protein allergens [IgE-mediated] or by irritants [probably non–IgE-mediated])
Hormonally related (hypothyroidism, pregnancy, menstrual cycle related, and some drugs [see below])
Drug-induced
- Angiotensin-converting enzyme inhibitors (ACEIs)
- α_1-blockers (used for treatment of BPH and HTN)
- Phosphodiesterase-5 inhibitors (used for treatment of ED)
- Aspirin and other NSAIDs (as an isolated side effect of AERD)
- Oral contraceptives and hormone replacement therapy
- Miscellaneous agents have been implicated (calcium channel blockers, some diuretics, centrally acting alpha-2 agonists, risperidone, gabapentin)

Atrophic rhinitis
Rhinitis associated with inflammatory or immunologic diseases (eg, granulomatous infections, SLE, Wegener granulomatosis, sarcoidosis, Churg–Strauss syndrome)
Malignancy

Mixed

Combination of allergic and nonallergic manifestations

AERD, aspirin-exacerbated respiratory disease; BPH, benign prostatic hyperplasia/hypertrophy; ED, erectile dysfunction; HTN, hypertension; NSAIDs, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

From Refs. 1–5.

Table 63–2

Categories of Allergic Rhinitis

Based on Etiologic Category

Seasonal—symptoms due to seasonal aeroallergens; present only during specific portions of the year, with length of exposure dependent on geographic location and climate conditions
Perennial—symptoms present throughout the year due to environmental aeroallergens,such as indoor allergens (eg, dust mites)
Episodic—symptoms present only during intermittent exposure to allergen trigger (eg, exposure to a friend's pet)

Based on ARIA 2016 Update

Symptoms: sleep disturbance, interference with daily activities (including leisure or sport), impairment of school/work, and troublesome symptoms
Mild versus moderate–severe
- Mild—none of the above symptoms present
- Moderate–severe—presence of any one of the above symptoms

Intermittent versus persistent
- Intermittent—symptoms are present for less than 4 days/week, or for less than 4 consecutive weeks
- Persistent—symptoms are present for 4 or more days/week and for more than 4 consecutive weeks
- Any one of the four possibilities of these variables can occur: mild intermittent, mild persistent, moderate–severe intermittent, and moderate–severe persistent

From Refs. 8, 9, and 10.

firstborn status; and emigration into a Western industrialized environment.[5,7,9,10,12,13] Certain disorders commonly occur with AR. The most important example is asthma. While different percentages are reported, most patients with asthma have rhinitis symptoms (many of which are AR), and only somewhat fewer with AR have asthma.[5,13] In fact, there is evidence that AR can predispose to the development and/or worsening of asthma.[1,5,13] Other conditions that can occur with AR include allergic conjunctivitis, eczema, sinusitis, sleep disorders, otitis media with effusion, and the oral food allergy syndrome.[5,10]

PATHOPHYSIOLOGY

LO 1

AR is an IgE-mediated disorder of people who are allergy prone. Initial contact is required to sensitize the patient to subsequent exposures. Patients with an inherited tendency to allergic disorders produce T-helper lymphocyte type 2 (Th-2)-directed responses, including production of specific IgE antibodies, to one or more allergens. Many types of cells, mediators, and intermediate substances (including cytokines) are involved. In response to subsequent exposures to the trigger antigen(s), there is an early-phase and often a late-phase allergic response. This distinction has therapeutic implications.[1,5,6-10]

During the early phase, the trigger allergen becomes bound to IgE that is fixed to mast cells in the nasal mucosa. This occurs within minutes of subsequent exposure to the antigen. Mast cells degranulate and release preformed mediators, the most important of which is histamine. This stimulates more mast cells, as well as macrophages, eosinophils, and basophils to produce more substances, including cysteine leukotrienes and prostaglandin D_2. These mediators bind to receptors in the nose and facilitate many of the manifestations of AR. The resultant vasodilation, mucosal edema, and hypertrophy all contribute to nasal congestion. Clear, watery, and often profuse rhinorrhea is also characteristic in this early phase, a result of mucous secretion and increased vascular permeability. Sneezing and nasal itch are other prominent features of the early phase. Many patients also have ocular symptoms.[1,5,6-10]

The late phase occurs in about 50% of AR sufferers. It can begin as soon as 2 hours after the early phase and usually peaks between 6 and 12 hours. The late phase involves a second release of many of the mediators of the early phase. In addition, the late phase is characterized by an inflammatory component caused by infiltration of several cell types into the nasal mucosa. The most significant manifestation during the late phase is nasal congestion that is often severe and long lasting.[1,5,6–10]

A phenomenon known as the priming response or nasal hyperresponsiveness is also of importance. This means that prolonged and/or repeated allergen exposure makes it easier to stimulate mediator release and symptoms. A vicious cycle results in which smaller doses of allergen can create symptoms (ie, the threshold is lowered). Thus, even when pollen exposure is decreased, symptoms may continue. In some patients, the threshold is lowered to the degree that even irritant substances (eg, formaldehyde, tobacco smoke, perfumes, automobile exhaust, and other environmental pollutants) may cause symptoms, on a nonallergic basis.[1,5,6–10]

TREATMENT

General Approach and Desired Outcomes

Guideline documents have been published on AR.[7–10] They provide some of the basis for the sections that follow. Although guideline documents are highly regarded by many, the patients enrolled

Clinical Presentation and Diagnosis of Allergic Rhinitis[1–3,6,7,13,14]

Typical Symptoms

- Rhinorrhea (usually clear and bilateral; primarily anterior but may be posterior [postnasal drip])
- Sneezing
- Itching (mostly nasal, but also palate, throat, eyes, ears)
- Nasal congestion (not in all patients, but when present, usually the most troublesome symptom)

Other Symptoms

- Ocular manifestations (itch, redness, tearing, chemosis, periorbital edema)
- Sleep disturbances often with fatigue, asthenia, malaise, and irritability
- Presenteeism (impaired performance at work or school)
- Absenteeism from work or school
- Quality of life impairment (including social function)
- Headache, mild facial or ear pain or fullness
- Cough (especially in those with concurrent asthma)
- Children (especially): snorting, sniffling, clearing the throat, learning or attention problems, poor appetite

Signs (Especially Common in Children)

- Pale, boggy nasal mucosa
- Rubbing the nose upward (allergic salute; may create horizontal crease just above tip of nose)
- Rubbing/scratching of eyes
- Mouth breathing
- Dark circles under the eyes (allergic shiners)
- Dennie-Morgan lines or folds under the eyes

Diagnosis

- Typical symptoms, confirmatory signs, especially in association with exposure to allergen triggers
- Other diagnostic testing usually optional, but may be necessary to rule out nonallergic causes or if immunotherapy is considered (appropriate physical examination, specific IgE antibody testing by either skin testing or in vitro serum testing, other specialized testing)
- Several sources particularly good for differential diagnosis of nonallergic rhinitis[3,13,15]
- Vasomotor rhinitis—sneezing and itch less common than AR; anosmia more common
- Unilateral symptoms—refer for possible obstruction, anatomic abnormality, tumor, cerebrospinal fluid (CSF) leak
- Atrophic rhinitis—older adults, history of nasal surgery

in the randomized clinical trials that are a major basis for their conclusions and recommendations are not always representative of patients in a primary practice population.[15] KEY CONCEPT The general approach for treatment of AR is fourfold: avoidance of allergen triggers, pharmacotherapy, immunotherapy, and patient/caregiver education.[8–10] Recommended approaches to AR management begin with allergen avoidance and patient/family education. If allergen avoidance is not sufficient and/or symptoms necessitate treatment, pharmacotherapy is utilized. Failure to respond to first-line over-the-counter (OTC) or prescription AR medication may warrant referral to an allergy specialist for further assessment. Based on assessment by a specialist, immunotherapy may also be an option in selected patients.

LO 4

Patient Encounter 1, Part 1

Mr. Z, a regular customer in your community pharmacy, asks your advice about helping his 5-year-old daughter, Kim. She has a diagnosis of "mild" asthma that is primarily exercise-induced but is well controlled on fluticasone 44 mcg 1 puff twice a day and has an albuterol metered-dose inhaler for use before exercise and as needed for shortness of breath. Kim has recent had frequent trouble with runny nose, sneezing, and watery and itchy eyes, as well as "throat" itching.

What information is suggestive of AR? What additional information is needed in order to make a recommendation in treatment?

Education of the patient and the patient's support system is essential.[7] All parties need to understand the potential seriousness of AR (including complications such as asthma) and the chronic, recurrent nature of AR. All should be told about the treatment options, including their relative advantages and disadvantages. Proper understanding and use of current medication in the patient's regimen should be assured. A better educated patient and support system will result in a better relationship with health care providers and hopefully will optimize patient outcomes.

KEY CONCEPT The goals of treatment of AR are to minimize the frequency and severity of symptoms, prevent comorbid disorders and complications, improve the patient's quality of life, improve work attendance and productivity and/or school attendance and performance, and minimize adverse effects of therapy. Until a cure is established, these are the only realistic goals.

Nonpharmacologic Therapy

Avoidance of allergen triggers is a core component of nonpharmacologic therapy of AR. Patient and caregiver education is fundamental in reducing preventable allergen exposure. Avoidance of allergen triggers, to the extent they have been identified and to the extent such avoidance is possible, underlies the treatment for all patients with AR (see Table 63–3).[7–10]

▶ *Saline*

Nasal administration of saline is an alternative and often used as an adjunctive, nonpharmacological treatment of AR.[5,7,16,17] This therapy may benefit any patient with rhinitis, including those with vasomotor rhinitis.[5] Saline may be administered as drops or a spray, but the irrigation mode of administration is popularly known by several terms, including neti pot, nasal wash, nasal douche, nose bidet, and as nasal irrigation. Although

Table 63–3

Allergen Avoidance Measures

Allergen avoidance underlies all other treatments of AR

There are several limitations to allergen avoidance:

- Allergen(s) must be identified.
- Literature support for a clinically significant improvement in symptoms from allergen avoidance is meager.
- Quality of life may be negatively impacted by forced removal of a pet from the household.

Outdoor plant pollen and mold/fungi parts:

- Limit outdoor exposure, especially during high pollen conditions (warm sunny days with wind and low humidity) and during mold/fungi spore release (shortly after rains).
- Wear a face mask during activities that disturb soil and decaying vegetation.
- Keep windows and doors closed.
- Use air conditioning, but maintain clean equipment.

Indoor allergens (house dust mite, mold/fungi, cockroaches, and pets):

- Use air-conditioning, as above.
- Maintain humidity below 50%, and maintain clean equipment.
- Clean frequently to prevent mold growth (dilute bleach with detergent).
- Avoid exposed food and garbage to deter insects.
- Clean kitchen frequently.
- Use roach traps that facilitate their removal.
- Vacuum frequently, and use a high-efficiency particulate air (HEPA) filter.
- Minimize carpeting, fabric covered furniture, and fabric wall/window coverings.
- Cover bedding (pillows, mattresses, box springs) with allergen-proof, zippered cases.
- Launder bedding frequently, in hot water (> 130°F or 54°C) to kill mite ova.
- Consider acaricide (eg, benzyl benzoate) treatment of carpets to kill mites and ova.
- Put items that cannot be laundered (eg, soft toys) in a plastic bag and freeze.
- Keep pets out of bedroom and bathe cats weekly, if possible.

Irritants:

- Avoid, as possible, all exposure to smoke, chlorine fumes, formaldehyde fumes, and other substances identified as irritant triggers (eg, perfumes, newspaper ink).

From Refs. 7–10.

Table 63–4

Intranasal and Oral Medications for AR

Corticosteroids
Intranasal[a] (budesonide [OTC], beclomethasone, ciclesonide, flunisolide, fluticasone [propionate and furoate] [OTC], mometasone, triamcinolone [OTC])
Oral (rarely used, eg, prednisone)

Antihistamines
Intranasal[a] (azelastine, olopatadine)
Oral[b]

- First generation/sedating (cautious use in selected patients) (most OTC depending on strength: diphenhydramine, chlorpheniramine, clemastine, and others)
- Second generation/low- or nonsedating[a]: loratadine (OTC), cetirizine (OTC), fexofenadine (OTC), levocetirizine (OTC), desloratadine,

Combination Antihistamine/Corticosteroid
Intranasal (azelastine and fluticasone propionate)

Mast cell stabilizer/cromone
Intranasal (cromolyn [OTC])

LTRA
Oral (montelukast)

Antimuscarinic
Intranasal (ipratropium)

Decongestant
Intranasal (short-term use) (tetrahydrozoline, phenylephrine [OTC], naphazoline [OTC], oxymetazoline [OTC])
Oral[b] (phenylephrine [OTC]; pseudoephedrine [BTC[c]])

[a]First-line choices.

[b]Some products combine an antihistamine with a decongestant, sometimes with other ingredients.

[c]Behind the counter (OTC plus other requirements necessary; see the Decongestants section of text).

Note: All products are prescription unless indicated as OTC.

From Refs. 7–10 and 18–20.

less effective than intranasal corticosteroids (INCSs), it has been shown to improve sneezing and nasal congestion. It can be used either alone or as add-on therapy. The formula provided by the American Academy of Allergy, Asthma and Immunology (AAAAI) should be followed for those making their own saline nasal irrigation solution.[17] Iodized salt is not recommended as it may be irritating. Hypertonic saline seems to have no advantage over 0.9% sodium chloride. Administration can be accomplished while the patient is in the shower or leaning over a sink. The head is bent forward and downward, then tilted to the side opposite the treated nostril. Then, with a bulb syringe or similar device, slowly introduce about 4 oz (118 mL) of the warm saline solution into one nostril. Soon, the solution will run out of the opposite nostril. The position of the head should be adjusted as necessary to avoid the solution running into the ears or down the throat.

Nasal irrigation is one delivery method, although the optimal method (spray, drops, nebulizer, or irrigation) is not known. Optimal frequency of administration is also not known. Nasal irrigation is usually given twice daily, but use of smaller volumes as spray products may be given up to four times daily. Side effects are usually limited to minor local nasal irritation, but nausea has been reported.

Pharmacologic Therapy

LO 3

KEY CONCEPT Routine first-line agents for the treatment of AR are INCSs and oral (or possibly intranasal) antihistamines. Secondary agents, each of which may have a first-line role in selected patients, include oral (and rarely intranasal) decongestants, the intranasal mast cell stabilizer (cromolyn), the oral leukotriene receptor antagonist (LTRA) (montelukast), the intranasal antimuscarinic (ipratropium), and intranasal saline irrigation. See Table 63–4 for intranasal and oral medications for the treatment of AR. Treatment selection, among common medications for AR, can vary based on best available evidence (ie, guidelines, clinical trials, etc) for a given medication in addition to the severity of AR of a given patient. See Figure 63–1. In all cases, therapy must be individualized, in cooperation with the patient. Considerations include frequency and severity of specific symptoms, realistic avoidance measures, patient age, patient preferences for route of administration, tolerance of side effects, adherence issues, comorbid disorders, and concurrent therapy.

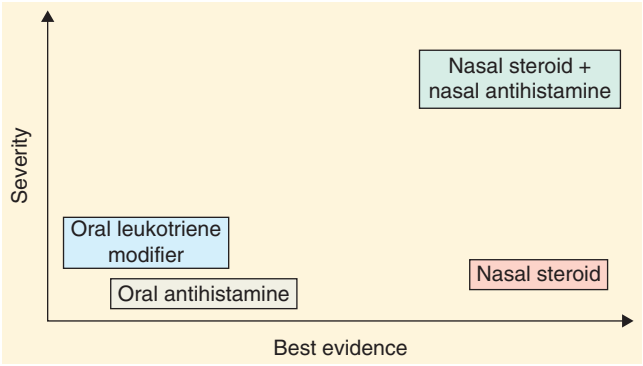

FIGURE 63–1. Evidence-based treatment options for AR based on current guidelines. (From Refs. 7–10.)

Some clinicians may elect to use an action plan for AR with their patients, similar to that used for asthma.[7] Some patients may benefit from having an AR action plan, depending on their AR severity and complexity of therapy.

▶ *First-Line Agents*

Corticosteroids. Corticosteroids are usually administered by the intranasal route for the treatment of AR. Occasionally, a short course of oral therapy (eg, prednisone burst and taper) is necessary. Oral corticosteroids may be used to overcome severe nasal congestion, particularly that due to rhinitis medicamentosa (see the section on Decongestants). Parenteral administration of corticosteroids for AR is discouraged due to side effects.[5,7,10]

INCSs provide very good relief for sneezing, itching, and rhinorrhea, and even nasal congestion and ocular symptoms. Nasal congestion is often the most bothersome symptom of AR, and the most difficult to control. This is probably because it results from inflammation that predominates in the late phase of the allergic response. KEY CONCEPT INCSs are the most effective therapy for AR, especially for nasal congestion. Their anti-inflammatory mechanism of action probably contributes to this superiority.[5,6,13] The majority of contemporary literature suggests that INCSs are superior to intranasal antihistamines, to oral antihistamines even when combined with a leukotriene antagonist, and to a leukotriene antagonist alone.[5,8–10] In recent guidelines by the American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma, and Immunology (ACAAI), INCSs are recommended as monotherapy versus in combination with an oral antihistamine for initial treatment of nasal symptoms of seasonal allergic rhintitis in patients ages 12 years and older. Additionally, in patients ages 15 years and older with moderate to severe SAR, INCSs are recommended over an LTRA such as montelukast.[7]

There are currently eight INCS products available in the United States, including two different salt forms of fluticasone. Most (budesonide, ciclesonide, fluticasone furoate, mometasone, and triamcinolone) are used once daily. However, fluticasone propionate may be given either once or twice daily, beclomethasone is usually given twice daily, and flunisolide is given two or three times daily. There is no good evidence that any single product is superior in efficacy. INCSs are best given regularly, as the onset of action usually takes up to 12 hours and the maximum effects may be delayed up to 14 days.[5,7–10,18] In some people the onset is within 3 to 4 hours, so these agents may even be used on an as-needed basis.[7,19] When nasal congestion is severe, intranasal administration may not be effective due to limited exposure to the nasal mucosa. Short-term use of intranasal decongestants may facilitate better exposure. Two agents are formulated as hydrofluoroalkane (HFA) metered-dose aerosols: beclomethasone (Qnasl) and ciclesonide (Zetonna), which may be better tolerated.[19,20] There is also a fixed dose intranasal combination of fluticasone propionate with azelastine (an antihistamine).[19,20] See Table 63–5 for INCS products.

The correct technique for administration of intranasal medication is important for optimum efficacy. Consult the individual product labeling for specific instructions. Also see Table 63–6 for general instructions for the optimal administration of intranasal solutions. The technique described maximizes exposure of the drug to the nasal mucosa to optimize efficacy and minimizes both exposure to the nasal septum and loss of medication down the esophagus.

Most patients tolerate INCSs very well. Local side effects include nasal burning, irritation, and dryness, which may occur in 2% to 10% of patients.[5,8,20] Also, 2% to 8% of patients may experience mild epistaxis.[5,8] This may be partly due to administration technique. Perforation of the nasal septum is very rare. This can be minimized by proper administration technique (see Table 63–6), specifically, directing the spray laterally and away from the (medial) nasal septum.[5,8,19,20]

The older INCSs (beclomethasone, flunisolide, and budesonide) have significant absorption, whereas, among the newer products, fluticasone, ciclesonide, and mometasone have bioavailability of less than 1% to 2%.[22] The decreased absorption minimizes systemic side effects. However, there is still some concern for hypothalamic–pituitary–adrenal (HPA) axis suppression (growth suppression), osteoporosis, and ocular effects (glaucoma, cataracts).[5,22,23] There is no confirmation that INCSs *cause* posterior subcapsular cataracts, increased intraocular pressure, or decreased bone density; however, those with risk factors for these conditions should be monitored carefully for their development.[5,22,23] Additionally, clinicians should examine total corticosteroid exposure (ie, from all sources, inhaled, oral, etc) in assessing potential risk for adverse effects from systemic exposure.[22,23] Ultimately, patient preference for a specific INCS may be determined more by cost, availability, and formulation differences that affect odor and aftertaste.

Antihistamines. Antihistamines used for AR treatment are administered by either the oral or the intranasal route. These agents interact with the histamine type 1 (H_1) receptor. They are technically inverse agonists, not competitive antagonists; however, there may be little clinical significance to the difference.[24] These drugs bind H_1 receptors, keeping them in the inactive state. This downregulation of H_1 receptor activity results in a decrease in end organ effects.

Activation of H_1 receptors in the nose, upper airway mucosa, and the eye produce the common manifestations of AR (sneezing, itching, rhinorrhea, nasal congestion, and ocular symptoms). The antihistamines are very effective for the sneezing, itching, and rhinorrhea. There is some improvement of nasal congestion, but less so than for the other symptoms. There is also benefit for the ocular symptoms (eg, itching, redness, tearing). Intranasal administration is more effective than oral administration for the nasal congestion, but less effective for the ocular symptoms. The onset of action by oral administration is usually within 1 to 2 hours, and for intranasal administration within 15 minutes.[5,6,19,20] Antihistamines probably provide better relief when used continuously during symptomatic periods, but they are also effectively used only when needed for mild and/or intermittent or episodic AR.

Table 63–5

Intranasal Corticosteroids

Generic (Brand) Name	mcg/dose	Adult Dosages (each nostril)	Pediatric Dosages (each nostril)[a]
Beclomethasone dipropionate (Beconase AQ)	42	1–2 sprays twice daily	6 yo and older: 1–2 sprays twice daily, once symptoms controlled decrease dose to 1 spray twice daily 12 yo and older: 1–2 sprays twice daily
Beclmethasone dipropionate (Qnasl [HFA MDP])	40 80	— 2 sprays once daily	4–11 years: 1 spray once daily 12 yo and older: 2 sprays once daily
Budesonide (Rhinocort Aqua)	32	1–4 sprays once daily	6–11 yo or older: 1–2 sprays once daily 12 yo and older: see adult dosing
Ciclesonide (Omnaris)	50	2 sprays once daily	2–11 yo: 1–2 sprays once daily (perennial AR) 6 yo and older: 2 sprays once daily (seasonal AR)
Ciclesonide (Zetonna [HFA MDP])	37	1 spray once daily	12 yo and older: 2 sprays once daily (perennial AR) 12 yo and older: 1 spray once daily (seasonal AR)
Flunisolide	25	2 sprays two or three times daily	6–14 yo or older: 1 spray three times daily or 2 sprays twice daily 15 yo and older: 2 sprays two or three times daily
Fluticasone furoate (Veramyst)	27.5	2 sprays once daily	2–11 yo or older: 1–2 sprays once daily 12 yo and older: 2 sprays once daily
Fluticasone propionate (Flonase)	50	1–2 sprays once daily or 1 spray twice daily	4–11 yo or older: 1 spray once daily
Mometasone (Nasonex)	50	2 sprays once daily	2–11 yo or older: 1 spray once daily 12 yo and older: 2 sprays once daily
Triamcinolone acetonide (Nasacort AQ)[b]	55	2 sprays once daily	2–5 yo: 1 spray once daily 6–12 yo: 1–2 sprays once daily

[a]Includes off-label dosing from Ref. 19,20.

[b]Available OTC.

Note: All products are FDA pregnancy category C except budesonide, which is B.

mcg, micrograms; yo, years old; HFA, hydrofluoroalkane (propellant); MDP, metered-dose pump.

From Refs. 7–10 and 18–20.

The oral agents are divided into first- and second-generation drugs. The first-generation agents are distributed among six chemical classes, including the more sedating ethanolamine class (eg, diphenhydramine) and the least sedating alkylamine class (eg, chlorpheniramine). Most sources now discourage the routine use of the first-generation agents for AR. This is due to their central nervous system (CNS) and antimuscarinic side effects. The CNS effects are primarily sedation and impairment of cognitive function and performance of tasks. Decision-making and driving or work/school performance can be impaired even when the patient is unaware of any overt effects.[6,7] The major antimuscarinic effects include blurred vision, dry mouth, urinary retention, and constipation. The only possible advantage of the antimuscarinic properties is an additional effect to decrease rhinorrhea. Another

Table 63–6

Administration Instructions for Intranasal Solution Medications (not HFA MDP products)

1. Clear the nose of mucus and debris.
2. Consult product labeling for preadministration instructions (eg, shaking the container, priming the spray pump).
3. Do not tilt head backward. This increases drug lost down the esophagus. This decreases efficacy and increases the potential for systemic absorption and thus systemic side effects.
4. Bend the head forward (flex the chin onto the chest) so that the nose is the lowest portion of the head. This is best for nasal sprays. If possible, lie down with the stomach on a flat surface or kneel down. Then, flex chin onto neck, so that the open nostrils are pointing upward, toward the ceiling. This position may be best for nose drops (more volume than sprays). An alternate position is to lie supine on a flat surface, then bend the neck backward (extend the head), so that the open nostrils point upward toward the ceiling.
5. Use the contralateral hand to insert the spray nozzle or dropper into one nostril (ie, the left hand for right nostril).
6. Use the other hand to occlude the opposite nostril (the one not being medicated).
7. Aim the spray or drops toward the outer (lateral) inside surface of each nostril and away from the nasal septum.
8. Breath in slowly but deeply through the medicated nostril.
9. Repeat this procedure to apply medication to the other nostril.
10. Consult the product labeling for instructions on cleaning the device.
11. See the text for information about preparation and use of saline irrigation.

HFA, hydrofluoroalkane (propellant); MDP, metered-dose pump.

From Refs. 8 and 21.

disadvantage of the first-generation antihistamines is that most are administered three to four times daily due to shorter half-life. Patients who take other sedative substances may have an additive effect from the antihistamine. Those taking any other medications with antimuscarinic properties may experience additive effects from the antihistamine. The elderly are, in general, more sensitive to both types of adverse effects.

Currently available oral second-generation H_1 antihistamines are cetirizine, loratadine, and acrivastine. All except acrivastine are available as a single agent, and some are marketed in combination with the decongestant pseudoephedrine. As these agents are active metabolites of preceding agents, fexofenadine (preceding agent was terfenadine, removed from marked due to cardiac toxicity), levocetirizine, and desloratadine are informally labeled as "third generation" antihistamines, but sometimes classified as "second generation" antihistamines. As of August 2014, cetirizine, loratadine, and fexofenadine are available OTC. The second-generation antihistamines have less antimuscarinic activity than the first-generation agents. Based on current literature, no single H_1 antihistamine (first- or second-generation) is clearly superior in efficacy; however, very few head-to-head comparative studies have been conducted. Individual variation is likely, and patients may need to try more than one product to realize optimal benefit. The oral second-generation antihistamines are effective for the sneezing, itching, and rhinorrhea of AR, but less effective for the nasal congestion. They also improve ocular symptoms. Intranasal antihistamines are somewhat better for nasal congestion.

Fexofenadine has virtually no sedative effects, even at doses higher than recommended. Loratadine and desloratadine are not sedative at recommended doses, but can be at higher doses. Cetirizine, levocetirizine, and acrivastine have some sedative effects, even at recommended doses. All the oral second-generation agents require some dosage reduction with impaired renal function, but specific recommendations vary with creatinine clearance.[25,26] Most of the oral second-generation antihistamines can be administered once daily (except for the lower dosage forms of fexofenadine and the acrivastine combination product).

There are only two intranasal antihistamine products available in the US market as of July 2017, azelastine and olopatadine. These are considered second-generation agents, although they also have anti-inflammatory effects.[27] Both are available only by prescription. The most common side effect of these products is a bitter taste. This is more common with the original formulation of azelastine (Astelin) and less common with olopatadine.[7,19] A specific formulation of azelastine (Astepro) has less bitter taste.[20,27] There is also an available combination product with azelastine and fluticasone propionate.[28] There is enough systemic absorption to cause sedation in some patients using azelastine (about 10%) and perhaps somewhat fewer on olopatadine.[7,20] See Table 63–7 for the single-agent second-generation antihistamine products.

Table 63–7

Single-Agent Second-Generation Antihistamine Products (Oral and Intranasal)

Oral Dosage Forms

Generic (Brand) Name	Formulation	Usual Adult Dosage	Usual Pediatric Dosage
Cetirizine[a,b] (Zyrtec, generic)	5, 10 mg tabs/chew tabs; capsule 5 mg/5 mL syrup	5–10 mg once daily	6–11 mo; 2.5 mg once daily 12–23 mo; 2.5 mg once or twice daily 2–5 yo; 2.5–5 mg once daily or 2.5 mg twice daily
Desloratadine[b] (Clarinex)	5 mg tabs; 2.5 mg/5 mL syrup 2.5, 5 mg orally disintegrating tabs	5 mg once daily	6–11 mo; 1 mg once daily 1–5 yo; 1.25 mg once daily 6–11 yo; 2.5 mg once daily
Fexofenadine[a,b] (Allegra, generic)	60, 180 mg tabs, 6 mg/mL suspension 30 mg orally disintegrating tabs	60 mg twice daily or 180 mg once daily	2–11 yo; 30 mg twice daily
Levocetirizine (Xyzal)	5 mg tabs 2.5 mg/5 mL solution	5 mg once daily	6 mo–5 yo; 1.25 mg once daily 6–11 yo; 2.5 mg once daily
Loratadine[a,b] (Claritin; Alavert, generic)	10 mg tabs and cap; 5 mg/5 mL syrup and susp; 10 mg disintegrating tabs; 5 mg chewable tab	10 mg once daily	2–5 yo; 5 mg once daily

Intranasal Sprays

Generic (Brand) Name	mcg/spray	Usual Adult Dosage (Each Nostril)	Usual Pediatric Dosage (Each Nostril)
Azelastine (Astelin, Astepro)	137	1–2 sprays twice daily	5–11 yo; 1 spray twice daily
Azelastine/fluticasone propionate (Dymista, Triclast)	137 (azelastine); 50 (fluticasone propionate)	1 spray twice daily	6–11 yo: 1 spray twice daily
Olopatadine (Patanase)	665	2 sprays twice daily	6–11 yo: 1 spray twice daily

[a]Available OTC.

[b]Available in combination with pseudoephedrine (consult labeling for pediatric dosage).

Note: Acrivastine is available only with pseudoephedrine and so is not included in this table.

mo, months old; yo, years old.

From Refs. 7–10, 19, 20, and 28.

Patient Encounter 1, Part 2

Additional history from both Mr. Z and Kim reveals the following information. Kim's symptoms began about a week ago after they moved into a new home that is older with quite a bit of dust. Both Mr. Z and his wife have seasonal allergies and are treated with oral antihistamines. Kim's symptoms have become problematic in that she had to miss school today due to her inability to stop itching her eyes and the constant runny nose. She has also not slept well for the past few days due to her symptoms. Mr. Z states that she was not recently sick (ie, no fever, aches) and is not congested. Her nasal secretions are clear. The family also recently visited a horse farm a month back while on spring vacation, where she had some itchy eyes after the visit. Kim was given an over-the-counter medication that made her "super hyper" and has not since been given medication for her symptoms.

How would you classify Kim's presumed allergic rhinitis? Why?

What OTC-specific treatment options are there for initial management of Kim's presumed AR?

KEY CONCEPT Second-generation antihistamines are often effective alone, specifically for mild or intermittent AR. They are preferred over first-generation antihistamines because of fewer side effects. Although effective for most symptoms of AR, they are less effective than INCSs for nasal congestion. Intranasal administration is more effective than oral administration for nasal congestion. Most patients can use oral second-generation products. Others may prefer the intranasal route of administration, but they require a prescription. If nasal congestion is not relieved, addition of a decongestant is reasonable, either alone or as a combination product (see Decongestant section). Perhaps even the combination of an oral with an intranasal antihistamine is reasonable for some patients, depending on their preferences. Other pharmacologic agents can be combined with oral and/or intranasal antihistamines, as necessary for optimal control of symptoms. The intranasal combination product of azelastine and fluticasone (Dymista, Triclast) may be appropriate for some patients.[28] In recent guidelines by the AAAAI and ACAAI, for patients age 12 years and older for initial management of moderate to severe SAR, use of both INCS and intranasal anthistamine may be considered.[7]

▶ *Adjunctive or Secondary Choice Agents*

Decongestants. Decongestant drugs are useful only for nasal congestion.[7–10] This results from their α_1 adrenergic agonist activity, which causes vasoconstriction in the nasal mucosa. They provide no benefit for the sneezing, itching, rhinorrhea, or the ocular manifestations. Decongestants can be given alone, either by the oral or by the intranasal route. Also, numerous combination products are available, consisting of a decongestant with an antihistamine (and sometimes other ingredients). There are some special considerations for use of decongestants in pediatric and pregnant patients (see the Special Populations section).

Oral decongestant products are currently limited to pseudoephedrine and phenylephrine.[5,19] Pseudoephedrine has been changed from truly OTC to a more controlled "behind-the-counter" (BTC) status because it is an ingredient in the illicit manufacture of methamphetamine. Some manufacturers changed the ingredients of their products by replacing pseudoephedrine with phenylephrine to maintain shelf presence in the OTC area. However, much controversy surrounds the efficacy of oral phenylephrine. Most contemporary literature suggests that the currently recommended adult dose is minimally effective as a nasal decongestant, even compared to placebo in SAR.[5,29]

The side effects of orally administered decongestants most often affect cardiovascular function or the CNS. The side effects are primarily due to sympathetic stimulation and are usually dose-related. Some elevation of blood pressure may occur, but in normotensive and well-controlled hypertensive patients, the elevation is usually small. It is not of clinical significance in most situations, especially considering that these drugs are most appropriately used only briefly or intermittently. Insomnia, nervousness, irritability, and anxiety are relatively common CNS side effects. Some patients may have decreased appetite, tremors, headache, and even hallucinations. Men with benign prostatic hyperplasia (BPH) and other patients with disorders causing bladder outlet obstruction may have increased urinary retention due to α_1 stimulation of the urethral sphincter.

The intranasal agents currently available in the United States include the OTC products phenylephrine, oxymetazoline, and naphazoline. Intranasal application of decongestants provides rapid and effective relief of nasal congestion. This therapy may provide relief for nasal congestion, even for those patients already on INCSs.[30,31] However, the continuous use of intranasal decongestants often causes a paradoxical rebound phenomenon of persistent nasal congestion, called rhinitis medicamentosa.[5,30,31] Although some patients do not develop rhinitis medicamentosa, even after several weeks of continuous use of intranasal decongestants, the usual recommendation is to use them for no more than 3 consecutive days.[7] Intranasal decongestants can cause local side effects, including stinging, burning, dryness, and even sneezing. These are usually mild and well tolerated. Due to very limited absorption, the intranasal route rarely causes systemic side effects.[5,7] Administration technique should be optimized as described in Table 63–6. Should rhinitis medicamentosa occur, the best management is first to discontinue the decongestant, possibly with a taper to minimize worsening the situation. However, the response to withdrawal is often delayed for days. Therefore, it may be necessary to start INCSs and/or begin a short course of oral corticosteroid.[30,31]

KEY CONCEPT Whenever possible, intranasal decongestants in AR should be limited to short term use to overcome severe nasal congestion and to facilitate improved efficacy of other intranasal agents. The intranasal administration of decongestants should usually not exceed 3 consecutive days. Despite the usual good tolerance of recommended doses of oral decongestants, caution is warranted when they are used in patients with cardiac disease (dysrhythmias, angina pectoris, heart failure), hypertension, cerebrovascular disease, bladder outlet obstruction (including BPH), glaucoma (especially closed angle), hyperthyroidism, and possibly diabetes.[5,19,20] The choice between the two routes of administration is based on several considerations, including cost, convenience, patient preference, speed of onset (within 30 minutes orally, within 5 to 10 minutes intranasally), and side effects.[7,11]

Mast Cell Stabilizer. Cromolyn is available as an OTC intranasal product. The mechanism of action in AR is mast cell stabilization. The drug binds to mast cells and prevents

release of the mediators of AR that would otherwise result from allergen exposure. The drug is moderately effective, but less so than both INCSs and oral or intranasal antihistamines. It does have effects on both early and late phases of AR.[5,7] Its effects begin within 4 to 7 days of use, but may not be maximal for up to 2 weeks.[7] However, it can be used effectively on an as-needed basis for episodic exposures to allergen.[7,20] Cromolyn is very well-tolerated. The most common side effects are mild local stinging and/or burning, sneezing, unpleasant taste, and possibly nose bleed. A disadvantage is the frequency of administration. At least initially, it should be used four times daily. Some patients may need only two or three daily doses when used continuously after the first few weeks at four times daily. It is most useful for patients with mild or intermittent symptoms, especially in the pediatric population and in pregnant women.

Leukotriene Receptor Antagonist. Leukotrienes are involved in the pathophysiology of AR and in particular contribute to the nasal congestion in the late phase.[1,5,7–10] There is some difference of opinion about benefits of LTRAs. LTRAs are recommended by some guidelines in the case of PAR (not SAR) over oral antihistamines.[9] Most sources indicate good benefit for nasal congestion and rhinorrhea, some benefit for ocular symptoms, but less for nasal itch and sneezing compared to INCSs and antihistamines.[5,20] Montelukast is the only LTRA approved for treatment of AR. It is marketed as oral granules and as both chewable and regular tablets. The combination of montelukast with an oral antihistamine may have improved efficacy over either agent alone, according to some sources; however, even the combination is probably not better than INCSs.[5,7,9] The onset of action of montelukast is delayed for a day or more.[6] The drug is usually considered to be very well-tolerated. However, there are postmarketing reports of neuropsychiatric events, including sleep disturbances, depression and suicidal ideation, as well as headache, gastrointestinal (GI) disturbances, skin rash, and Churg–Strauss syndrome.[7,19,32] It is administered once daily, considered safe (Food and Drug Administration [FDA] pregnancy category B and indicated for children as young as 6 months of age), and particularly well-suited to those patients who also have asthma.[19,20]

Antimuscarinic Agent. Ipratropium is currently the only antimuscarinic agent indicated for treatment of AR. Systemic absorption is minimal. It is available by prescription as an intranasal spray. Its use is limited to those patients whose rhinorrhea has not been controlled by other therapy (antihistamines and/or INCSs).[5,7,13] There are two strengths available, 0.03% and 0.06%. The 0.03% product is approved for AR in children as young as 6 years of age. This agent may be particularly helpful for patients who have vasomotor (idiopathic, autonomic) rhinitis, or those who may have a mixed etiology.[5] Local side effects are usually limited to nasal and oral dryness, throat irritation, and mild epistaxis.[19,20]

Omalizumab. Omalizumab is a monoclonal antibody that binds to IgE. The product is approved for moderate to severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids in patients ages 6 years and older. It is not approved for treatment of AR as of October 2017. It is administered by subcutaneous injection. Dosage is determined by the patient's circulating IgE levels. The cost is high compared with that of other modes of therapy. Investigational use has demonstrated efficacy in AR, although relative efficacy is unknown. Its use is best limited to those with concurrent asthma and AR until further data is known.[7,33]

Complementary and Alternative Medicine (CAM) Therapy. Complementary and alternative therapy for AR has been reviewed.[34] For example, capsaicin (Capsicum annum), once regarded as CAM, in the form of a nasal spray is being investigated as a possible agent in treatment of AR.[35] Previous data behind this compound was inconclusive, citing the need for future studies.[36] Consistent evidence for efficacy has not been established, and there are some safety concerns.

Patient Encounter 1, Part 3

About 6 months later, Kim and Mr. Z come back to speak with you. Kim is getting nose bleeds occasionally and stopped wanting to use any nasal product and only uses the OTC antihistamine you originally recommended. She is due to see her pulmonologist for a follow-up visit. She still has nasal symptoms (rhinorrhea, some congestion) and eye itching. Her allergies are now beginning to affect her asthma with some additional use of her albuterol over the last couple of weeks (ie, used 1 time each week at night, with relief of symptoms).

What suggestions would you offer for control of Kim's symptoms, now? What should be monitored?

Immunotherapy

Immunotherapy could be considered a type of pharmacotherapy. Allergen-specific immunotherapy (SIT) involves repetitive dosing of allergen(s). This approach to treatment can be considered for patients with moderate–severe AR, especially those who have limited response to usual therapy (eg, intranasal steroid, antihistamine) and limiting environmental exposure.[37–39] Immunotherapy is almost always initiated by an allergist or otolaryngologist, after referral for specific allergen testing to determine individualized therapy. This type of therapy is intended for patients with IgE-mediated AR by history and confirmed with specific allergen testing.[8] Historically, immunotherapy was considered for patients in three categories.[5] The first were those with severe, complicated or worsening rhinitis. This was partly for additional diagnostic testing to rule out nonallergic causes of rhinitis. The second were those patients with AR who did not tolerate or responded poorly to appropriate pharmacotherapy. The third were those patients who had a single, or one major allergen identified, for which there was an immunotherapy product available for treatment. In addition, some patients requested immunotherapy, on the basis of superior and durable effectiveness.

Currently, the role of any other health care provider is limited to referral of appropriate candidates to allergy specialists.[35]

Currently, SIT can be done via subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). The major advantage of SLIT over SCIT is ease of administration. Possible adverse effects of SLIT include oral or ear pruritis, throat irritation, tongue pruritis, and mouth edema, with decrease in occurrence and severity of such events in subsequent years of treatment. Potential adverse effects of SCIT include local injection reactions, systemic reactions, and rare, allergic, anaphylaxis reactions. The first dose of immunotherapy is given

Patient Encounter 2, Part 1

Jane D is 30 years old, married, with two children. She works full time as a museum curator for the local museum and has moved to the area about a year ago. Both her children, ages 6 and 10 years, are in school. She has allergies, which she jokingly states that she's "allergic to her work" as it is the dust from artifacts and displays that make her sneeze and have itchy, watery eyes. She is currently on cetirizine 10 mg daily and mometasone nasal spray. She has found that she is sleepier since starting cetirizine about a month ago. Prior to cetirizine, she was on loratadine. She tried taking the cetirizine at night but she still feels quite drowsy in the morning.

What additional information do you need to better evaluate Jane D?

What preliminary suggestions would you make?

in the prescriber's office, for purposes of safety. Subsequent doses are self-administered by the patient. SCIT is always done under medical supervision, requiring regular clinic visits and observation after SCIT administration.[8,40,41] Potential risk factors for SLIT-associated anaphylaxis include previous systemic reaction to SCIT, severe or uncontrolled asthma, acute infection, interruption of dose regimen, and oral lesions.[37]

As of July 2017, four products have been FDA approved for administration as SLIT. There are currently two products for grass pollen, Oralair and Grastek. Oralair contains a mixure of pollens from Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass, and is approved for adults and children ages 10 years and older.[42] Grastek, which contains only Timothy grass pollen, is approved for adults and children ages 5 years and older.[43] Ragwitek is a SLIT for short ragweed pollen, approved for adults ages 18 to 65 years.[44] Odactra, the SLIT for house dust mites, is approved for adults ages 18 to 65 years.[45]

Special Populations

▶ *Children*

LO 6

KEY CONCEPT Generally speaking, the treatment of AR in children is the same as it is for adults. There are, however, limitations in terms of FDA-approved products for different age groups. Also, depending on the age of the patient, there may be administration issues with some products. Most children affected by AR are more than 2 years old, because usually, several years of antigen exposure is required to establish sensitization. Children who have rhinitis before the age of 2 should be evaluated for other etiologies.[7,46]

There has been concern about use of combination cough and cold products (many contain an antihistamine and a decongestant) in children due to side effects. Most negative outcomes have resulted from inadvertent overdosage, often by giving the same drug from more than one product concurrently. These products are discouraged in children less than 4 years old.[47]

First-generation H_1 antihistamines are discouraged for children as they are for adults, due to the possible detrimental effects on school performance and learning. They may also cause paradoxical CNS stimulation in the very young (< 2 years old).[20,46]

Second-generation (less sedating) H_1 antihistamines (primarily for mild or intermittent symptoms) or INCSs (for moderate–severe or persistent manifestations) are first-line modes of therapy. Antihistamines may need to be used even for more severe and/or persistent symptoms in those children who have difficulty with use of intranasal products. If necessary, these two classes can be combined.[46] See Table 63–7 for dosages of second-generation antihistamines by age groups for which they are indicated. Special care should be given to avoid administration of the same medication from different (especially combination) products. The side effects of second-generation antihistamines in children are similar to those for adults.

See Table 63–5 for dosages of INCSs by age groups. The consensus of opinion about INCSs and systemic side effects, especially delay in growth, is that most products are safe. Three INCSs, mometasone, fluticasone furoate, and triamcinolone, are FDA approved for children as young as 2 years of age.[18] The local side effects of INCSs are the same in children as for adults.

Other therapy options may be worth consideration for some pediatric patients. Montelukast provides an oral alternative, especially for those who are too young to cooperate with intranasal administration of corticosteroids.[7–10,46] It may be used in combination with an oral antihistamine for additional efficacy.[7–10] Another option for mild or intermittent symptoms is intranasal cromolyn, primarily due to its excellent safety.[46] This OTC product is labeled for use in children 2 years of age and older.[17,46] Intranasal ipratropium is indicated for patients 6 years of age or older and may benefit unresponsive rhinorrhea.[46]

▶ *Pregnant Women*

LO 6

Women who have AR may suffer an exacerbation of symptoms during pregnancy.[5,48] However, only minor changes in the routine approach to therapy are necessary as a result of the pregnancy. Nasal saline irrigations are safe, effective, and improve the response to most other modes of therapy. They can be the foundation of AR therapy for pregnant patients.[5,48] Physical exercise increases vasoconstriction of the nasal mucosa, decreasing congestion and rhinorrhea.[38] External adhesive strips can be used to help keep the nares open, especially during sleep.[48] Second-generation antihistamines are generally considered safe, based on an increasing number of studies and experience.[5,48] While budesonide is the only product which is FDA pregnancy category B, data is somewhat lacking regarding fetal harm from either INCSs or inhaled corticosteroids.[20,49,50] Cromolyn is also FDA pregnancy category B and is considered safe.[20,47] The disadvantages are frequent administration and less efficacy than antihistamines and INCSs. Montelukast is also FDA pregnancy category B, but some recommend it primarily in those with concurrent asthma or who have demonstrated a good response prior to pregnancy.[7,19] Ipratropium is FDA pregnancy category B, and is useful for troublesome rhinorrhea.[10,19] Oral decongestants are best avoided, especially in the first trimester. If nasal congestion is severe enough to warrant a decongestant, the intranasal route of administration is preferable, due to decreased systemic exposure.[7,48] Limiting the duration of use to 2 to 3 days is wise.[7,48]

▶ *Breast-Feeding Women*

LO 6

There is available information about the relative safety of AR medication use in breast feeding women.[19,51] Budesonide is probably the safest INCS and loratadine is probably the safest antihistamine. Intranasal cromolyn is also considered safe. Nasal

Table 63–8

Intraocular Medications

Category	Generic (Brand) Name	Formulation	Frequency	Age
Decongestant/vasoconstrictor	Naphazoline[a] (Naphcon, Privine, others)	0.012% + 0.025%	Four times daily	Adult
Decongestant/vasoconstrictor + antihistamine	Naphazoline + pheniramine[a] (Visine A)	0.025%/0.3%	Four times daily	6 yo or more
Antihistamine	Emedastine (Emadine)	0.05%	Four times daily	3 yo or more
	Alcaftadine (Lastacaft)	0.25%	Once daily	2 yo or more
Mast cell stabilizer	Cromolyn (generic)	4%	Every 4–6 hours	4 yo or more
	Lodoxamide (Alomide)	0.1%	Four times daily	2 yo or more
	Nedocromil (Alocril)	2%	Twice daily	3 yo or more
	Pemirolast (Alamast)	0.1%	Four times daily	3 yo or more
Antihistamine + mast cell stabilizer	Azelastine (Optivar)	0.05%	Twice daily	3 yo or more
	Epinastine (Elestat)	0.05%	Twice daily	2 yo or more
	Ketotifen[a] (Zaditor, Alaway, Claritin, Zyrtec, generic)	0.025%	Every 8–12 hours	3 yo or more
	Olopatadine (Patanol/Pataday)	0.1%/0.2%	Twice daily/once daily	3 yo or more
	Bepotastine (Bepreve)	1.5%	Twice daily	2 yo or more
NSAIDs	Ketorolac (Acular)	0.5%	Four times daily	3 yo or more
Corticosteroid	Loteprednol (Alrex)	0.2%	Four times daily	Adult

[a]Available OTC.

Also, see Chapter 62, Ophthalmic Disorders, for more details.

NSAID, nonsteroidal anti-inflammatory drug; yo, years old.

From Refs. 7, 19, and 20.

saline irrigation could also be considered as a safe alternative in breast-feeding women.

▶ *Elderly*

LO 6

AR in elderly patients is treated generally as it is in younger adults; however, consideration of increased risk for certain side effects (eg, antimuscarinic) should weigh into therapy choices. Therefore, first-line agents are primarily INCSs and second-generation oral or possibly intranasal antihistamines.[5,7] Older patients may also have a component of atrophy of nasal tissues that can result in more nasal congestion. Most will benefit from regular nasal saline irrigation.[5] The elderly are more sensitive to the sedative and antimuscarinic effects of (especially first-generation) antihistamines and to the cardiovascular and CNS stimulant effects of decongestants. These drugs should be used cautiously if at all. An increase in cholinergic activity may result in more rhinorrhea. This may respond well to ipratropium.

Patient Encounter 2, Part 2

Jane D returns months later after having taken your advice. She is now noticing symptoms no matter where she is, especially when outdoors. She was prescribed a combination nasal corticosterioid and antihistamine by her primary care physician, but it does not seem to be helping much with her symptoms. She does saline nasal rinses several times a week with limited relief. She has missed work several times in the last few months due to unbearable congestion in addition to her nasal and ocular itching. One of her friends, who has asthma, told her about an injectable medication for asthma that has helped her asthma and allergy symptoms. She asks you, "Would this be something I can take? Would it help me with my allergies?"

What is your explanation to Jane D about her inquiry and what is your recommendation at this time?

Ocular Symptoms

Several products are available for instillation directly into the eyes for those patients with predominant or unresponsive ocular manifestations. They may be appropriate for occasional moderate–severe flares or episodic AR when other modes of therapy are not optimally effective. The combination (antihistamine and mast cell stabilizing) agents may be the most effective, and they have the advantages of rapid onset of action and (usually) only twice daily administration.[5,19,20] Ketotifen is in this category and because it is available OTC, it can be an appropriate initial agent. See Table 63–8 for these products.

Summary of Treatment

LO 5

Once an agent appropriate for initial therapy is chosen, ongoing management requires repeated checks to ascertain response and freedom from intolerable or adherence limiting side effects. Either "step-up" or "step-down" therapy may be appropriate, depending on individual response. See Table 63–9 for a summary of the approach to treatment of AR. Table 63–10 attempts to rank the relative effectiveness of the classes of agents for treatment of AR by specific symptoms.

OUTCOME EVALUATION

- Confirm the patient's understanding of the disorder (see Clinical Presentation and Diagnosis of Allergic Rhinitis).
- Confirm the patient's understanding about allergen avoidance measures (see Table 63–3).

Table 63–9

Routine Approach to Therapy of AR

All patients should practice avoidance of identified allergens

Mild Intermittent

First line:
Oral antihistamine (OTC, initially; preferably second generation)

Adjunctive/secondary (may use more than one; no specific order intended):
- Add nasal saline (eg, as irrigation)
- Consider intranasal cromolyn, especially preexposure for episodic AR
- Consider OTC INCS for refractory symptoms
- Consider intraocular medications, as needed for ocular symptoms (see Table 63–8)
- Consider OTC oral decongestant for nasal congestion
- Consider OTC intranasal decongestant for refractory nasal congestion (not more than 3 days)
- Consider prescription therapy for inadequate response (see below)

Possibly consider referral for immunotherapy

Persistent or Moderate–Severe

First line:
Intranasal corticosteroid
Add oral antihistamine (preferably second generation) for possible additional benefit if necessary

Adjunctive/secondary (may use more than one):
- Add nasal saline (eg, as irrigation)
- Consider intranasal antihistamine
- Consider combination intranasal antihistamine with corticosteroid
- Consider intraocular medications, as needed for ocular symptoms (see Table 63–8)
- Consider OTC oral decongestant for nasal congestion
- Consider short-term intranasal decongestant for refractory nasal congestion
- Consider montelukast
- Consider intranasal ipratropium for inadequately controlled rhinorrhea

Consider referral for immunotherapy

Episodic (no order of preference intended)
Oral antihistamine (OTC, initially; preferably second generation)
Consider addition of or replacement with intranasal cromolyn (OTC) or intranasal antihistamine or intranasal corticosteroid

Special Situations (children, pregnant women, elderly, ocular symptoms)
See Special Populations section of text

From Refs. 6–10, 46, and 48.

Table 63–10

Relative Efficacy (Semiquantitative) by Classes of Agents for Specific Symptoms of Allergic Rhinitis

Drug Class	Nasal Congestion	Sneezing	Rhinorrhea	Nasal Itch	Ocular Symptoms
Intranasal corticosteroids[a]	+++	+++	+++	+++	+
Oral antihistamines[a]	+	++	++	++	++
Intranasal antihistamines	++	++	++	++	+
Oral decongestants[a]	++	0	0	0	0
Intranasal decongestants[a,b]	+++	0	0	0	0
Oral leukotriene antagonist	++	+	++	+	++
Intranasal mast cell stabilizer[a]	++	++	++	++	++
Intranasal antimuscarinic	0	0	++	0	0

[a]Some products in these classes are available OTC.

[b]Intranasal decongestants are best used for severe, unresponsive nasal congestion, or to facilitate mucosal contact of other intranasal medications, but in either case, should usually be limited to no more than 3 days.

Note: There are different opinions about some of the rankings, partly due to inadequate study. Individual variation may create different relative efficacy in some patients. +++ = greatest relative efficacy, 0 = no relative efficacy.

From Refs. 8, 9, and 10.

Patient Encounter 2, Part 3

It is now several years later. Jane D's AR is under control after seeing the allergy specialist. She has not needed to see the specialist for over a year now, but comes to you with a question about medications and family planning. She has read that women sometimes have increased allergy symptoms in pregnancy and given her history, feared this would be something she will face. She asks which OTC allergy medications are safest while she is trying to become pregnant and once she is pregnant.

What do you recommend and why?

- Assess the patient's symptom response, tolerance, and adherence.
- Assess the patient's administration technique with intranasal products.
- Recommend second-generation oral antihistamine therapy for most patients with mild or intermittent symptoms (see Clinical Presentation and Diagnosis of Allergic Rhinitis and Table 63–9).
- Recommend INCS therapy for moderate–severe or persistent symptoms. Suggest additional therapy for those with incomplete control (see Clinical Presentation and Diagnosis of Allergic Rhinitis and Table 63–9).
- Consider step-up therapy for exacerbations or incomplete response.
- Consider step-down therapy if symptoms are minimal or stable for several months.
- Consider referral to rule out nonallergic causes of rhinitis in nonresponding patients or those with an atypical presentation (see Clinical Presentation and Diagnosis of Allergic Rhinitis).
- Consider referral for patients who request immunotherapy.
- Consider referral for patients with comorbid conditions, especially asthma.

Patient Care Process

Collect Information:

- Collect information from the history of present illness (HPI), past medical history (PMHx), and physical assessment. HPI includes location, onset, quality, quantity, setting, associated symptoms, and modifying factors (see Clinical Presentation and Diagnosis of Allergic Rhinitis). PMHx should include conditions associated with AR and its complications (see Epidemiology section). Physical assessment includes observation of patient and examination of nasal mucosa (see Clinical Presentation and Diagnosis of Allergic Rhinitis).
- Identify therapies attempted and their efficacy.
- Determine additional considerations in treatment (eg, pregnancy, lactation, child or elderly; see Selected Populations section).

Assess the Information:

- Rule out nonallergic type of rhinitis (see Table 63–1).
- Determine extent and severity of patient's assessing frequency and severity of AR symptoms (see Clinical Presentation and Diagnosis of Allergic Rhinitis and Table 63–2).
- Determine the patient's understanding of AR.
- Assess response to past and current AR treatment. If clinical response is inadequate assess adherence and technique. See Table 63–6. If nonadherence and poor technique do not explain suboptimal response, consider alternative treatments or specialist referral. See Table 63–9.

Develop a Care Plan:

- Advise allergen avoidance. See Table 63–3.
- Review optimal administration technique and adherence.
- Base therapy recommendations on symptoms and response to current and past treatment.

Implement the Care Plan:

- For mild AR where OTC agents can be used, provide patient with recommended therapy including drug name, dose, and dosing frequency. Educate on appropriate administration, expected outcomes, and possible side effects.
- For moderate to severe AR where physician management is likely needed, communicate recommendations to primary care provider and assist with follow-up if needed by monitoring patient symptoms control and treatment of side effects.

Follow up: Monitor and Evaluate:

- Follow up weekly at first, especially during worse times/seasons for change in symptoms and possible side effects.
- When optimal control is approached, increase duration between follow-up visits (eg, monthly, every 2–3 months, or less frequently).

ACKNOWLEDGMENT

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Abbreviations Introduced in This Chapter

AAAAI	American Academy of Allergy, Asthma, and Immunology
ACAAI	American College of Allergy, Asthma, and Immunology
ACEI	Angiotensin-converting enzyme inhibitor
AERD	Aspirin-exacerbated respiratory disease
AR	Allergic rhinitis
ARIA	Allergic rhinitis and its impact on asthma
BPH	Benign prostatic hyperplasia/hypertrophy
BTC	Behind-the-counter
CHPA	Consumer Health Protection Agency
H_1	Histamine type 1 (receptor)
HEPA	High-efficiency particulate air (filter)

HFA	Hydrofluoroalkane ("green" propellant for metered-dose INCSs)
HPA	Hypothalamic–pituitary–adrenal (axis)
HPI	History of present illness
HTN	(essential or primary) hypertension
IAR	Intermittent allergic rhinitis (ARIA system)
IgE	Immunoglobulin E
INCS(s)	Intranasal corticosteroid(s)
LTRA	Leukotriene receptor antagonist
MDP	metered-dose pump
NARES	Nonallergic rhinitis with eosinophilia [on nasal smear] syndrome
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
PAR	Perennial allergic rhinitis (AAAAI/ACAAI system)
PDE-5	Phosphodiesterase (isoenzyme)-5
PER	Persistent allergic rhinitis (ARIA system)
PMHx	Past medical history
QT	Interval between the Q and T waves in an ECG
SAR	Seasonal allergic rhinitis (AAAAI/ACAAI system)
SCIT	Subcutaneous immunotherapy
SIT	Allergen-specific immunotherapy
SLIT	Sublingual immunotherapy

REFERENCES

1. Dion GR, Weitzel EK, McMains KC. Current approaches to diagnosis and management of rhinitis. South Med J. 2013;106(9):526–531.
2. Ng ML, Warlow RS, Chrishanthan N, Ellis C, Walls R. Preliminary criteria for the definition of allergic rhinitis: a systematic evaluation of clinical parameters in a disease cohort (I). Clin Exp Allergy. 2000;30:1314–1331.
3. Ng ML, Warlow RS, Chrishanthan N, Ellis C, Walls R. Preliminary criteria for the definition of allergic rhinitis: a systematic evaluation of clinical parameters in a disease cohort (II). Clin Exp Allergy. 2000; 30:1417–1422.
4. Papadopoulos NG, Guibas GV. Rhinitis subtypes, endotypes, and definitions. Immunol Allergy Clin North Am. 2016;36(2):215–233.
5. Corren J, Baroody FM, Pawankar R. Allergic and nonallergic rhinitis. In: Adkinson Jr NF, Bochner BS, Burks WA, et al., eds. Middleton's Allergy—Principles and Practice, 8th ed. Philadelphia: Saunders-Elsevier; 2014:664–685.
6. Bernstein DI, Schwartz G, Bernstein JA. Allergic rhinitis: mechanisms and treatment. Immunol Allergy Clin North Am. 2016;36(2):261–278.
7. Dykewicz MS, Wallace DV, Baroody F, et al.; Workgroup Chair and Cochair, Dykewicz MS, Wallace DV. Treatment of seasonal allergic rhinitis: an evidence-based focused 2017 guideline update. Ann Allergy Asthma Immunol. 2017;119(6):489–511.e41.
8. Seidman MD, Gurgel RK, Lin SY, et al; Guideline Otolaryngology Development Group. AAO-HNSF. Clinical practice guideline: allergic rhinitis. Otolaryngol Head Neck Surg. 2015;152 (1 suppl):S1–S43.
9. Brożek JL, Bousquet J, Agache I, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. J Allergy Clin Immunol. 2017;140(4):950–958.
10. Angier E, Willington J, Scadding G, Holmes S, Walker S; British Society for Allergy & Clinical Immunology (BSACI) Standards of Care Committee. Management of allergic and non-allergic rhinitis: a primary care summary of the BSACI guideline. Prim Care Respir J. 2010;19(3):217–222.
11. Braun-Fahrlander C. Environmental exposure to endotoxin and other microbial products and the decreased risk of childhood atopy: evaluating developments since April 2002. Curr Opin Allergy Clin Immunol. 2003;3:325–329.
12. Matheson MC, Dharmage SC, Abramson MJ, et al. Early-life risk factors and incidence of rhinitis: results from the European Community Respiratory Health Study—an international population-based cohort study. J Allergy Clin Immunol. 2011; 128(4):816–823.e5.
13. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet. 2011;378:2112–2122.
14. Scadding GK, Scadding GW. Diagnosing allergic rhinitis. Immunol Allergy Clin North Am. 2016;36(2):249–260.
15. Costa DJ, Amouyal M, Lambert P, Schünemann HJ, Daures JP, Bousquet J, Bousquet PJ; Languedoc-Roussillon Teaching General Practitioners Group. How representative are clinical study patients with allergic rhinitis in primary care? J Allergy Clin Immunol. 2011;127(4):920–926.
16. Rabago D, Zgierska A. Saline nasal irrigation for upper respiratory conditions. Am Fam Physician. 2009;80(10):1117–1119.
17. Saline sinus rinse recipe. American Academy of Allergy Asthma & Immunology. Available from: https://www.aaaai.org/conditions-and-treatments/library/allergy-library/saline-sinus-rinse-recipe. Accessed July 27, 2017.
18. Kirtsreesakul V, Chansaksung P, Ruttanaphol S. Dose-related effect of intranasal corticosteroids on treatment outcome of persistent allergic rhinitis. Otolaryngol Head Neck Surg. 2008;139(4):565–569.
19. Wolters Kluwer Clinical Drug Information, Inc. (Lexi-Drugs). Wolters Kluwer Clinical Drug Information, Inc.; July 25, 2017.
20. Drugs for allergic disorders. Treat Guidel Med Lett. 2013;11(129):43–52.
21. How to use nasal sprays properly. Safe Medication. American Society of Health-System Pharmacists. Available from: http://www.safemedication.com/safemed/MedicationTipsTools/HowtoAdminister/HowtoUseNasalSpraysProperly. Accessed July 25, 2017.
22. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. J Investig Allergol Clin Immunol. 2012;22(1):1–12.
23. Ahmet A, Kim H, Spier S. Adrenal suppression: a practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. Allergy Asthma Clin Immunol. 2011;7:13.
24. Hasala H, Moilanen E, Janka-Junttila M, Giembycz MA, Kankaanranta H. First-generation antihistamines diphenhydramine and chlorpheniramine reverse cytokine-afforded eosinophil survival by enhancing apoptosis. Allergy Asthma Proc. 2007;28(1):79–86.
25. Brier ME, Aronoff GR, eds. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children, 5th ed. Philadelphia, PA: American College of Physicians, 2007.
26. Golightly LK, Teitelbaum I, Kiser TH, et al., eds. Renal Pharmacotherapy—Dosage Adjustment of Medications Eliminated by the Kidneys. New York: Springer, 2013.
27. De Weck AL, Derer T, Bähre M. Investigation of the anti-allergic activity of azelastine on the immediate and late-phase reactions to allergens and histamine using telethermography. Clin Exp Allergy. 2000;30(2):283–287.
28. Azelastine/Fluticasone propionate (Dymista) for seasonal allergic rhinitis. Med Lett Drugs Ther. 2012;56(1402):85–87.
29. Meltzer EO, Ratner PH, McGraw T. Oral phenylephrine HCl for nasal congestion in seasonal allergic rhinitis: a randomized, open-label, placebo-controlled study. J Allergy Clin Immunol Pract. 2015;3(5):702–708.
30. Ramey J, Bailen E, Lockey R. Rhinitis medicamentosa. J Investig Allergol Clin Immunol 2006;16(3):148–155.
31. Lockey RF. Rhinitis medicamentosa and the stuffy nose. J Allergy Clin Immunol. 2006;118:1017–1018.
32. Updated Information on Leukotriene Inhibitors: Montelukast (marketed as Singulair), Zafirlukast (marketed as Accolate),

and Zileuton (marketed as Zyflo and Zyflo CR). Available from: https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforheathcareprofessionals/ucm165489.htm. Accessed July 25, 2017.
33. Tsabouri S, Tseretopoulou X, Priftis K, Ntzani EE. Omalizumab for the treatment of inadequately controlled allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. J Allergy Clin Immunol Pract. 2014;2:332–340.
34. Kern J, Bielory L. Complementary and alternative therapy (CAM) in the treatment of allergic rhinitis. Curr Allergy Asthma Rep. 2014;14(12):479.
35. Ricketti PA, Alan, Alandijani S, Lin CH, Casale TB. Investigational new drugs for allergic rhinitis. Expert Opin Investig Drugs. 2017;26(3):279–292.
36. Cheng J, Yang XN, Liu X, Zhang SP. Capsaicin for allergic rhinitis in adults. Cochrane Database Syst Rev. 2006;(2):CD004460.
37. Meltzer EO. Hot topics in primary care: sublingual immunotherapy: a guide for primary care. J Fam Pract. 2017; 66(4 suppl):S58–S63.
38. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 suppl):S1–S55.
39. Kim JM, Lin SY, Suarez-Cuervo C, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. Pediatr. 2013;131(6):1–13.
40. Lin SY, Erekosima N, Kim JM, et al. Sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma—a systematic review. JAMA. 2013;309(12):1278–1288.
41. Chelladurai Y, Suarez-Cuervo C, Erekosima N, et al. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. J Allergy Clin Immunol Pract. 2013;1(4):361–369.
42. Oralair [package insert]. GREER Laboratories, Inc. Lenoir, NC; 2014. Available from: https://www.oralairhcp.com/wp-content/uploads/2017/06/ORALAIR_Prescribing_Information.pdf. Accessed July 25, 2017.
43. Grastek [package insert]. Merck and Co Inc. Whitehouse Station, NJ; 2014. Available from: https://www.grastek.com/app/uploads/sites/3/2016/12/grastek_pi.pdf. Accessed July 25, 2017.
44. Ragwitek [package insert]. Merck and Co Inc. Whitehouse Station, NJ; 2014. Available from: https://www.ragwitek.com/app/uploads/sites/4/2016/12/ragwitek_pi.pdf. Accessed July 25, 2017.
45. Odactra [package insert]. Merck and Co Inc. Whitehouse Station, NJ;2017. Available from: https://www.fda.gov/downloads/biologicsbloodvaccines/allergenics/ucm544382.pdf. Accessed July 25, 2017.
46. Natale SD, Shah NN. Allergies and anaphylaxis. In: Benavides S, Nahata MC, eds. Pediatric Pharmacotherapy, 1st ed. Lenexa: American College of Clinical Pharmacy; 2013:718–735.
47. Use caution when giving cough and cold products to kids. U.S. Department of Health & Human Services. U.S. Food and Drug Administration. Drugs. Available from: https://www.fda.gov/drugs/resourcesforyou/specialfeatures/ucm263948.htm. Accessed July 25, 2017.
48. Schatz M, Zeiger RS, Falkoff R, et al. Asthma and allergic diseases during pregnancy. In: Adkinson NF, Bocher BS, Burks AW, et al., eds. Middleton's Allergy: Principles and Practice, 8th ed. Philadelphia: Elsevier; 2014:951–969.
49. Rahimi R, Nikfar S, Abdollahi M. Meta-analysis finds use of inhaled corticosteroids during pregnancy safe: a systematic meta-analysis review. Hum Exp Toxicol. 2006; 25:447–452.
50. Bérard A, Sheehy O, Kurzinger ML, Juhaeri J. Intranasal triamcinolone use during pregnancy and the risk of adverse pregnancy outcomes. J Allergy Clin Immunol. 2016;138(1): 97–104.e7.
51. Hale TW. Medications and Mothers' Milk—A Manual of Lactational Pharmacology—2017, 17th ed. Amarillo, TX: Hale Publishing, Inc.; 2017.

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64 Psoriasis

Amy Kennedy

LEARNING OBJECTIVES

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

1. Discuss the etiology of, and risk factors for, psoriasis.
2. Describe the pathophysiology and clinical presentations of psoriasis.
3. Delineate treatment goals for each patient.
4. Develop an appropriate treatment and care plan for psoriasis patients.
5. Recommend nonpharmacologic and pharmacologic treatments for psoriasis.
6. Recommend appropriate monitoring parameters for a patient diagnosed with psoriasis.
7. Provide patient education for patients and caregivers as part of the care plan.

INTRODUCTION

KEY CONCEPT Psoriasis is a chronic inflammatory condition that exhibits a cyclical pattern of relapse and remission. There is currently no cure for the disease and treatment is designed to manage signs and symptoms associated with the disease.[1] Remission may last for years in some patients, whereas, in others, exacerbations may occur as frequently as every few months. Patient factors known to exacerbate the condition are stress, environmental factors including seasonal changes, and certain medications.[2] Depression, alcohol-related problems, cardiovascular diseases, metabolic syndrome, irritable bowel disease (Crohn disease and ulcerative colitis), and skin cancers are select comorbidities associated with the severe form of psoriasis.[1] The severity of the condition ranges from mild to severely disabling. Thus management of patients with psoriasis is lifelong and treatment approaches may change according to the severity of illness at the time. Treatment modalities should be individualized to meet patient needs. The disease may result in emotional distress that requires empathy, a caring attitude, and consideration when weighing treatment approaches.

EPIDEMIOLOGY AND ETIOLOGY

Psoriasis is a common chronic inflammatory skin disorder with a population prevalence of 2% to 3% worldwide. The prevalence found in the United States is approximately 2.1%, while African, African American, and Asian populations have an estimated 0.4% to 0.7% prevalence of the disease.[3] This difference may be attributed to genetic variations of the disease. While the overall incidence rate does not differ between men and women, male patients tend to die at least 3.5 years earlier and females 4.5 years earlier than nonpsoriasis patients normalized for differences in mortality by gender.[3] The disease may present at any age, but new diagnoses peak between ages 15 and 30 and again from 50 to 60 years.[3] Psoriasis can manifest as several different types including **plaque**, **flexural** (aka inverse or intertriginous), **erythrodermic**, **pustular**, **guttate**, **nail**, and **psoriatic arthritis (PsA)**. Eighty to ninety percent of patients diagnosed with psoriasis present with plaque psoriasis. Plaque psoriasis presents with red-pink lesions of varying sizes covered with silvery-white scales (**Figure 64–1**).[2] Up to 42% of patients with psoriasis have co-occurring PsA.[1,4] PsA is limited to joints, ligaments, and tendons, and clinical presentation includes pain, stiffness, swelling, and/or tenderness in the affected area. PsA progresses from mild symptoms to the destruction of joints, negatively impacting quality of life for patients.

Recent research has shown that psoriatic patients have an increased risk of cardiovascular disease, especially myocardial infarction (MI).[4-6] Risk is present in both mild and severe disease, with the highest risk in younger patients with severe psoriatic disease.[6] These findings persist even when corrected for other cardiovascular risk factors.[5-7]

In 2012, the first gene directly linked to psoriasis was identified. Through the use of the National Psoriasis Foundation biobank, researchers identified that a mutation in the CARD14 gene, when activated by an environmental trigger, led to plaque psoriasis.[8] Up to 36 additional gene loci are suspected to be involved in the manifestation of psoriasis and the histocompatibility complex region of chromosome 6 (HLA-Cw*06) has been suspected in the disease.[9] KEY CONCEPT While genetic variations have a significant role, modifiable risk factors greatly impact the likelihood of developing or exacerbating existing psoriasis. These include stress, skin injury (including trauma), medications, infection, obesity, tobacco, and cold, dry weather. First-degree relatives with psoriasis can increase risk of presentation, affecting males more than females. Women exposed to tobacco smoke have a higher risk of developing psoriasis than their male counterparts with the same exposure. Risk is also found to be higher in urban settings versus rural settings. Additional factors exacerbating psoriasis include drugs such as lithium, nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, β-adrenergic blockers, and corticosteroid withdrawal.[10]

PATHOPHYSIOLOGY

The pathogenesis of psoriasis involves multiple components of the immune system. Cytokines such as interleukins and tumor necrosis factor-α (TNF-α), T cells, and keratinocytes are

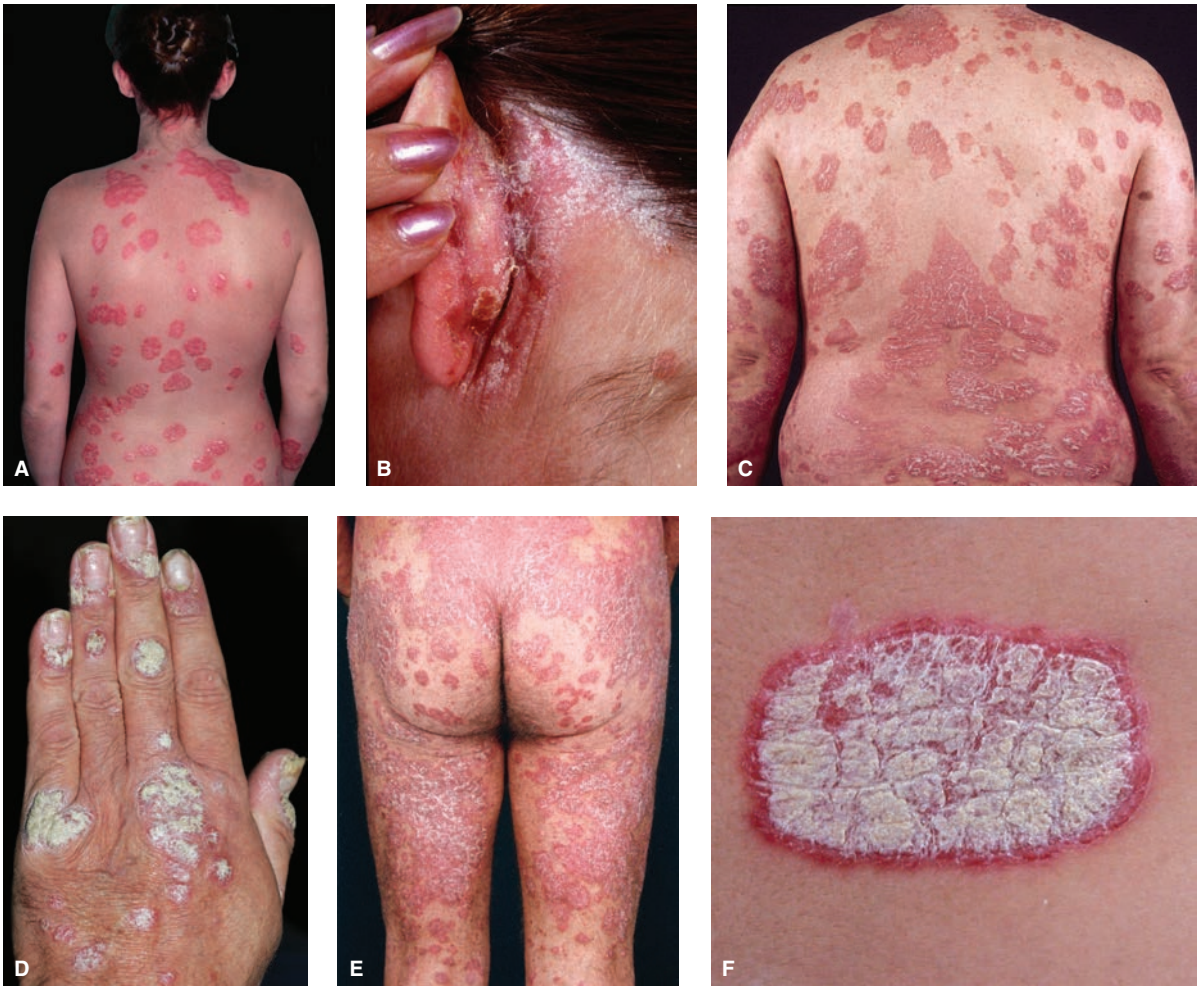

FIGURE 64–1. Chronic plaque psoriasis located at typical sites. Note marked symmetry of lesions. (From Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, eds. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York, NY: McGraw-Hill; 2012. Photos used with permission from Dr. Johann Gudjonsson and Mr. Harrold Carter.)

central to the inflammatory process associated with psoriasis. Additionally, it has been found that when keratinocytes are disturbed, the release of antimicrobial peptide LL-37 takes place. This peptide binds with DNA and RNA. This complex potentially leads to the activation of plasmacytoid and myeloid dendritic cells. These activated dendritic cells secrete interleukin (IL)-12 and IL-13. The production of these two interleukins eventually results in IL-17 and T helper cell type 1 differentiation.[2] The T cells then release IL-17A, IL-17F, IL-22, and IL-23 as mediators which then subsequently activate keratinocytes. This process then generates a complex cascade including proinflammatory cytokines such as TNF-α, interferon (IFN-α and IFN-γ), and interleukin (IL-1β and IL-6). The entire process then leads to alteration of the immune system and chronic inflammation that manifests in the skin causing vascular changes and formation of psoriatic lesions.[2] Hyperkeratosis that results from immune derangements causes the characteristic thick, scaly skin lesions seen in patients with psoriasis. The pathologic pathway of PsA is the same, except that the changes that occur as a result of T-cell mediators happen in the synovial fluid within the joints. Osteoclast activation, osteolysis, and bone resorption produce the damage that occurs within the joints.[2]

LO 2

LO 2

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Diagnosis of psoriasis is usually based on recognition of the characteristic plaque lesion and is not based on lab tests.

The severity of the disease is classified as mild/limited disease, moderate, or severe disease based on body surface area (BSA) involvement (Table 64–1). Additionally, classification may be based on assessment tools used such as the Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI).[11,12]

Table 64–1

Disease Severity Classification[11,12]

Mild or limited disease	Less than or equal to 5% BSA involvement
Moderate disease	PASI greater than or equal to 8 (higher in trials of biologics)
Severe disease	The Rule of Tens: PASI ≥ 10 or DLQI ≥ 10 or BSA ≥ 10% (in some phototherapy trials, BSA ≥ 20% is used as the lower limit)

BSA, body surface area; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.

Clinical Presentation and Diagnosis of Plaque Psoriasis

General Characteristics

Small, discrete lesions to generalized confluent lesions over a large body surface area (BSA)

Symptoms

Severe itching (some patients will not experience)

Signs

- Raised lesion red to violet in color (commonly known as plaques)
- Sharply demarcated borders lesions, except where confluent
- Lesions are loosely covered with silvery-white scales, which, if lifted off, show small pinpoints of bleeding (Auspitz sign).
- Plaques appear on the elbows, knees, scalp, umbilicus, and lumbar areas, and often extend to involve the trunk, arms, legs, face, ears, palms, soles, and nails.
- Nail involvement presents as pitting, discoloration ("oil spots"), crumbling, splinter hemorrhages, growth arrest lines, or tissue buildup around the nails.

Patient Encounter Part 1

GG is a 32-year-old woman who has noticed red lesions that flake covering her elbows, back of knees, and scalp. When questioned, the patient says her skin has been relatively clear, until about 3 months ago. Since then, the lesions have been becoming more noticeable, increasing in size. She is feeling self-conscious about what is happening and does not know what to do.

FH: Mother has psoriasis and rosacea. Father has hypertension. Younger brother has depression and Type 1 diabetes.

SH: GG is in a same sex partnership with 2 children: ages 5 and 3. She works for the city parks department and routinely forgets to wear sunscreen. She does not drink and admits to smoking on her lunch breaks.

Meds: Multivitamin daily

PE:

Gen: She appears very distressed about the lesions.

VS: BP 124/77 mm Hg, P 98 beats/min, RR 20 breaths/min, T 37.0°C (98.6°F), Ht 5'3" (160 cm), Wt 175 lb (79.5 kg)

Abd: Soft, NTND; (+) bowel sounds

Exts: Within normal limits; no joint pains; lesions covering both elbows

Skin: Red lesions with silvery scale on elbows, knees, and scalp (BSA 4%)

Labs: All within normal limits, including lipids, renal function tests, and LFTs

What type of psoriasis is GG experiencing?

What risk factors does she have for psoriasis?

TREATMENT

Desired Outcomes and Goals

KEY CONCEPT Given its manifestations, inflammation, involvement of multiple areas of the affected skin, and the chronic nature of psoriasis, treatment goals must be individualized to each patient. The goals of treatment must be set based on clinical presentation, disease-related comorbidities, treatment-related morbidity, mortality, quality of life, staging of the disease, and remission status of the disease at any given point in time.[4,11-13] It is imperative to remember that no cure currently exists for any type of psoriatic disease. However, evidence shows that current treatment options increase remission periods and reduce severity of the disease.[13] The treatment goals should include the following:

LO 3

- Minimize or eliminate, when possible, the signs of psoriasis, such as plaques and scales.
- Alleviate pruritus and minimize excoriations when present.
- Extend remission cycles.
- Ensure appropriate management of associated comorbidities such as PsA, cardiovascular disorders, Crohn disease, or clinical depression.
- Avoid or minimize adverse effects from treatments.
- Provide cost-effective therapy.
- Provide counseling as needed (eg, stress-reduction techniques).
- Maintain or improve the patient's quality of life.

Clinical Presentation and Diagnosis of Other Types of Psoriasis

- Flexural psoriasis:
  - Appears in intertriginous areas
  - Scaling is minimal
- Guttate psoriasis:
  - Sudden eruption of small, disseminated erythematosquamous papules and plaques
  - Often preceded by a streptococcal infection 2 to 3 weeks prior
- Pustular psoriasis:
  - May be localized or generalized
  - May be an acute emergency requiring systemic therapy due to loss of skin integrity
- Generalized pustular psoriasis:
  - Disseminated deep-red erythematous areas and pustules
  - May merge to become "lakes of pus"
- Erythrodermic psoriasis: generalized, life-threatening condition
  - Erythema, desquamation, and edema
  - May require life support measures as well as systemic therapy

General Approach to Treatment

LO 4

The management of the disease should target the type of psoriasis that the patient presents with. General treatment considerations must include disease severity, location, the extent

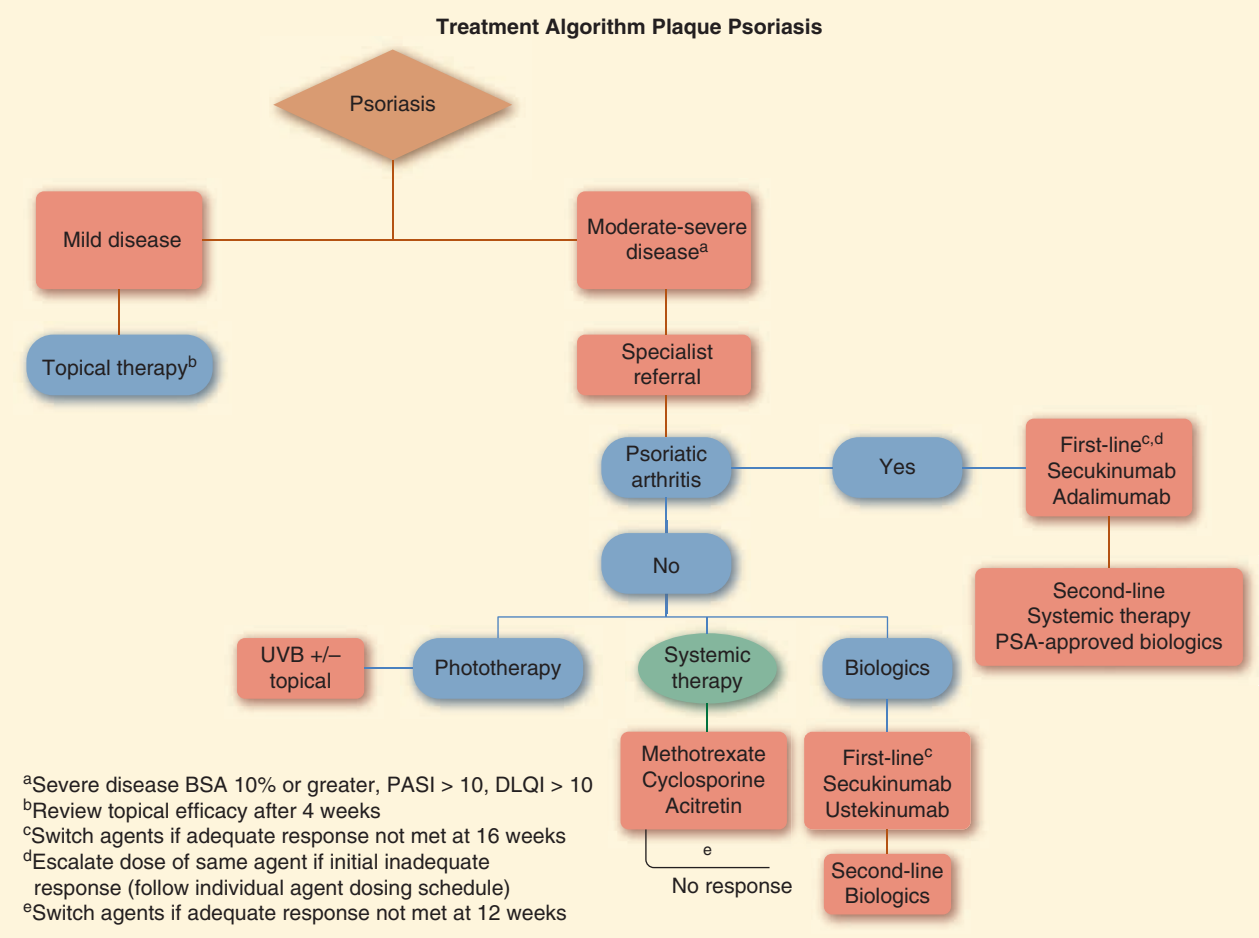

FIGURE 64–2. Treatment algorithm for plaque psoriasis.[4,6,7,15,16,21,28]

of BSA involvement, and pertinent lifestyle modifications.[11] The psychological impact of psoriasis may not correlate with the severity of the skin presentation, and it is important to continually evaluate the psychosocial effects of psoriasis on each patient.[6,7]

LO 4 For PsA the goal of treatment is to reduce pain and swelling, slow down or minimize joint damage, and maintain joint function.[2,4,6,7] KEY CONCEPT Effective psoriasis treatment should include both pharmacologic and nonpharmacologic approaches.[11] See Figure 64–2.

Nonpharmacologic Management

KEY CONCEPT Several effective nonpharmacologic options are available to patients with psoriasis. However, considering the inflammatory nature of the disease, these treatments should be used as adjunctive treatments to therapeutic agents when appropriate.[12]

LO 5 Stress reduction techniques such as psychotherapy, guided imagery, and relaxation techniques have been shown to reduce the extent and severity of psoriasis.[14] Oatmeal baths in tepid water may help soothe the itching associated with psoriasis. Nonmedicated moisturizers (occlusive agents, humectants, and/or emollients) help the skin retain moisture and reduce the silvery-white scaling of skin lesions. Emollients can be applied multiple times during the day to prevent skin dryness. Patients with skin sensitivities should consider the use of fragrance-free products to prevent flareups.[15] Harsh soaps, detergents, and other skin irritants should be avoided as they may worsen symptoms. Skin cleansing is appropriate; however, it should be done with lipid-free cleansers and tepid water when possible. Trauma to the skin must always be avoided as damage to skin integrity can precipitate a flare. Sunburn is one of the most frequent skin traumas that can result in a flare. Consequently, the use of sunscreen with sun protection factor (SPF) of 30 is recommended. Loose-fitting clothes are desired to help reduce skin irritation.[15]

LO 5

Pharmacologic Therapy

The pathogenesis of the disease involves a complex mechanism that disturbs the immune system, causes vascular changes, and results in the development of skin lesions.[2] It is paramount that therapeutic agents that oppose these processes are well represented in the treatment of psoriasis. KEY CONCEPT These agents are anti-inflammatory, anti-cytokines, and biologic therapies. They are classified into topical, phototherapy, conventional systemic therapy, and biologics.[2,11] Several factors must be taken into consideration in identifying the right therapy for a patient with psoriasis. Some of these factors are the affected area of the disease, cost, availability of medication, and the preferred lifestyle of the patient. Full patient history including allergies must be collected to make the chosen therapeutic approach a success. Topical agents are recommended for mild to moderate disease due to their affordability and fewer adverse effects. Low potency corticosteroids are used as first line for mild conditions.

If the condition persists, it is recommended to switch to a very high potency steroid in combination with vitamin D analogue or topical retinoids. In general, a patient disease surface area should be less than 5% to qualify for topical therapy alone. A general recommendation after unsuccessful treatment with topical agents is to add phototherapy. Psoralen and ultraviolet A (PUVA) was found to be more effective than ultraviolet B (UVB) in the treatment of patients with moderate to severe psoriasis.[16] The traditional systemic agents can be used for patients with severe disease and these are often combined with topical therapy to improve effectiveness in these patients. Clinical trials indicate that immunosuppressants are more effective than oral retinoids. Biological agents may be the drug of choice for severe disease depending on patient comorbidities, those intolerant to, or that fail traditional systemic agents. The choice of biologic agents depends on the patient's preference and comorbidities.[17] Psoriasis affecting more than 5% of the BSA should be the justification for initiating systemic/biologic therapy. For patients with liver disease, kidney dysfunction, and skin cancer, it is recommended to avoid methotrexate, cyclosporine, and PUVA treatment, respectively.[18]

► *Topical Treatment*

These agents are first-line treatment for mild to moderate psoriasis (Tables 64–2 and 64–3). They are specifically known for their anti-inflammatory, antiproliferative, and anti-immunologic properties. They are classified as corticosteroids, vitamin D analogues, retinoids, calcineurin inhibitors, coal tar, anthralin, and salicylic acid derivatives. Different dosage forms are available such as creams, lotions, gels, foams, ointments, shampoos, oil solutions, tapes, and sprays. KEY CONCEPT The choice of specific dosage form or vehicle is dependent on several factors including the surface area involved, location, thickness of the lesions, and the appearance of the plaques.[19] Ointments are recommended for dry and thick lesions to enhance absorption and reduce loss of skin moisture. Creams are indicated for acute, but moist appearing, lesions that do not require ointment-based products. Solutions/shampoos and gels are recommended for scalp lesions and foams and sprays are usually used for lesions in genital areas.[15,19]

LO 5

Vehicle selection is an important consideration as it can impact topical efficacy and may vary from one body part to another. Ointments and tapes provide occlusion, enhancing drug penetration to improve efficacy. Shampoos incorporating coal tar distillates or salicylic acid with corticosteroids are useful for scalp psoriasis. Coal tar and salicylic acid are rarely used as lone agents due to tolerability issues related to staining and irritation, respectively. Pastes, such as Lassar's paste, have an inherent stiffness, minimizing the spread of medication, and are useful for incorporating drugs such as anthralin, which, especially in higher concentrations used in short-contact methods, may cause skin irritation and burning if in contact with normal skin. It is important to remember that changing to a different vehicle may significantly alter drug potency. Ultimately, the optimal vehicle may be the vehicle that the patient is willing to use. Occlusive ointments may be too greasy and cosmetically unappealing, resulting in poor adherence. Sometimes using a cream formulation during the day and an ointment at night may be the best option.[18]

LO 5

KEY CONCEPT Corticosteroids are the topical first-line treatment for mild to moderate psoriasis. They exert anti-inflammatory and immunosuppressive effects resulting in reduced scaling and overall plaque size. Additionally, topical corticosteroids can be combined with other topicals or systemic/biologic agents to enhance therapy. Adverse effects include skin atrophy with prolonged use (especially if used with an occlusive agent), hypopigmentation, and striae. More than 2 weeks of continuous use should be avoided to prevent these complications.[13]

LO 5

Phototherapy for Psoriasis Phototherapy and photochemotherapy are generally used in the management of moderate to severe disease.[11,12]

Phototherapy is traditionally done by using narrowband UVB (NB-UVB) radiation. It can be used as monotherapy or in combination with topical or systemic agents. The UVB disrupts the synthesis of proteins and nucleic acids in skin, which reduces epidermal keratin proliferation. Education should be provided to all patients and include information about the importance of wearing goggles for eye protection when undergoing phototherapy. Phototherapy may be administered during pregnancy and is considered a first-line therapy for those patients.[21]

LO 5

Photochemotherapy is the administration of phototherapy together with topical or systemic agents.[11,15,18] UVA has a long wavelength, and therapy with UVA is always combined with psoralens (eg, methoxsalen or trioxsalen), which are used as photosensitizers to increase efficacy. The use of PUVA for psoriasis causes two types of reactions: (a) an anoxic reaction that affects cellular deoxyribonucleic acid (DNA) that inhibits the proliferation of epidermal cells and induces cell death (apoptosis), and (b) an oxygen-dependent reaction that gives rise to the formation of free radicals and reactive oxygen that may damage membranes by lipid peroxidation.[22]

PUVA therapy applies to a group of therapies utilizing psoralens to sensitize cells to UVA light.[21] Bath PUVA, topical PUVA, and oral PUVA regimens are available.[11,21] Bath topical PUVA uses psoralens directly on the skin, followed by UVA therapy.[21] Psoralens act much more on cells that are actively dividing than on resting cells. Their action on actively dividing or activated immune cells, especially on T cells, explains their action in immune mediated diseases like psoriasis.

► *Systemic Therapy*

LO 5

Systemic therapies are used for patients with moderate to severe disease. To minimize drug toxicities or increase efficacy, systemic therapies are sometimes used in conjunction with topical or phototherapy.[4,11,12,17,23] These oral agents are classified into immunosuppressants, oral retinoids, T-cell activation inhibitors, cytokine modulators, TNF-α inhibitors, and IL-12 and IL-23 blockers.[1] See Tables 64–4 and 64–5.

Acitretin is an oral retinoid that is likely safer, but less effective, than methotrexate or cyclosporine since potentially serious adverse effects can usually be minimized by appropriate

Patient Encounter Part 2

The diagnosis is that the patient has plaque psoriasis. Patient expresses to you at this time that she "does not have the best insurance," but she wants something that will take care of her psoriasis.

What nonpharmacologic alternatives are appropriate for this patient?

What pharmacologic agents are appropriate for this patient?

Table 64–2

Topical Medications[2,12,20,24]

Actions and Effects	Selected Agents	Criteria	Approach to Therapy	Efficacy Assessment (PGA) Scores	Dosage Form/ Strength	Place in Therapy
Corticosteroids						
Anti-inflammatory Vasoconstriction Immunosuppression Antiproliferative	**Very High Potency** • Bethamethasone • Clobetasol • Diflorasone	Mild to moderate	Monotherapy for acute episode	41%–92% with increase in potency	Ointment, creams, lotions, gel, foams, solutions, shampoo, spray, and tape	First-line
	High Potency • Amcinoride • Betamethasone dipropionate and valerate • Desoximetasone		Monotherapy for acute episode			
	Intermediate Potency • Betamethasone • Desoximetasone		Monotherapy for acute episode			
	Low Potency • Alclometasone • Desonide • Hydrocortisone		Monotherapy for acute episode			
Vitamin D Analogues						
Not well known Vitamin D receptor binding is proposed Keratinocytes proliferation is attenuated	Calcipotriene	Mild to moderate	Mono- or steroid sparing adjunctive therapy. First consideration with steroid when rapid lesion eradication is desired	60%–70%	Cream Scalp solution	First-line with or without steroid
	Calcipotriol			60%–70%	Ointment	
Retinoids						
Not well known Modifies gene transcription Decrease inflammation and proliferation due to its retinoid acid receptors binding	Tazarotene	Mild to moderate	Mono- or adjunctive therapy with steroid. More effective with high potency steroids	63%	Gel	Second-line with or without steroid
Calcineurin Inhibitors						
Decrease lymphokines activity by phosphatase inhibition Act as immunomodulators	Tacrolimus (Protopic)	Mild to moderate	Monotherapy for more sensitive areas such as face	65%–70%	Ointment strengths: 0.03% and 0.1%	Third-line with or without steroid
	Pimecrolimus (Elidel)	Mild to moderate	Monotherapy for more sensitive areas of the skin such as face	56%–62%	Cream strength: 1%	

(*Continued*)

Table 64–2

Topical Medications[2,12,20,24] (*Continued*)

		Other Agents				
Actions and Effects	**Selected Agents**	**Mild to Moderate**	**Approach to Therapy**	**Partly Indicated**	**Various**	**Place in Therapy**
Moisturizers						
Unknown	Nonmedicated moisturizers	Mild to moderate	Commonly used throughout the day	31%	Creams and ointments	
Salicylates						
Act as keratolytic agents and reduce lesion scaling to improve absorption of applied medications	Salicylic acid	Mild to moderate	More effective when used as an adjunctive therapy to other topical agents	Unknown	Creams, foams ointments, shampoos Strengths: 1.8%–2.5% and 3%	Adjunct therapy for scalp psoriasis used with steroids to increase efficacy (breaks down keratin)
Anthralin						
Inhibition of T-Cell proliferation and migration of neutrophils Keratolytic agent	Anthralin	Mild to moderate	Use infrequently due to irritation	Unknown	Creams, shampoos Strengths: 1%–1.2%	Adjunct therapy often used in conjunction with steroids in a paste
Coal Tar						
Inhibition of cell proliferation Acts as keratoplastic agent	Coal tar, crude coal tar, combinations (Polytar and Sebutone)	Mild to moderate	Use infrequently due to skin irritation	Unknown	Creams, gels, shampoo, solutions, lotions, oil Strengths: 0.5%–3%	Adjunct therapy with steroids to increase efficacy

PGA, Physician Global Assessment score.

patient selection, careful dosing, and monitoring.[24] Acitretin given concurrently with phototherapy, acitretin + ultraviolet B (ReUVB) or oral retinoid + PUVA (RePUVA), has a synergistic treatment effect. Acitretin monotherapy is usually given for 14 days before instituting UVB or PUVA.[13] ReUVB and RePUVA are well-established treatment regimens for psoriasis.[4,6,7,11,21,23] Pregnancy and blood donation must be avoided during treatment and for 3 years after discontinuation of therapy.[6,7,12,23] Acitretin can transform spontaneously or be converted by ethanol (transesterification) into etretinate, which may take up to 3 years to completely clear the body. Due to this, abstinence from alcoholic beverages should be observed during therapy and for at least 2 months after acitretin is discontinued.

Methotrexate is a folic acid antagonist that interferes with purine synthesis and thus inhibits DNA synthesis and cell replication. In addition to the antimitotic effect, it suppresses T-cell effects, and, in low doses, anti-inflammatory and antiproliferative effects. Compared with cyclosporine, methotrexate has a more modest effect but can be used continuously for years, with persistent benefits.[11] Folic acid is added to the treatment with methotrexate to reduce gastrointestinal symptoms and bone marrow toxicity. It may take up to 4 weeks to see a clinical response after a dose increase.[23]

Cyclosporine is an immunosuppressant that specifically inhibits helper T cells and keratinocyte activation and proliferation. Cyclosporine is efficacious in both inducing and maintaining remission for patients with moderate to severe plaque psoriasis and is also effective in treating pustular, erythrodermic, and nail psoriasis.[11,12]

Mycophenolate mofetil may be useful in resistant cases of moderate to severe psoriasis and in patients with cyclosporine-induced nephrotoxicity as a switch-over agent. Although PASI increased, patients' renal function improved.[24] As adjunctive or monotherapy, there are a few studies in relatively small groups of patients with moderate to severe psoriasis that showed some benefit (at least a 50% reduction in PASI).[23]

LO 5

Biologic Response Modifiers Biologic response modifiers (BRMs) and their biosimilars are currently recommended for consideration as first-line therapies alongside traditional systemic agents for moderate to severe disease.[11] These are agents employed in the treatment of psoriasis that act by inhibiting various molecular signaling steps of the immunological signaling cascade that are key determinants of the pathogenesis of psoriasis.

LO 5

The following agents are available for the treatment of chronic plaque psoriasis[25]:

1. Inhibitors of TNF-α, which includes biologic agents such as etanercept, adalimumab, infliximab, and golimumab
2. Inhibitors of interleukin which includes ustekinumab, ixekizumab, brodalumab and secukinumab

Table 64–3

Topical Medications[2,12,20,24]

Drug Class	Dosing and Application	Administration Guidelines	Cautions and Side Effects
Corticosteroid	• Mostly once or twice daily • Every other day or weekends only application may be suitable for chronic conditions • Treatment is recommended for 2–3 weeks • Low and intermediate potency can be used up to 3 months	• Intermediate and low potency agents are indicated for acute and mild lesions and tapering is recommended with the lowest dose when the condition improves • Low potency agents are suitable for lesions in infants due to large body surface area and elderly for the sensitive and thin layer of the skin • High and very high potency agents are indicated for chronic and severe lesions • Palms and soles of the skin require high and very high potency agents to maximize absorption and penetration due to the thickness of the skin	• Skin irritation • Dryness • Withdrawal effects
Vitamin D analogues	Mostly once or twice daily for a maximum of 2 months for effective results	• Recommended to be used with topical steroids to speed up the healing process • Considered less toxic than topical steroids • Combination therapy with steroids has shown to be more effective than the single agent • Onset of action is slow • Avoid calcipotriene use with salicylic acid due to instability of calcipotriene	• Pruritus • Skin irritation on facial area and skin folds • Skin irritation is less with calcitriol • Skin rashes • Burning • Changes in systemic vitamin D levels
Retinoids	Preferred as once daily at bedtime	• Best used to achieve better efficacy results with high-potent steroids or UVB phototherapy	• Skin irritation • Pruritus • Dryness • Photosensitivity
Calcineurin inhibitors	Mostly once or twice daily depending on the product until effective result is observed	• Comparison data to other agents or in combination is lacking • Use with salicylic acid for 8 weeks showed efficacy improvement in facial lesions	• Skin irritation • Pruritus • Photosensitivity • Risk of malignancy
Other agents: • Salicylic acid • Coal tar • Anthralin	As directed	• Decreases the scaling of the skin lesion to allow application of other agents • Infrequent use of tars and anthralins due to irritation and staining	• Skin irritation • Potential salicylic acid toxicity manifesting as nausea and ringing in ears

Their safety profile in comparison with other systemic agents and relatively good acceptability by patients are all positive factors.[10] However, given that immunosuppression is an adverse effect of many of these agents, clinicians should ensure that appropriate vaccinations are administered and tuberculosis skin testing performed prior to initiation of therapy. Additionally, clinicians should monitor for signs/symptoms of infection throughout therapy. Primary response success with BRMs is defined as a 50% or greater reduction in baseline disease severity. Patients should be switched to an alternative therapy if the primary response is not achieved or if the psoriasis initially responds but then loses its response.

Oral apremilast is one of a class of "small molecule" systemic BRMs specifically approved for PsA. It inhibits phosphodiesterase 4 (PDE4) which controls part of the inflammatory actions within cells via cyclic adenosine monophosphate (cAMP) to decrease nitric oxide synthase, TNF-α and IL-23 and increase IL-10. Many other BRMs may be used when PsA is present, but certolizumab (TNF-α inhibitor), guselkumab (interleukin inhibitor), and abatacept (T-cell inhibitor) can only be used for PsA and not severe psoriasis.

OUTCOME EVALUATION

LO 6

- Monitor for clearance of skin lesions. Depending on the agent(s) used and site of lesions, it may take 2–6 weeks or longer to see a response. Complete clearance may not be achieved for all patients. A BSA of 3% or less or a BSA improvement of 50% or more from baseline is considered an acceptable response.
- Beginning 3 months after the start of new therapies (important to wait at least 90 days since it can take up to 16 weeks to effect [induction phase]):
  - A BSA of 1% or less is recommended for target therapy
- During maintenance or remission, monitor every 6 months.
  - A BSA of 1% or less is the target response at every 6 months during maintenance evaluation.
- In Europe, successful treatment is defined as a decrease in the PASI score of 75% or greater. The PASI is a scoring instrument that ranges from 0 (absence of disease) to 72 (most severe form of the disease).[17]

Table 64–4

Systemic Agents[26,27]

Drug	Mechanism of Action	Doses and Administration	Dosage Forms	Adverse Effects	Therapeutic Efficacy on PASI 75	Therapeutic Application	Therapeutic Monitoring
Immunosuppressants							
Cyclosporine	An immunosuppressive agent that specifically inhibits helper T cell and keratinocyte activation and proliferation	2.5 mg/kg/day in two divided doses for at least 4 weeks This dose may be subsequently titrated and increased by 0.5 mg/kg/day Q 2 weeks until there is control of plaques (maximum dose of 4 mg/kg /day)	Oral and IV solution	Nephrotoxicity, lowering of seizure threshold, tremor, gingival hyperplasia, hypertension, squamous cell carcinoma (cutaneous)	~41%–71%	First-line agent Used in psoriasis only (children only as last line therapy)	LFTs (Baseline and routine) SCR, BUN CBC Uric acid Blood pressure Drug interaction with cytochrome p450 substrate and inhibitors Pregnancy
Methotrexate	Folic acid antagonist Acts by interfering with purine synthesis, thus inhibit DNA synthesis and cell replication	-7.5 to 10 mg weekly (max of 25 mg) -2.5 mg Q 12 hours times 3 doses	Oral and injectable	Nausea, vomiting, stomatitis, fatigue, hepatotoxicity, bone marrow suppression, pulmonary fibrosis	24%–60%	First-line agent Used in psoriasis and psoriatic arthritis (adults and children)	CBC SCR, BUN LFTs (baseline and Q 4 weeks), avoid in cirrhosis and alcohol use disorders Pregnancy category X
Oral Retinoids							
Acitretin	Stimulates differentiation and normalizes epidermal cell proliferation	10–50 mg/day	Oral capsule	Myalgia, hair loss, hepatotoxicity, pancreatitis, hypervitaminosis A, hyperlipidemia	70%–75%	Second-line agent Used in psoriasis only (adults and children)	Lipids CBC SCR, BUN (baseline and Q 3 months) Pregnancy category X CYP450 medications

BUN, blood urea nitrogen; CBC, complete blood count; CYP450, cytochrome P450; LFT, liver function test; Q, every; SCR, serum creatinine.

Table 64–5

Biological Therapy[28–33] (*Continued*)

Medication	Mechanism of Action	Dose and Administration	Dosage Forms	Adverse Effects	Therapeutic effects on PASI	Place in Therapy	Therapeutic Monitoring
Cytokine Modulators-Tumor Necrosis Factors							
Etanercept	Fusion protein that binds to both TNF-α and TNF-β	50 mg SC twice weekly for 12 weeks then 50 mg SC weekly	SC solution Biosimilar available: Etanercept-szzs	Upper respiratory tract infection, nausea, vomiting, headaches; injection site reaction	47%–59% at weeks 12 and 24	Second-line agent Used in psoriasis (people > 4 years old) and psoriatic arthritis (adults)	CBC LFTs PPD (tuberculosis)
Abatacept	Blocks T-cell activation	125 mg once weekly	SC self-injection, IV infusion	HA, upper respiratory infection, cold-flu-like symptoms		Used in psoriatic arthritis only (adults)	Signs of infection (especially when used with a TNF inhibitor) PPD prior to starting therapy (TB testing)
Adalimumab	Human monoclonal antibody that targets TNF-α	80 mg SC, first dose then 40 mg SC on week 2, then 40 mg SC Q 2 weeks	SC solution Biosimilars available: adalimumab-adbm, adalimumab-atto	Upper respiratory tract infection, pharyngitis, nausea, dyspepsia, fatigue, headaches; injection site reaction	53%–80% at weeks 12 and 16	First-line Used in psoriasis and psoriatic arthritis (adults)	CBC LFTs PPD (tuberculosis)
Certolizumab	Blocks TNF-α	400 mg (2 injections of 200 mg each) weeks 0, 2, and 4 then every other week	SC injection	Upper respiratory infection, rash, UTI, serious allergic reaction, Lupus-like syndrome		Used in psoriatic arthritis only (adults)	CBC LFTs Signs and symptoms of infection
Infliximab	Chimeric monoclonal antibody that targets TNF-α	5 mg/kg IV on weeks 0, 2, 6 and then 5 mg Q 8 weeks (10 mg/kg dosing is reserved for IBD)	IV and SC solutions Biosimilars available: infliximab-abda, infliximab-dyyb, infliximab-qbtx	Upper respiratory tract infection, pharyngitis, diarrhea, fatigue, hypersensitivity reaction	76%–82% at weeks 10 and 24	Second-line Used in psoriasis and psoriatic arthritis (adults)	PPD (tuberculosis)
Golimumab	Human monoclonal antibody that binds to both soluble and transmembrane bioactive forms of human TNF-α (a cytokine protein), resulting in inhibition of TNF-α biological activity by preventing the binding of TNF-α to its receptors	50 mg SC once monthly	SC solution	Hypertension, injection site reaction, rash, ALT/SGPT level raised, AST/SGOT level raised, dizziness, paresthesia, bronchitis, sinusitis, upper respiratory infection, new or worsening heart failure		Used in psoriatic arthritis only (adults) alone or with methotrexate	LFTs Infection Edema

Cytokine Modulators: Interleukin Inhibitors							
Ustekinumab	Human monoclonal antibody that targets IL-12/23 p40	45–90 mg SC on week 0 and 4, then every 12 weeks	SC solution	Headache, upper respiratory tract infection, pharyngitis, abdominal pain	66%–78% at weeks 12 and 28	First-line Used in psoriasis (people > 12 years) and psoriatic arthritis (adults)	PPD (TB testing), signs of serious infection
Secukinumab	Human monoclonal antibody that antagonizes IL-17A	300 mg SC at weeks 0, 1, 2, 3, and 4 then 300 mg every 4 weeks	SC solution	Nasopharyngitis, diarrhea, upper respiratory tract infection	82%–86% at week 12	First-line Used in psoriasis and psoriatic arthritis (adults)	PPD (tuberculosis), inflammatory bowel disease, caution in patients with chronic or recurrent infection
Ixekizumab	Human monoclonal antibody that inhibits the release of proinflammatory cytokines and chemokines by selectively binding with IL-17A cytokine	160 mg (two 80 mg injections) SC at week 0, followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12, then 80 mg SC every 4 weeks	SC solution	Injection site reaction, neutropenia, upper respiratory infection, hypersensitivity reaction	71%–100% at week 12	Second-line Used in psoriasis and psoriatic arthritis (adults)	PPD (uberculosis), caution in patients with chronic or recurrent infection, Inflammatory bowel disease
Brodalumab	Human monoclonal IgG2 antibody that blocks the release of proinflammatory cytokines and chemokines by selectively binding to human IL17 receptor A (IL-17RA) and inhibiting its interactions with cytokines IL-17A, IL-17F, IL-17C, and IL-17A/F heterodimer and IL-25	210 mg SC on weeks 0, 1, and 2, then every 2 weeks thereafter	SC solution	Diarrhea, mycosis, arthralgia, headache, pain in throat, fatigue, neutropenia, cryptococcal meningitis, suicidal thoughts	83%–86% at week 12	Second-line Used in psoriasis only (adults)	PPD (tuberculosis), caution in patients with chronic or recurrent infection
Guselkumab	Blocks IL-23	100 mg weeks 0 and 4, then every 8 weeks	Subcutaneous self-injection	Upper respiratory infection, HA, joint pain, diarrhea		Used in psoriasis only (adults)	Signs of infection PPD prior to starting therapy (TB testing)

(*Continued*)

Table 64–5

Biological Therapy[28–33] (*Continued*)

Medication	Mechanism of Action	Dose and Administration	Dosage Forms	Adverse Effects	Therapeutic effects on PASI	Place in Therapy	Therapeutic Monitoring
PDE 4 Inhibitors							
Apremilast	Phosphodiesterase 4 (PDE4) inhibitor, with specificity for cyclic adenosine monophosphate (cAMP) that results in increased intracellular cAMP levels	Initial titration over 5 days: Day 1, 10 mg orally in the morning Day 2, 10 mg twice daily Day 3, 10 mg in the morning, 20 mg in the evening Day 4, 20 mg twice daily Day 5, 20 mg in the morning, 30 mg in the evening Maintenance: Day 6 and thereafter, 30 mg orally twice daily	Oral tablet	Diarrhea, nausea, headache, tension-type headache, weight decreased, depression, suicidal behavior, suicidal thoughts		Used in psoriasis and psoriatic arthritis (adults)	Coadministration with strong CYP450 inducers (eg, rifampin, phenobarbital, carbamazepine, and phenytoin) is not recommended
Janus Kinase (JAK) Inhibitors							
Tofacitinib	Inhibits janus kinase which are intracellular enzymes, and modulates a signaling pathway that influences the cellular processes of hemopoiesis and immune cell function	Immediate release: 5 mg twice daily Extended release: 11 mg once daily	Oral tablet (immediate and extended release)	URI, headache, diarrhea, cold or flu-like symptoms		Second-line Used in psoriatic arthritis only (adults) (in combination with nonbioologic DMARDs)	Serious infection, malignancies, GI perforations, changes in CBC, LFTs, or lipids, caution with administration of live vaccines when switching from IR to ER give ER tablet day after last IR dose

ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; cAMP, cyclic adenosine monophosphate; CBC, complete blood count; CYP450, cytochrome p450; DMARDs, disease-modifying antirheumatic drugs; ER, extended release formulation; GI, gastrointestinal; IBD, inflammatory bowel disease; IgG, immunoglobulin G; IL, interleukin; IR, immediate release formulation; IV, intravenous; LFT, liver function test; PDE, phosphodiesterase 4; PPD, purified protein derivative; Q, every; SC, subcutaneous; SCR, serum creatinine; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; TB, tuberculosis; TNF-α, tumor necrosis factor-α; tumor necrosis factor-α; TNF-β, tumor necrosis factor-β; URI, upper respiratory infection; UTI, urinary tract infection.

- Treatment failure is defined as a decrease in the PASI score of less than 50% necessitating a new treatment.

LO 6

- Monitor for improvement of symptoms and control of comorbid conditions. Incomplete clearance of lesions, but improvement in these metrics can be considered at least partial treatment success. The National Institute for Health and Care Excellence (NICE) clinical guidelines on psoriasis outline other qualitative measures to be used in assessing the holistic approach to disease management.[1] It emphasizes evaluating the physical, psychological, and social impact of the disease on the patients' quality of life. The impact of psoriasis on the patients' daily living activities should be assessed. Depending on how the patient is coping, advice and support may be needed in the overall treatment plan for the patient. Efficacy achievement alone may not have the overall desired effect on patients wellbeing.[1,19] Dermatology Quality of Life Scales, DLQI, Dermatology Specific Quality of Life Instrument, and Skindex-29 are validated instruments that are used to measure these quality outcomes in patients with psoriasis by specialists.[12,19]

LO 6

- Monitor for specific adverse effects and drug interactions, depending on agent(s) used.

Patient Encounter Part 3

The patient was started on clobetasol 0.1% ointment and has been doing well for 18 months. She reports that her condition was well controlled during this time, but recently, she lost her spouse and she has noticed the lesions have reappeared. She continued her clobetasol, but her lesions have now spread to her back (BSA 11%).

Current Meds: Nonmedicated moisturizer after bathing and as needed; clobetasol 0.1% ointment twice daily

What is your main treatment goal for this patient?

What pharmacologic treatments would be appropriate for this patient at this time?

What are the monitoring parameters of your proposed treatment?

- Total clearance of skin disease is not impossible during periods of remission; remissions may be days, months, years, and even decades in length, with patients being weaned from their medications entirely or have them reduced to a low maintenance dose.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings (eg, BMI, BSA % covered in plaques).
- Speak with the patient and review records to identify lifestyle habits (take note of tobacco use), preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.
- Identify any sources of stress that could worsen psoriasis.

Assess the Information:

- Determine whether the patient is taking any substance that could adversely affect psoriasis control or interact with prescribed medications.
- Based on the medical history, determine whether the patient has any contraindications to therapy.
- Document pertinent family medical history (eg, heart disease, stroke, diabetes, dyslipidemia).
- Based on physical examination and review of systems, determine the severity of psoriasis.
- Identify comorbidities associated with psoriasis.
- Document location and BSA % covered by plaques.
- Assess the efficacy, safety, and patient adherence of current pharmacotherapy.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- If patient is not at the desired level of remission, determine which pharmacologic treatment is indicated (Figure 64–2).
- Select lifestyle modifications that are likely to be effective, safe, and applicable to the individual patient.
- Choose medications and doses that are optimal for the patient (Tables 64–2, 64–3, 64–4, and 64–5). Use combination therapy when appropriate to take advantage of complementary mechanisms of action and to reduce side effects.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about psoriasis and its management.
- Discuss importance of medication adherence and lifestyle modifications to prolong remission.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary.
- Educate patient about the involvement of dermatologists (eg, when biologic therapy is warranted).

Follow-up: Monitor and Evaluate:

- Follow up at 6–12 week intervals to assess effectiveness and safety of therapy until remission is achieved.
- Review medication adherence and BSA % covered measurements, evaluating the degree of control.
- Once psoriasis is in remission, monitor patient twice yearly to assess psoriasis control and pertinent lab monitoring. Determine whether the patient is experiencing any adverse reactions or drug interactions.

SUMMARY

It should be recognized that psoriasis is a chronic disease with no current cure but requires lifelong management of the disease state. No two cases of psoriasis are identical and treatment modalities must be tailored to the patient with the help of a dermatologist. The disease can severely impact the patients' quality of life by affecting their physical, psychological, and social well-being. The NICE guidelines recommend a holistic approach in assessing all areas of life in caring for patients that live with this disease.

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Abbreviations Introduced in This Chapter

BRM	Biologic response modifier
BSA	Body surface area
cAMP	Cyclic adenosine monophosphate
IFN-γ	Interferon-γ
IL-2	Interleukin-2
IL-10	Interleukin-10
IL-12/23	Interleukin-12 and interleukin-23
LFT	Liver function test
MI	Myocardial infarction
NB-UVB	Narrowband ultraviolet B
NSAIDs	Nonsteroidal anti-inflammatory drugs
PASI	Psoriasis Area and Severity Index
PPD	Purified protein derivative
PsA	Psoriatic arthritis
PUVA	Psoralen and ultraviolet A
RePUVA	Oral retinoid + PUVA
ReUVB	Acitretin + ultraviolet B
TNF	Tumor necrosis factor
UVB	Ultraviolet B

REFERENCES

1. Smith CH, Samarasekera EJ. Psoriasis: guidance on assessment and referral. Clin Med. 2014;14(2):178–182.
2. Papoutsaki M, Costanzo A. Treatment of psoriasis and psoriatic arthritis. Biodrugs. 2013;27(suppl 1):1–12.
3. Perera GK, Meglio PD, Nestle FO. Psoriasis. Annu Rev. 2012;7:385–422.
4. American Academy of Dermatology Work Group. Guidelines of Care for the management of psoriasis and psoriatic arthritis. Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol. 2011;65(1):137–174.
5. Egeberg A, Skov L, Joshi AA, et al. The relationship between duration of psoriasis, vascular inflammation, and cardiovascular events. J Am Acad Dermatol. 2017;77(4):650–656.
6. American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826–850.
7. American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008;59(5):851–864.
8. Jordan CT, Cao L, Roberson ED, et al. PSORS2 is due to mutations in CARD 14. Am J Hum Genet. 2012;90(5):784–795.
9. Umapathy S, Pawar A, Mitra R, et al. HLA-A and HLA-B alleles associated in psoriasis patients from Mumbai, Western India. Indian J Dermatol. 2011;56(5):497.
10. Jankovic S, Raznatovic M, Marinkovic J, Jankovic J, Maksimovic N. Risk factors for psoriasis: a case–control study. J Dermatol. 2009;36(6):328–334.
11. Canadian Psoriasis Guidelines Addendum Committee. 2016 Addendum to the Canadian guidelines for the management of plaque psoriasis: 2009. J Cutan Med Surg. 2016;20(5):375–431.
12. Law RM, Gulliver WP. Psoriasis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: The McGraw-Hill Companies; 2016.
13. Mason A, Mason J, Cork M, Hancock H, Dooley G. Topical treatments for chronic plaque psoriasis: an abridged Cochrane Systematic Review. J Am Acad Dermatol. 2013;69(5):799–807.
14. Rosenkranz MA, Davidson RJ, MacCoon DG, Sheridan JF, Kalin NH, Lutz A. A comparison of mindfulness-based stress reduction and an active control in modulation of neurogenic inflammation. Brain Behav Immun. 2013;27:174–184.
15. American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60(4):643–659.
16. Almutawa F, Alnomair N, Wang Y, Hamzavi I, Lim HW. Systematic review of UV-based Therapy for Psoriasis. Am J Clin Dermatol. 2013;14:87–109.
17. Nast A, Gisondi P, Ormerod AD, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris—Update 2015—Short version—EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol. 2015;29;2277–2294.
18. Feldman SR, Matheson R, Bruce S, et al. Efficacy and safety of calcipotriene 0.005% foam for the treatment of plaque-type psoriasis. Results of two multicenter, randomized, double-blind, vehicle-controlled phase iii clinical trials. Am J Clin Dermatol. 2012;13(4):261–271.
19. Psoriasis: the assessment and management of psoriasis. NICE 153 clinical guidelines 2012. Available from: http://guidance.nice.org.uk/cg153. Updated October 2012. Accessed August 8, 2017.
20. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp, Inc.; 2017; August 8, 2017.
21. American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. J Am Acad Dermatol. 2010;62(1):114–135.
22. Mouli P, Selvakumar T, Kumar S, Parthiban S, Priya R, Deivanayagi M. Photochemotherapy: a review. Int J Nutr Pharmacol Neurol Dis. 2013;3(3):229–235.
23. American Academy of Dermatology Work Group. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61(3):451–485.
24. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med. 2017;376(10):957–970.
25. Panchal MR, Coope H, McKenna DJ, Alexandroff AB. Long-term safety of biologics in the treatment of psoriasis. Psoriasis: Targets and Therapy. 2014;4:1–9.

26. Boca AN, Badalica-Petrescu M, Buzoianu AD. Current therapeutic options in psoriasis. International Journal of the Bioflux Society. 2014;6(1):6–10.
27. Armstrong AW, Siegel M, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. J Am Acad Dermatol. 2017;76:290–298.
28. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al. British Association of Dermatologists guidelines for biologic therapy in psoriasis 2017. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/bjd.15665. Accessed May 14, 2018.
29. Ohtsuki M, Morita A, Abe M, et al. Secukinumab efficacy and safety in Japanese patients with moderate-to-severe plaque psoriasis: subanalysis from ERASURE, a randomized, placebo-controlled, phase 3 study. J Dermatol. 2014;41(12):1039–1046.
30. Paul C, Lacour JP, Tedremets L, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015;29(6):1082–1090.
31. Bagel J, Duffin KC, Moore A, et al. The effect of secukinumab on moderate-to-severe scalp psoriasis: results of a 24-week, randomized, double-blind, placebo-controlled phase 3b study. J Am Acad Dermatol. 2017;77:667–674.
32. Kimball AB, Luger T, Gottlieb A, et al. Impact of ixekizumab on psoriasis itch severity and other psoriasis symptoms: results from 3 phase III psoriasis clinical trials. J Am Acad Dermatol. 2016;75(6):1156–1161.
33. Blauvelt A, Reich K, Tsai TF, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: results from the CLEAR study. J Am Acad Dermatol. 2017;76(1):60–69.

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65 Common Skin Disorders

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LEARNING OBJECTIVES

LO

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

1. Describe the pathophysiology of common skin disorders.
2. Assess the signs and symptoms of common skin disorders in a presenting patient.
3. List the goals of treatment for patients with common skin disorders.
4. Select appropriate nonpharmacologic and pharmacologic treatment regimens for patients presenting with common skin disorders.
5. Identify adverse effects that may result from pharmacologic agents used in the treatment of common skin disorders.
6. Develop a monitoring plan that will assess the safety and efficacy of the overall disease state management of common skin disorders.
7. Create educational information for patients about common skin disorders, including appropriate self-management, available drug treatment options, and anticipated therapeutic responses.

INTRODUCTION

Several thousand skin disorders are currently documented, and many patients seek the assistance of a health care provider when a complication with their skin develops. Others will utilize self-care to effectively treat their symptoms.

This chapter discusses acne vulgaris, contact dermatitis (irritant and allergic), and diaper dermatitis; other common skin and soft tissue infections and superficial fungal infections are discussed in Chapters 73 and 83, respectively. Providing patients with appropriate therapy options, as well as patient education on treatment and prevention, will assist the successful management of many common skin disorders.

ACNE VULGARIS

Acne vulgaris is an inflammatory skin disorder of the pilosebaceous units of the skin. Although most commonly seen on the face, acne can also present on the chest, back, neck, and shoulders (Figure 65–1).[1] Acne is not just a self-limiting disorder of teenagers. The clinical course of acne can be prolonged or recur, resulting in long-term physical complications, such as extensive scarring and psychological distress.[2]

Epidemiology and Etiology

With an estimated 40 to 50 million people affected, acne vulgaris is the number one skin disease in the United States.[3] Acne affects approximately 85% of adolescents and adults aged 12 to 25 years, with severity of acne correlating with pubertal maturity.[3,4] Additionally, acne may persist beyond puberty and has been found to affect 64% and 43% of individuals into the 20s and 30s, respectively. Acne is more likely to occur in males during adolescence and females during adulthood. Individuals with a positive family history of acne have been shown to develop more severe cases of acne at an earlier age. Prevalence of acne among ethnic groups is similar.[4]

The link between diet and acne has continued to be controversial, with emerging evidence suggesting a link to foods with high glycemic indexes as well as dairy products (ie, skim milk); however, no specific dietary changes are recommended in the management of acne.[5-7] Local irritation from occlusive clothing or athletic equipment, oil-based cosmetics or beauty products, prolonged sweating or environments of high humidity, and a variety of medications may also worsen acne.[8]

Pathophysiology

LO 3

KEY CONCEPT The development of acne lesions results from four pathogenic factors: excess sebum production, **keratinization**, bacterial growth, and inflammation.[1,2,7]

The **pilosebaceous unit** of the skin consists of a hair follicle and the surrounding sebaceous glands. Sebum is released by the sebaceous glands and naturally maintains hair and skin hydration. Increased androgen levels, especially during puberty, can cause an increased size of the sebaceous gland and production of abnormally high levels of sebum within those glands. Keratinization, the sloughing of epithelial cells in the hair follicle, is also a natural process. In acne, however, *hyper*keratinization occurs resulting in an increased adhesiveness of the sloughed cells.

An initial acne lesion invisible to the naked eye, called a microcomedo, forms as a result of the increased cell division and cohesiveness. Sub-clinical microcomedo formation is a precursor for noninflammatory acne lesions called comedos. A **closed comedo** or "whitehead" appears when accumulation of epithelial cells and sebum partially obstruct the follicular opening. If the follicular opening is dilated, the keratin build-up can darken and form an **open comedo** or "blackhead."

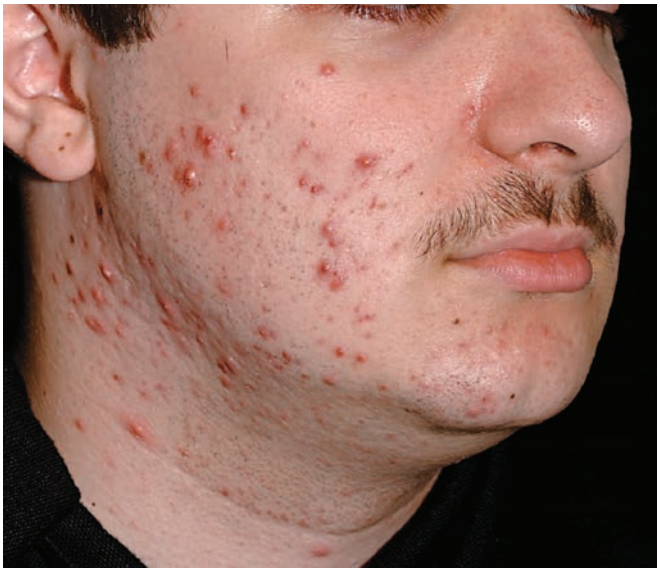

FIGURE 65–1. Twenty-year-old man. In this case of papulopustular acne, some inflammatory papules become nodular and thus represent early stages of nodulocystic acne. (From Wolff K, Johnson RA. Disorders of sebaceous and apocrine glands. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York: McGraw-Hill; 2009:3.)

Propionibacterium acnes (*P. acnes*), an anaerobic organism, is also found in the normal flora of the skin. This bacteria proliferates in the mixture of sebum and keratinocytes and can result in an inflammatory response producing more severe acne lesions such as papules, pustules, and nodules. Inflammatory lesions may result in scarring if treated inadequately.

Treatment

▶ *Desired Outcomes and Goals*

LO 3

Although traditionally thought of as a self-limiting disorder, acne can have patterns of recurrence. Because acne cannot be cured, proper treatment must involve both short-term and long-term strategies. KEY CONCEPT Goals of therapy are to (1) reduce the number and severity of existing lesions, (2) prevent the development of new lesions and recurrence, and (3) prevent long-term disfigurement and permanent scarring.[7] Acne can cause psychological symptoms of stress, anxiety, frustration, embarrassment, and even depression.[2,5,7] Evaluating both physical and psychological aspects of acne is imperative.

General Approach to Treatment

LO 4

KEY CONCEPT Acne treatment regimens should be based on acne severity and type of acne lesion. Other factors such as response to previous treatment, patient preference, cost, and adherence should also be considered. Topical therapy is considered first-line for mild acne with oral therapies added to topical therapy in moderate to severe acne. Using multiple topical agents that target different aspects of acne pathogenesis is more effective, reduces adverse effects, and minimizes treatment resistance.[2,5,12] Topical therapies should be applied to the entire area affected by acne to prevent new lesions from developing.[2,7]

Optimal management includes aggressive induction treatment and maintenance therapy to prevent recurrence. Improvement of symptoms following induction therapy occurs gradually, sometimes taking 6 to 8 weeks for results to be physically apparent. Patients need to be educated on continual treatment compliance during this time and should not get discouraged if acne lesions appear to worsen before getting better. Maintenance therapy should begin after 12 weeks of induction therapy and it

Clinical Presentation and Diagnosis of Acne

LO 2

Acne lesions are most often seen on the face, but can also present on the chest, back, neck, and shoulders and are described as either noninflammatory or inflammatory. Severe inflammatory lesions may lead to scarring and hyperpigmentation.

Noninflammatory Lesions

Closed comedo or "whitehead": A partially plugged follicle containing sebum, keratinocytes, and bacteria that remains beneath the surface of the skin. Closed comedos usually appear as small white bumps about 1 to 2 mm in diameter.

Open comedo or "blackhead": A partially plugged, dilated follicle containing sebum, keratinocytes, and bacteria approximately 2–5 mm in diameter that protrudes from the surface of the skin and appears black or brown in color. Although dark in color, blackheads do not indicate the presence of dirt, but rather, an accumulation of melanin.

Inflammatory Lesions

Papules: Solid, elevated lesion less than 0.5 cm in diameter

Pustules: Vesicles filled with purulent fluid less than 0.5 cm in diameter

Nodules: Warm, tender, firm lesions greater than 0.5 cm in both width and depth

Cysts: Nodules that harden into larger, pus-filled lesions

Scars

Inflammatory acne can result in permanent scarring that ranges from small, depressed pits to large elevated blemishes.

Hyperpigmentation

Inflammatory acne may result in hyperpigmentation of the skin that can last for weeks to months.

Diagnosis

The diagnosis of acne vulgaris is clinical. Lesion cultures may be warranted when treatment regimens fail to rule out Gram negative folliculitis and other skin infections. Endocrinological laboratory evaluation is only recommended for patients who have acne and additional signs of androgen excess.[5]

Assessment

No standard acne grading scale has been identified. While several grading scales exist,[2,5,7,11,12] most clinicians describe acne as mild (noninflammatory lesions), moderate (many inflammatory lesions), or severe (numerous severe inflammatory lesions and evidence of scarring).

was continued for 3 to 4 months in most clinical trials. Due to frequent acne recurrences, clinical experience indicates that a longer duration of maintenance therapy may be beneficial for most patients.[2,5,7]

Nonpharmacologic Therapy

LO 4

There is significant variance in the clinical benefit of many nonpharmacologic interventions for acne vulgaris. Patients should be counseled to avoid aggressive skin washing and to use a mild, noncomedogenic facial soap twice daily. Excessive washing or use of harsh or abrasive cleansers can disrupt the skin barrier and promote comedones and bacterial colonization. Manipulating or squeezing lesions should also be avoided to minimize scarring. Use of an oil-free, noncomedogenic moisturizer daily may improve the tolerability of topical drug therapy.[8,9,10]

▶ *Pharmacologic Therapy*

Topical Agents

LO 4

Retinoids Topical retinoids are the foundation of first-line therapy for induction and maintenance regimens in all forms of acne. Although success is seen with monotherapy in comedonal acne, using topical retinoids in combination with benzoyl peroxide, topical antibacterial agents, or oral antibacterial agents is preferred for inflammatory acne lesions.[2,5,12]

Retinoids normalize epithelial cell turnover, which in turn promotes clearing of obstructed follicles and prevents microcomedo formation. Retinoids also exhibit anti-inflammatory properties through the inhibition of neutrophil and monocyte chemotaxis.[13,14]

Available topical retinoids include tretinoin, adapalene, and tazarotene. Adapalene, available by prescription and over-the-counter, is considered the drug of first choice because it has similar efficacy and a lower incidence of adverse effects.[5,8,12–14] Newer topical retinoid formulations using a microsphere gel (Retin-A Micro) or a prepolyolprepolymer-2 gel or cream (Avita) gradually release the active ingredient over time and may also cause less initial skin discomfort.[13] Table 65–1 describes available products and adverse effects of topical retinoids.

Topical retinoids should be applied once daily at bedtime, beginning with a low-potency formulation. Increased strengths are then initiated according to treatment results and tolerance. Patients should be advised that a worsening of acne symptoms generally occurs in the first few weeks of therapy, with lesion improvement occurring in 3 to 4 months.[14,15] The safety and efficacy of topical retinoids in children younger than 12 years of age and in pregnant women is not well established.[9,13]

LO 4

Benzoyl Peroxide Benzoyl peroxide is easy to use and is recommended as an alternative to, or in combination with, topical retinoids, topical antibacterial agents, or oral antibacterial agents in the treatment of acne of all severities.[2,5,12] Benzoyl peroxide has a **comedolytic** effect that increases the rate of epithelial cell turnover and helps to unclog blocked pores. It also has antibacterial activity against *P. acnes*, which appears to be the main reason for its effectiveness.[16,17]

Benzoyl peroxide is available with or without a prescription and remains the most commonly purchased over-the-counter topical treatment for acne.[8,10] Some data suggest that lower strengths offer similar efficacy to higher strengths. Beginning benzoyl peroxide treatment regimen with the lowest strength and titrating to higher effective strengths over several weeks, if needed, will reduce the incidence of localized adverse effects. Newer formulations of benzoyl peroxide are combined with moisturizers to help decrease skin redness and irritation.[9,16,17]

A typical regimen for benzoyl peroxide is to apply the product to clean and dry skin no more than two times a day. The strength and dosage form selected may vary from patient to patient depending on acne severity and the sensitivity of the patient's skin. Gel preparations are the most potent dosage form. Patients with dry or overly sensitive skin should try a cream, lotion, or facial wash first.[5,7] If severe irritation or an allergic reaction develops, benzoyl peroxide should be discontinued. Table 65–1 describes available products and adverse effects.

LO 5

LO 4

Antibacterials Topical antibacterials directly suppress *P. acnes* and are first-line agents used in combination with benzoyl peroxide, topical retinoids, or azelaic acid for the treatment of mild to moderate inflammatory acne. To reduce the likelihood of bacterial resistance, topical antibiotics should never be used as monotherapy or as long-term maintenance therapy.[2,5,12]

Clindamycin is currently the preferred topical antibiotic for acne therapy due to increased bacterial resistance to erythromycin preparations.[5] Applied once or twice daily for 3 months, these agents are available in various formulations and combinations with benzoyl peroxide and topical retinoids.[2,5,12] Table 65–1 describes the strengths, formulations, and adverse effects of the available antimicrobial agents.

LO 4

Azelaic Acid With antibacterial and anti-inflammatory properties, and the ability to stabilize keratinization, azelaic acid is an effective alternative in the treatment of mild to moderate acne in patients who cannot tolerate benzoyl peroxide or topical retinoids.[2,12,15] It can also even out skin tone and may prove effective in patients who are prone to postinflammatory hyperpigmentation resulting from acne.[5,15,18] Azelaic acid 20% cream should be applied twice daily, with improvement of symptoms seen within 4 weeks.[15]

LO 4

Dapsone Dapsone gel, a sulfone drug, has antimicrobial and anti-inflammatory properties.[19] Dapsone gel may be used as an alternative agent for inflammatory acne as monotherapy or in combination with topical or oral agents. Topical dapsone gel has been shown to be more effective in adult females than in males or adolescents.[5]

Dapsone 5% is a gritty gel that should be applied in a thin layer to the affected areas twice daily.[19,20] When administered concomitantly with benzoyl peroxide, topical dapsone may become oxidized, causing orange-brown coloration of the skin which can be brushed or washed off. If no improvement is seen after 12 weeks, treatment should be reevaluated.[5,20]

LO 4

Keratolytics Sulfur, resorcinol, and salicylic acid have limited evidence available to support efficacy, but can be used as second-line therapies in the treatment of mild to moderate acne.[2,5]

Although these agents may cause less skin irritation than benzoyl peroxide or the topical retinoids, several disadvantages exist. Sulfur preparations produce an unpleasant odor when applied to the skin, whereas resorcinol may cause brown scaling. And although rare, the possibility of salicylism exists with continual salicylic acid use.[8,10,15]

Oral Agents

LO 4

Antibacterials Oral antibiotics are indicated for use in patients with moderate to severe acne and forms of inflammatory acne that are resistant to topical therapy. When used, oral antibiotics should be combined with a topical retinoid and/or benzoyl peroxide.[2,5,12] Because of the ability to decrease *P. acnes* colonization, oral antibiotics can prevent acne lesions from developing. Use of

Table 65–1

Topical Agents Used in the Treatment of Acne

Drug	Brand	Dosage Form	Adverse Reactions	Comments
Retinoids				
Tretinoin	Atralin	0.05% gel 0.025% cream 0.025% gel	Erythema, dryness, scaling, stinging/burning, pruritus, initially may worsen acne	Local adverse reactions most likely occur in first 2–4 weeks of use and will usually lessen with continued use
	Avita	0.025%, 0.05%, 0.1% cream	Possibly teratogenic	Category C
	Retin-A	0.01%, 0.025% gel	Photosensitivity	Minimize exposure to sun light and sun lamps
	Retin-A Micro	0.04%, 0.1% gel		Sunscreen use and protective clothing recommended
	Tretin-X	0.038%, 0.075% cream		
Tazarotene	Tazorac	0.05%, 0.1% cream 0.05%, 0.1% gel	Erythema, dryness, scaling, stinging/burning, pruritus, initially may worsen acne	Local adverse reactions most likely occur in first 2–4 weeks of use and will usually lessen with continued use
	Fabior	0.1% foam	Teratogenic	Category X. Use in pregnancy is contraindicated
			Photosensitivity	Minimize exposure to sun light and sun lamps
				Sunscreen use and protective clothing recommended
Adapalene	Differin	0.1% cream; 0.1%, 0.3% gel; 0.1% lotion	Erythema, dryness, scaling, stinging/burning, pruritus, initially may worsen acne	Local adverse reactions most likely occur in first 2–4 weeks of use and will usually lessen with continued use
	Differin Gel (over the counter)	0.1% gel		Less irritation compared to other retinoids
	Epiduo	0.1%–2.5% and 0.3%–2.5% benzoyl peroxide combination gel	Photosensitivity	Minimize exposure to sun light and sun lamps
				Sunscreen use and protective clothing recommended
				Pregnancy category C
Other Topical Agents				
Benzoyl peroxide	2.5%–10%, various over-the-counter and prescription products	Lotion, gel, foam, pads, liquid wash, bar	Excessive drying, peeling, erythema, allergic contact sensitization/dermatitis	Local reactions are dose-dependent Gradually increase dose as tolerance develops
			Bleaching of hair and colored fabric	Minimize exposure to sun light and sun lamps
			Body odor on clothes/ bedding	Sunscreen use and protective clothing recommended
			Photosensitivity	Pregnancy category C
Azelaic acid	Azelex	20% cream	Erythema, skin irritation	Alternative to benzoyl peroxide Pregnancy category B
Clindamycin	Cleocin T	1% solution, lotion, gel, swab	Burning, itching, dryness, erythema, peeling	Rare cases of colitis have been observed with topical use. Discontinue immediately and seek medical attention if diarrhea occurs
	Clindagel	1% gel	Diarrhea, colitis (pseudomembranous colitis)	Should be combined with topical benzoyl peroxide
	ClindaMax	1% gel, lotion		Pregnancy category B (C when combined with benzoyl peroxide or tretinoin)
	Evoclin	1% foam		
	BenzaClin	1%–5% benzoyl peroxide combination gel		
	Duac	1.2%–5% benzoyl peroxide combination gel		
	Veltin, Ziana	0.025%–1.2% tretinoin combination gel		
Erythromycin	ERYGEL	2% gel	Burning, peeling, dryness, pruritus, erythema	Should be combined with topical benzoyl peroxide
	Ery	2% pad		Pregnancy category B (C when combined with benzoyl peroxide)
	Benzamycin	5%–3% benzoyl peroxide combination gel		
Dapsone	Aczone	5% gel	Dryness, erythema, oiliness, and peeling	Does not have a risk of phototoxicity Pregnancy category C

Data from (1) Lexicomp [Internet]. Hudson (OH): Wolters Kluwer Health, Inc. 1978–2017 [cited 2017 June 13]. Available from: http://online.lexi.com/lco/action/home/switch. (2) Facts & Comparisons eAnswers. St. Louis (MO) 2014: Wolters Kluwer health, Inc. 2017 [cited 2017 June 13]. Available from: http://fco.factsandcomparisons.com/lco/action/home

oral antibiotics should be limited to short periods of time, ideally 3 to 4 months, or less.[5] Assessment of response to oral antibiotics after 6 to 8 weeks of therapy is recommended.[2] After inflammatory lesions have stopped emerging, oral antibiotics should be discontinued and replaced with topical retinoid or benzoyl peroxide containing maintenance regimens.[5,9] As with topical antibiotics, oral antibiotics should never be used as monotherapy or as long-term maintenance therapy. Additionally, the use of topical antibiotics in combination with oral antibiotics should be avoided due to increased risk of bacterial resistance.[2,5,12]

Tetracycline, doxycycline, and minocycline are the most commonly prescribed oral antibiotics for acne. Doxycycline and minocycline are more effective than tetracycline, but neither is superior to each other.[5] Erythromycin, azithromycin, and trimethoprim (± sulfamethoxazole) are appropriate second-line agents for use when patients cannot tolerate or have developed resistance to tetracycline or its derivatives. Although effectiveness is similar to the tetracyclines, erythromycin use is often limited due to potential adverse outcomes and increased bacterial resistance.[5,21] (See Table 65–2 for antibiotic dosing guidelines and adverse effects.)

Isotretinoin. Isotretinoin works on the four pathogenic factors that contribute to acne development and can produce acne remission rates of up to several years. Oral isotretinoin is Food and Drug Administration (FDA)-approved for patients with severe recalcitrant nodular acne unresponsive to other topical and oral treatment regimens.[5,12] Although studies are lacking, expert clinicians suggest that oral isotretinoin may be useful in treatment resistant moderate acne or acne that is producing physical scarring or psychosocial distress.[2,5,12] Contrary to some expert clinicians, the 2012 European Guidelines suggest that oral isotretinoin therapy may be used as first-line therapy in patients with severe nodular acne due to clinical effectiveness, prevention of scarring, and quick improvements in patient's quality of life.[12]

LO 4

Adverse effects with the use of isotretinoin are frequent and generally dose related. Table 65–2 lists common isotretinoin adverse effects and management strategies for those symptoms.

LO 5

Because isotretinoin is teratogenic and classified as pregnancy category X, the FDA mandates an online registry program called iPLEDGE to ensure that females do not become pregnant while taking isotretinoin. Wholesalers, pharmacies, doctors, and patients must be registered in the iPLEDGE computer-based system in order to control the distribution, prescribing, and dispensing of isotretinoin. Two negative pregnancy tests prior to initiating therapy and one negative pregnancy test each month thereafter must be obtained and confirmed in the system before a prescription can be dispensed to female patients of child-bearing potential. These patients must also commit to using two effective forms of birth control 1 month prior, during, and at least 1 month after discontinuation of isotretinoin therapy. Contact the program at their website https://www.ipledgeprogram.com/ for further details.

Initial dose for treatment of severe acne is typically 0.5 mg/kg daily in two divided doses, then increasing to 1 mg/kg daily, as tolerated, with goal cumulative doses of 120 to 150 mg/kg. Increasing the total daily dose to 1 mg/kg daily resulted in a significantly lower relapse and retreatment rate.[5,9,12] For patients with treatment resistant moderate acne, low-dose isotretinoin (0.25–0.4 mg/kg/day) has comparable efficacy to conventional dosing with decreased adverse effects and improved tolerability. Intermittent dosing of isotretinoin is not recommended due to lack of efficacy and increased relapse rates.[5] Treatment with oral isotretinoin should be continued for 4 to 6 months, but may be extended for patients with an insufficient response.[5,12]

LO 4

Hormonal Agents Oral contraceptives and anti-androgens are valuable second-line treatment options for moderate to severe inflammatory acne in female patients.[5,12,22] Hormonal agents primarily work by decreasing androgen production resulting in reduced sebum formation. Because sebum production occurs early in the pathogenesis of acne, several months to see the full effect of hormonal agents.[5]

Although many contraceptives are effective, agents containing ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone acetate/ferrous fumarate, and ethinyl estradiol/drospirenone have been FDA-approved for the treatment of acne.[5] While not FDA-approved, spironolactone, at higher doses, is effective for acne through anti-androgenic properties.[5,12] (See Table 65–2 for hormonal agent dosing guidelines and adverse effects.)

Other Agents. Although use is infrequent, several other agents are available as second- or third-line treatment options for acne when first-line therapies fail:[2,5,12]

- Corticosteroids
- Chemical peels
- Surgical extraction
- Phototherapy/photodynamic therapy
- Laser treatments

Figure 65–2 shows useful algorithms for the effective treatment of the various stages of acne.

OUTCOME EVALUATION

LO 6

KEY CONCEPT Depending on severity, complete resolution of acne lesions may take weeks to months. Monitor patients every 4 to 8 weeks during pharmacologic therapy to assess for efficacy.[5,9]

- Decreased number of lesions
- Decreased severity of lesions
- Relief of pain/irritation
- Presence of scarring or pigmentation
- Psychological effects
- Medication adherence

If no improvement is reported after 6 weeks of drug therapy or if symptoms have worsened, patients should be reevaluated and a change to an alternative drug regimen may be necessary (Figure 65–2).

Educate patients on potential adverse effects of drug therapy (Tables 65–1 and 65–2). Consider changing therapy if a patient experiences effects that are not tolerated or are a compromise to their health.

CONTACT DERMATITIS

Contact dermatitis is a condition in which exposure to an offending substance produces inflammation, erythema, and pruritus of the skin.[23,24] More specifically, contact dermatitis can be divided into either irritant or allergic forms.[25,26] KEY CONCEPT Irritant contact dermatitis (ICD) results from first-time exposure to irritating substances such as soaps, plants, cleaning solutions, or solvents. Allergic contact dermatitis (ACD) is a delayed hypersensitivity reaction that occurs after an initial exposure to an allergen results in sensitization. With additional exposure, activation of the immune system results in dermatitis. Allergens that commonly

Table 65–2

Oral Agents Used in the Treatment of Acne

Drug	Dosage Form (mg)	Dosing Regimen	Adverse Reactions	Comments
Oral Antibiotics				
Tetracycline	250, 500 capsule	250–500 mg twice daily	GI upset, headache, blurry vision, vaginal candidiasis, possible teratogenic risk, tooth discoloration in children Vaginal candidiasis Photosensitivity Drug–food interactions	Avoid use in children < 8 years. Pregnancy category D. Avoid use in pregnancy. Minimize exposure to sun light and sun lamps. Sunscreen use and protective clothing recommended. Take 1 hour before or 2 hours after dairy products, antacids, vitamins, or iron supplements.
Doxycycline	50, 75, 100 tablets and capsules	100 mg twice daily on day 1, then 100 mg once daily	GI upset, headache, blurry vision, possible teratogenic risk, tooth discoloration in children Vaginal candidiasis Photosensitivity Drug–food interactions	Avoid use in children < 8 years. Pregnancy category D. Avoid use in pregnancy. Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended. Take 1 hour before or 2 hours after dairy products, antacids, vitamins, or iron supplements.
Minocycline	50, 75, 100 immediate release tablets 45, 55, 65, 80, 90, 105, 115, 135 extended release tablets 50, 75, 100 immediate release capsules	Immediate release: 50–100 mg twice daily Extended release: 1 mg/kg daily for 12 weeks.	GI upset, headache, blurry vision, lupus-like syndrome, hepatitis, exfoliative dermatitis, possible teratogenic risk, tooth discoloration in children Vaginal candidiasis Photosensitivity Drug–food interactions	Avoid use in children < 8 years. Pregnancy category D. Avoid use in pregnancy. Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended. Take 1 hour before or 2 hours after dairy products, antacids, vitamins, or iron supplements.
Erythromycin	250, 500 tablets	250–500 mg twice daily	GI upset, rash, hearing loss, hypersensitivity reactions Vaginal candidiasis	Highest incidence of GI intolerance and increasing bacterial resistance. Possible drug interactions: CYP3A4 substrate and p-glycoprotein inhibitor. Alternative to tetracyclines Pregnancy category B. Drug of choice in pregnant women and children < 8 years.
Azithromycin	500 tablet	Dosing regimens used in clinical trials have varied greatly, using pulse dose regimens (eg, 500 mg once daily for 4 consecutive days per month for 3 consecutive months)	GI upset, rash, headache, drowsiness	Alternative if other antibiotics cannot be used. Pregnancy category B
Trimethoprim	100 mg tablet	100 mg three times daily or 300 mg twice daily	GI upset, allergic rash, Stevens-Johnson syndrome Photosensitivity	Alternative if other antibiotics cannot be used. Pregnancy category C. Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended.
Sulfamethoxazole + trimethoprim	400/80, 800/160 tablets	400–800/80–160 mg one to two times daily	GI upset, allergic rash, urticaria, Stevens-Johnson syndrome, possible teratogenicity Photosensitivity	Alternative if other antibiotics cannot be used. Pregnancy category D. Avoid use in pregnancy. Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended

(*Continued*)

Table 65–2

Oral Agents Used in the Treatment of Acne (*Continued*)

Drug	Dosage Form (mg)	Dosing Regimen	Adverse Reactions	Comments
Hormonal Agents				
Oral contraceptives	Norgestimate/ethinyl estradiol (Ortho Tri-Cyclen) Norethindrone acetate/ethinyl estradiol (Estrostep)	One tablet daily	Nausea, headache, weight gain, breast tenderness, break through bleeding, venous thromboembolism	Not for treatment of acne in men. Use only in adolescent girls ≥ 15 years of age. Pregnancy category X.
Spironolactone	25, 50, 100	50–200 mg daily	Menstrual irregularities, breast tenderness, nausea, dizziness, headache, transient diuretic effect, hyperkalemia	Not recommended for treatment of acne in men. Monitor serum creatinine and potassium. Pregnancy category C.
Oral Etinoid				
Isotretinoin	10, 20, 30, 40 tablets	0.5–1 mg/kg/day in two divided doses with food	Cheilitis, dryness of the nose, eyes, and mouth, peeling, pruritus, and drying of the face and skin, alopecia, acne flair up at start of therapy Teratogenicity Depression/suicidality Musculoskeletal pain Increased serum lipids, creatine phosphokinase, and blood glucose Photosensitivity	Nasal sprays, lip moisturizers, and hard candy may help to reduce drying of mucous membranes. Apply oil-free moisturizers to face to relieve drying of skin. Contraindicated in pregnancy category X. Monitor patient closely for changes in mood. May use nonsteroidal anti-inflammatory drugs to relieve pain Monitor lipid panel, liver function tests, and blood glucose. Minimize exposure to sunlight and sun lamps. Sunscreen use and protective clothing recommended

GI, gastrointestinal; CYP, cytochrome.

Data from (1) Lexicomp [Internet]. Hudson (OH): Wolters Kluwer Health, Inc.1978-2017 [cited 2017 June 13].Available from: http://online.lexi.com/lco/action/home/switch. (2) Facts & Comparisons eAnswers. St. Louis (MO) 2017: Wolters Kluwer health, Inc. 2017 [cited 2017 June 13]. Available from: http://fco.factsandcomparisons.com/lco/action/home

Patient Care Process: Acne

Collect Information:

- Perform dermatologic examination and note the number and type of acne lesions: open and closed comedos, papules, pustules, nodules, cysts.
- Obtain age of onset and family history of acne, including severity.
- Determine patient's current skin care routine, including use of cosmetics, facial washes, moisturizers, and other possible exacerbating factors.
- Review patient preferences and beliefs, health goals, and socioeconomic factors.
- Conduct a medication history (nonprescription, prescription, and herbal medications). Identify previous acne treatment regimens.
- Note allergies to medications or other substances.

Assess the Information:

- Assess patient symptoms and acne lesions to determine acne severity: mild, moderate, or severe.
- Determine if any medications or behaviors may be exacerbating acne.
- If patient is already receiving pharmacotherapy, assess whether active and/or previously tried therapies were effective, safe, and used as directed.

Develop a Care Plan:

- If acne is not well controlled, determine appropriate pharmacotherapy options for the patient's acne severity (Figure 65–2).
- Determine whether patient has prescription medication coverage to identify possible recommendations included in the plan formulary.

(*Continued*)

Patient Care Process (*Continued*)

- Select nondrug and drug therapy likely to be effective and safe and determine drug, dose, route, and frequency of administration/application. Use combination products as appropriate to improve adherence and reduce adverse effects (Tables 65–1 and 65–2).
- Choose appropriate changes to lifestyle.

Implement the Care Plan:

- Provide patient education on acne:
  - What is acne and how does it develop?
  - Physical and psychological complications that can result from acne.
- Educate patient on proper use, adverse effects, and expectations of acne drug therapy.
- Inform the patient of recommended changes, deletions, and additions to acne drug regimen.
- Review drug, dose, route/proper administration technique, and duration of therapy. Topical acne therapy should be applied to entire acne-prone area and existing lesions.
- Review possible side effects of drug therapy.
- Inform patient of possible initial worsening of acne and/or delay of therapeutic effectiveness of acne drug therapy.
- Emphasize medication compliance and adherence to lifestyle modifications for treating existing acne lesions and preventing recurrence.
- Address any patient concerns.

Follow-up: Monitor and Evaluate:

- Follow-up every 1 to 2 months to assess effectiveness and safety of nondrug and drug therapy (Tables 65–1 and 65–2).
- If acne lesions do not respond after 3 months of drug therapy, consider an alternative acne regimen (Figure 65–2).
- If the patient experiences resolution of acne symptoms, transition to maintenance drug therapy.

cause ACD include poison ivy, latex, and certain types of metal[27,28] (Figures 65–3 and 65–4). Table 65–3 lists agents commonly responsible for irritant and ACD. Although generally occurring on the exposed skin, such as the hands and face, contact dermatitis can appear anywhere on the body.[25]

Epidemiology and Etiology

Contact dermatitis is the most common occupation-related skin disease.[29] Although most often seen in adults, contact dermatitis can affect all age groups, with females at slightly greater risk than males due to increased risk of exposure.[28]

	Mild	Moderate	Severe
1st Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone	Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

FIGURE 65–2. Algorithms for acne treatment. The double asterisks (**) indicate that the drug may be prescribed as a fixed combination product or as separate component. (BP, benzoyl peroxide.) (From Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol. 2016;74:945–973.)

Patient Encounter 1

A 22-year-old woman complains of uncontrollable acne. She has experienced acne off and on since she was 12 years old. Her acne has been very mild for the past several years, but recently worsened. She expresses... "I thought I would have grown out of acne by this age." She has always been embarrassed by her acne, and is very self-conscious. Engaged to be married in roughly 4 months, she is anxious that her acne will negatively affect her image on her wedding day. Visual examination reveals numerous noninflammatory lesions, a few papules and pustules adjacent to her nose and on her chin, and one nodule noted on her cheek. Her skin is also very dry and irritated. A month ago, she was evaluated by her primary care physician who prescribed Retin-A 0.05% cream at bedtime. She reports that she has been applying her acne cream directly to each lesion daily, but continues to break out. She washes her face at least twice a day with an over-the-counter face wash containing salicylic acid with warming action to "get the dirt out of her blackheads." She is very adamant about adjusting her acne regimen to ensure her acne is cleared up prior to her wedding. She is very frustrated because her current regimen is not improving her complexion and is making her skin very dry and irritated. She has never seen a dermatologist. The patient appears to be in good physical health.

What reported symptoms support the diagnosis of acne?

What other information would you obtain from this patient before determining a treatment plan for her?

Describe your treatment goals for this patient.

What nonpharmacologic treatment options and lifestyle modifications would you suggest to this patient?

What pharmacologic treatment options are available for this patient?

Given the information presented, develop a treatment regimen for this patient that includes (a) a statement of the drug-related needs and/or problem, (b) a patient-specific therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

Pathophysiology

LO 1

ICD is not the result of an immunologic process, but rather occurs from direct injury to the skin. An irritating agent comes into contact with the skin, damages the protective layers of the epidermis, and can cause erythema, the formation of vesicles and pruritus.[23,25,26] Symptoms occur within minutes to hours of exposure and begin to heal soon after removal of the offending substance.

LO 1

ACD is a type IV hypersensitivity reaction.[27] Upon initial exposure, a substance penetrates the skin, is processed by antigen presenting cells, and subsequently activate allergen-specific T cells. Subsequent exposures to that substance will elicit a response by circulating memory T cells, resulting in an allergic reaction.[23,25,26,27] Symptoms of ACD are similar to those of the irritant type, but may take several hours to several days to develop following reexposure.[23,30]

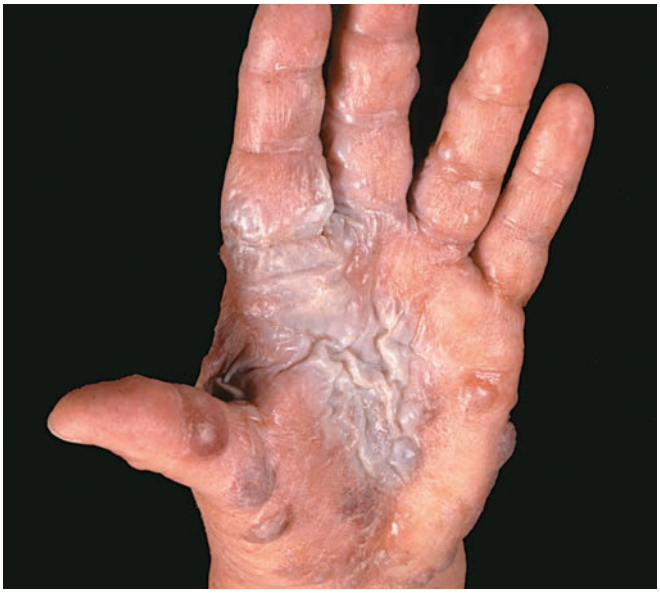

FIGURE 65–3. Acute irritant contact dermatitis on the hand due to an industrial solvent. There is massive blistering on the palm. (From Wolff K, Johnson RA. Eczema/dermatitis. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York: McGraw-Hill; 2009:23.)

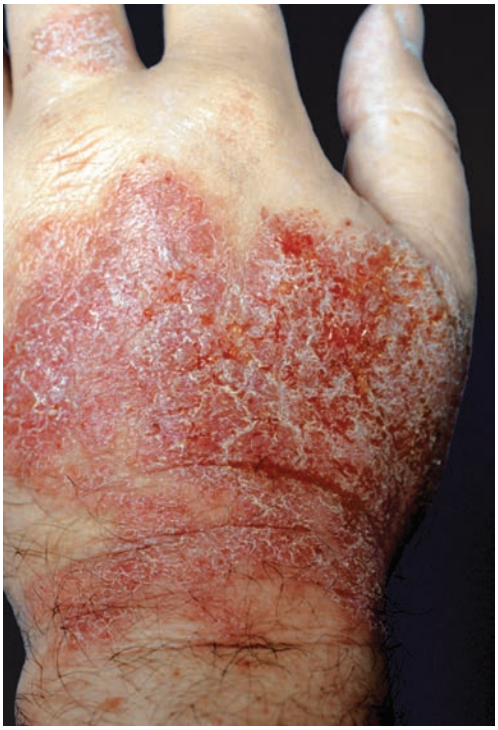

FIGURE 65–4. Allergic contact dermatitis of the hand: chromates. Confluent papules, vesicles, erosions, and crusts on the dorsum of the left hand in a construction worker who was allergic to chromates. (From Wolff K, Johnson RA. Eczema/dermatitis. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York: McGraw-Hill; 2009:27.)

Table 65–3

Common Agents Causing Contact Dermatitis

Irritant Contact Dermatitis
Soaps
Detergents
Cosmetics
Solvents
Acid, mild or strong
Alkali, mild or strong

Allergic Contact Dermatitis
Plant resins, poison ivy, poison oak, sumac
Metals (nickel or gold in jewelry)
Latex and rubber
Cigarette smoke
Local anesthetics (lidocaine, benzocaine)

Treatment

▶ *Desired Outcomes and Goals*

LO 4 KEY CONCEPT Identifying the causative substance and eliminating its exposure is the initial treatment goal for contact dermatitis. Although physical symptoms can develop almost immediately after contact, removal of the offending agent will improve existing symptoms and prevent further complications.[5] Removing the offending agent includes washing the skin and any clothing or objects that may have come into contact with the agent to prevent reexposure. LO 2 KEY CONCEPT The second treatment goal is symptom relief. Since inflammation and pruritus, as well as lesion formation, are likely to result from contact dermatitis, appropriate selection of nonpharmacologic and pharmacologic agents for these symptoms is necessary.[31]

Clinical Presentation and Diagnosis of Contact Dermatitis

Contact dermatitis is generally confined to the area of contact, but, in a highly sensitive person, a widespread or even generalized eruption may occur. Contact dermatitis is divided into two forms—irritant and allergic. Both forms may include, but are not limited to:

- Erythema
- Pruritus
- Vesicles
- Papules
- Crusts
- Burning
- Pain

Irritant Form

The irritant form usually presents within hours of exposure and the rash is often localized. Irritant contact dermatitis may also result in fissuring and scaling.

Allergic Form

The allergic form can take several days to present and the condition may extend beyond the borders of the region exposed. Allergic contact dermatitis may cause intense itching and include oozing pustules and skin erosion.

Diagnosis

Contact dermatitis may be suspected based on clinical presentation, especially if the causative agent is known; however, patch testing may be necessary to confirm the diagnosis.[30]

▶ *Nonpharmacologic Therapy*

In many cases, contact dermatitis may not require medical treatment. Nondrug therapy for contact dermatitis is aimed at relieving pruritus and maintaining skin hydration.[27] Effective agents used for this include the following[23,33]:

LO 4
- Colloidal oatmeal baths
- Cool or tepid soapless showers
- Cool, moist compresses applied to the area for 20–30 minutes as often as needed
- Emollients applied to the area after bathing

Preventative measures to prevent additional exposure should be considered including gloves, protective clothing, barrier creams, and skin conditioning products.

▶ *Pharmacologic Therapy*

LO 4 **Topical Steroids** Erythema, inflammation, pain, and itching caused by ACD can be effectively treated with topically applied corticosteroids. The use of topical corticosteroids for the management of ICD is controversial, as patients with ACD generally respond better to therapy than those with ICD.[31] With such a wide range of products and potencies, appropriate steroid selection is based on severity and location of lesions (see Table 65–4 for a list of topical steroids and potencies). Higher potency preparations are used in areas where penetration is poor, such as the elbows and knees. Lower potency products should be reserved for areas of higher penetration, such as the face, axillae, and groin. Low-potency steroids are also recommended for the treatment of infants and children.[31–33] The use of topical corticosteroids for prolonged periods of time should be avoided.

LO 5 Adverse effects from topical steroids are usually related to the potency of the steroid, frequency of application, duration of therapy, and the site of application. Skin atrophy, hypopigmentation, striae, and steroid-induced acne are all possible side effects associated with long-term use.[26] Ointments, because of their occlusive properties, should be avoided on weeping lesions.[23,34]

Topical steroids are typically applied two to four times daily. As improvement begins, maintenance therapy should be limited to the lowest strength steroid that continues to control the condition. Once symptoms are completely resolved, use should be discontinued and should not exceed 1 to 2 weeks.[35]

LO 4 **Antihistamines** Whether due to their antihistaminic activity or their sedative side effects, pruritus caused by contact dermatitis can be relieved with the use of sedating oral antihistamines, such as diphenhydramine or hydroxyzine. Topical antihistamines are available, but use is limited due to their high-sensitizing potential.[23,36] In addition to sedation, many oral antihistamines can cause hypotension, dizziness, blurred vision, and confusion.

LO 4 **Astringents** The drying effect of astringents will decrease oozing from lesions and relieve itching.[23,30] Due to their ability to cause blood vessel constriction, astringents can also

Table 65–4

Topical Corticosteroid Potency Chart

Potency Rating	Topical Dosage Forms
Class 1: Superpotent	Betamethasone dipropionate 0.05% ointment (Diprolene and Diprosone ointment)
	Clobetasone propionate 0.05% lotion/spray/shampoo (Clobex lotion/spray/shampoo, OLUX foam)
	Clobetasone propionate 0.05% cream and ointment (Cormax, Temovate, Dermovate)
	Desoximetasone 0.25% spray (Topicort)
	Flucinonide 0.1% cream (Vanos)
	Halobetasol propionate 0.05% cream, lotion, ointment (Ultravate)
	Flurandrenolide tape 4 mcg/cm^2 (Cordran)
Class 2: Potent	Amcinonide 0.1% ointment (Cyclocort ointment)
	Betamethasone dipropionate 0.05% cream/gel (Diprolene cream, gel, and Diprosone cream)
	Desoximetasone 0.25% cream, oinment (Topicort)
	Diflorasone diacetate 0.05% (Florone, Psorcon)
	Fluocinonide 0.05% cream, gel, ointment (Lidex)
	Halcinonide 0.1% cream (Halog)
Class 3: Upper mid-strength	Amcinonide 0.1% cream (Cyclocort cream)
	Betamethasone valerate 0.1% ointment (Betnovate/Valisone ointment)
	Diflorasone diacetate 0.05% cream (Psorcon cream)
	Fluticasone propionate 0.005% ointment (Cutivate ointment)
	Mometasone furoate 0.1% ointment (Elocon ointment)
	Triamcinolone acetonide 0.5% cream and ointment (Aristocort)
Class 4: Mid-strength	Betamethasone valerate 0.12% foam (Luxiq)
	Clocortolone pivalate 0.1% cream (Cloderm)
	Desoximetasone 0.05% cream, ointment and gel (Topicort LP)
	Fluocinolone acetonide 0.025% ointment (Synalar ointment)
	Fluocinolone acetonide 0.2% cream (Synalar-HP)
	Flurandrenolide 0.05% ointment (Cordran)
	Hydrocortisone valerate 0.2% ointment (Westcort ointment)
	Mometasone furoate 0.1% cream (Elocon cream)
	Triamcinolone acetonide 0.1% ointment (Kenalog)
Class 5: Lower mid-strength	Betamethasone dipropionate 0.05% lotion (Diprosonelotion)
	Betamethasone valerate 0.1% cream and lotion (Betnovate/Valisone cream & lotion)
	Desonide 0.05% lotion (DesOwen)
	Fluocinolone acetonide 0.01% shampoo (Capex shampoo)
	Fluocinolone acetonide 0.025%, 0.03% cream (Synalar cream)
	Flurandrenolide 0.05% cream and lotion (Cordran)
	Fluticasone propionate 0.05% cream and lotion (Cutivate cream and lotion)
	Hydrocortisone butyrate 0.1% cream (Locoid)
	Hydrocortisone valerate 0.2% cream (Westcort cream)
	Prednicarbate 0.1% cream (Dermatop)
	Triamcinolone acetonide 0.1% cream and lotion (Kenalog cream and lotion)
Class 6: Mild	Alclometasone dipropionate 0.05% cream and ointment (Aclovate)
	Betamethasone valerate 0.05% cream and ointment
	Desonide 0.05% cream, ointment, gel (DesOwen, Desonate, Tridesilon)
	Desonide 0.05% foam (Verdeso)
	Fluocinonide acetonide 0.01% cream and solution (Synalar)
	Fluocinonide acetonide 0.01% FS oil (Derma-Smoothe)
Class 7: Least potent	Hydrocortisone 0.5%, 1%, 2%, 2.5% cream, lotion, spray, and ointment (various brands)

From Law RM, Gulliver WP. Psoriasis. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill. http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146069987. Accessed September 4, 2017.

decrease inflammation. Aluminum acetate (Burow's solution), aluminum sulfate/calcium acetate solution (Domeboro), calamine lotion, colloidal oatmeal baths/soaks, and witch hazel are safe and effective.[23] Aluminum acetate or aluminum sulfate/calcium acetate may be applied as a compress for 30 minutes at least four times daily as needed. Colloidal oatmeal baths or soaks may be applied for 15–20 minutes at least twice daily.

LO 5

Adverse effects reported with these agents are minimal and include drying and tightening of the skin.

T-Cell Selective Inhibitors Topical T-cell selective inhibitors, such as tacrolimus and pimecrolimus are approved for the treatment of atopic dermatitis, but may also be effective in the treatment of ACD.[30,32,35]

Outcome Evaluation

LO 6

With adequate treatment, most cases of contact dermatitis should improve within 7 days. Complete resolution of symptoms may take up to 3 weeks.[23] If patients experience severe symptoms

Patient Care Process: Contact Dermatitis

Collect Information:

- Assess symptoms.
- Obtain a thorough patient history. Can the agent/exposure be identified? Has there been prior exposure to that agent? If so, what treatment regimens were used to alleviate symptoms?
- Obtain patient's allergy status.

Assess the Information:

- Determine whether the patient has ICD or ACD.
- Discuss testing needed to suggest or confirm the etiologic agent (patch testing).

Develop a Care Plan:

- Develop a treatment plan for ICD or ACD. In most cases, nondrug and nonprescription treatment options are most appropriate. If case is severe or if the patient has ACD, the plan may also include prescription therapy.

Implement the Care Plan:

- Provide patient education on ICD or ACD and treatment:
  - Possible adverse effects of drug therapy
  - Symptoms that warrant physician referral
  - Importance of treatment compliance
  - Educate on the recognition of agents that may cause contact dermatitis.

Follow-up: Monitor and Evaluate:

- Symptoms should improve within 2–3 days. If no improvement, the patient should be advised to follow-up with the provider.

associated with fever or difficulty breathing, they should be instructed to seek medical attention immediately. Furthermore, patients should return to their health care provider if any of the following occur:

- Rash has not improved (increased in size or spread to other locations) after several days of treatment.
- Patient is experiencing adverse effects from the treatment regimen.

DIAPER DERMATITIS

Epidemiology and Etiology

Diaper dermatitis, more commonly known as diaper rash, is a form of ICD that affects the buttocks, upper thighs, lower abdomen, and genitalia of an estimated 7% to 35% of all infants.[37] Onset of occurrence is usually between 3 weeks and 2 years of age, with the most cases reported between 9 and 12 months of age.[37] The use of diapers for incontinence in adults also increases the risk of developing diaper dermatitis.[37]

Pathophysiology

KEY CONCEPT Although many factors contribute to diaper rash, it is most likely the result of prolonged contact of the skin with urine and feces in the diaper. If a diaper is not changed soon after urination or defecation, the excessive hydration, friction of the diaper, and enzymes in the feces lead to breakdown in the protective layer of the skin making the area more susceptible to irritation and infection.[38,39] Although most mild cases of diaper rash present as erythema, moderate to severe cases can result in the formation of papules, vesicles, and even ulceration. If these cases are not effectively treated, the likelihood of secondary fungal or bacterial infections developing is greatly increased.[40]

LO 1

Treatment

▶ *Desired Outcomes and Goals*

KEY CONCEPT The primary goal in the treatment of diaper rash is prevention and is most often accomplished through frequent diaper changes. KEY CONCEPT When a diaper rash is already present,

LO 2

Patient Encounter 2

A 36-year-old man presents to your pharmacy with complaints of intense itching and shows you a red, raised rash with papules on his legs. The patient tells you that he recently spent the weekend hiking and camping with several friends. He states that he mostly wore T-shirts, shorts, and hiking boots, but occasionally went barefoot or wore sandals to let his "feet breathe." He does not think he saw any poison ivy on the trip, but his friend suggested that his rash looks like it may be caused by poison oak or poison ivy. The patient states he tried some kind of soap that said it would help treat poison ivy, but has not tried anything else to manage his symptoms, which are worsening. From the information he has presented, you conclude that he did likely come in contact with an agent while camping and that exposure caused an allergic contact dermatitis to develop.

What information supports the possibility of exposure to an allergic agent?

Describe the symptoms that support this diagnosis.

Determine what the patient has tried to relieve her symptoms.

Describe the differences between allergic and irritant contact dermatitis.

What are your treatment goals for this patient?

What nonpharmacologic and pharmacologic treatment options are available for this diagnosis?

Given the information presented, develop a treatment regimen for this patient that includes (a) a statement of the problem, (b) a patient-specific therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

Clinical Presentation and Diagnosis of Diaper Dermatitis

Typical Symptoms

- Erythema is the most common symptom presented with a diaper rash. The rash may begin as light to medium pink with poorly defined edges, but may become dark red and raised lesions with distinct edges.
- Rashes generally appear in the folds of the skin around the diaper area, thighs, genitals, and buttocks.
- Other typical symptoms include irritation and pruritus.

Atypical Symptoms

Patients presenting with the following symptoms may indicate the need for more aggressive antibiotic or antifungal therapy and should be referred to a physician for further evaluation:

- Rashes not responding to typical creams and concurrent nonpharmacologic treatment
- Rashes extending beyond the diaper region (upper abdomen, back)
- Formation of papules, bullae, ulceration
- Excessive oozing
- Presence of genital discharge
- Concurrent fever
- Rashes appearing when diapers have not been used or rashes that fail to improve upon discontinuing diaper usage for extended periods of time (several days or more)
- Bleeding or open skin

Diagnosis

- The diagnosis of diaper dermatitis is clinical. The presence of *Candida albicans* can be determined by KOH testing or culture, but is generally not necessary.

repairing the damaged skin, relieving discomfort, and preventing secondary infections from occurring are important factors to consider when developing an effective treatment regimen.[39]

▶ *Nonpharmacologic Therapy*

LO 4 Most mild cases of diaper rash can be resolved with the use of nonpharmacologic therapies. Keeping the diaper area clean and dry by changing diapers as soon as practically possible (at least every 2 hours or more frequently) is highly effective for treatment and prevention.[30,40] Other nondrug options include[31,39,41]:

- Washing the area with lukewarm water and mild soap and allowing to completely dry before applying a new diaper
- Using water and a cotton cloth or commercial "baby wipes" without coloring, fragrances, or other additives
- Keeping diapers loose and well ventilated
- Avoiding plastic pants over diapers
- Allowing infants to take naps on an open diaper or absorbent pad to promote drying and healing

▶ *Pharmacologic Therapy*

LO 4 **Protectants** Protectants form an occlusive barrier between the skin and moisture from the diaper. Cream and ointment preparations are effective in providing a sufficient barrier in mild, irritant, and noninfected diaper rashes. For more severe cases, a paste is the topical agent of choice. Pastes are thicker and often contain additional ingredients (petrolatum, moisturizers) to decrease discomfort and promote healing.[39] Zinc oxide is one of the most commonly used topical protectants. In addition to forming an effective barrier against moisture, it has astringent and antiseptic properties that provide added symptom relief.[39]

Protectants are generally applied to the affected area after every diaper change and can be discontinued when the rash resolves. Other available protectants that can be used alone or in combination for the safe and effective treatment of diaper rash include white petrolatum, vitamins A and D, lanolin, and topical cornstarch. Many agents contain a combination of occlusive and protective agents such as Triple Paste and Calmoseptine.

Topical Steroids Because of the increased permeability of their skin, infants are at risk for excessive absorption and toxicity from the use of topical steroids. Although effective in decreasing inflammation and relieving pruritus, steroid use in infants for the treatment of diaper dermatitis should be limited to only low-potency preparations.[41]

LO 7 A thin layer of hydrocortisone cream (0.25% to 1%) applied twice a day for no more than 2 weeks is an appropriate regimen. Use of higher potency steroids or use extending beyond 2 weeks should be at the discretion of a physician only.

LO 4 **Antifungals** Diaper rashes lasting longer than 48 to 72 hours are at increased risk for the development of fungal infections. These complications are most frequently caused by *C. albicans* and will require treatment with a topical antifungal[42] (Figure 65–5).

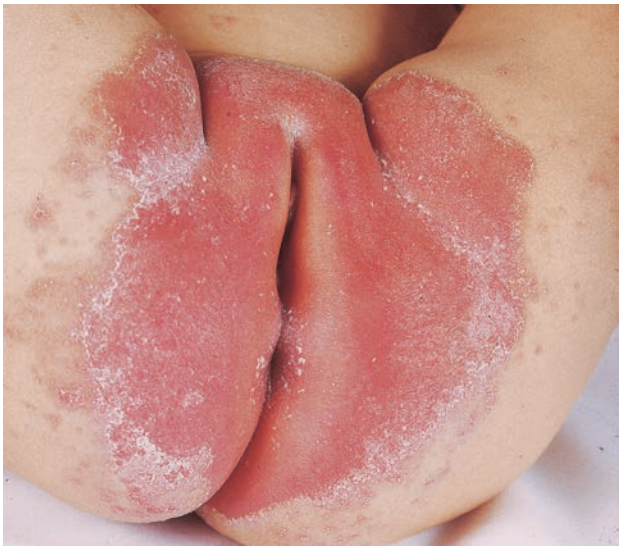

FIGURE 65–5. Candidiasis: diaper dermatitis. Confluent erosions, marginal scaling, and "satellite pustules" in the area covered by a diaper in an infant. (From Wolff K, Johnson RA. Cutaneous fungal infections. Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 6th ed. New York: McGraw-Hill; 2009:723.)

Patient Encounter 3

A woman presents to a community pharmacy inquiring about a product to purchase for her 3-month-old daughter who recently developed diaper rash. The rash has been present on the infant's buttocks for 3 to 4 days and has increasingly worsened from light pink to bright red. The mother reports that her daughter cries during each diaper change, especially when she cleans the areas with diaper wipes. She tells you that she has been trying to wash the area more frequently. She has tried using A & D ointment a few times and is now concerned about the risk of infection.

What reported symptoms support the diagnosis of diaper rash?

What additional information would aid in your assessment of this patient?

What are your treatment goals for this patient?

What nonpharmacologic and pharmacologic treatment options are available for this diagnosis?

Given the information presented, develop a treatment regimen for this patient that includes (a) a statement of the problem, (b) a patient-specific therapeutic plan, and (c) monitoring parameters to assess efficacy and safety.

LO 5 Adverse events with the use of topical antifungals are generally limited to local irritation at the site of application.

Nystatin, clotrimazole, and miconazole creams or ointments applied two to four times daily with diaper changes have all shown to be effective in the treatment of candidal diaper rash.[43] LO 7 Although some of these products are available over the counter, parents and caregivers should be advised to initiate treatment with antifungal agents only after physician's recommendation.

Antibacterials If conventional treatment fails, unresolved diaper rash can also lead to secondary bacterial infections. *Staphylococcus aureus* and *Streptococcus* are the most likely pathogens responsible for these infections and require treatment with systemic antibiotics.[38,40] While topical protectants may be used as an adjunct in treatment, suspected bacterial infections should always be referred to a physician for accurate diagnosis and the selection of an appropriate antibacterial regimen.[38] Figure 65–6 shows a useful algorithm for the effective treatment of diaper dermatitis.

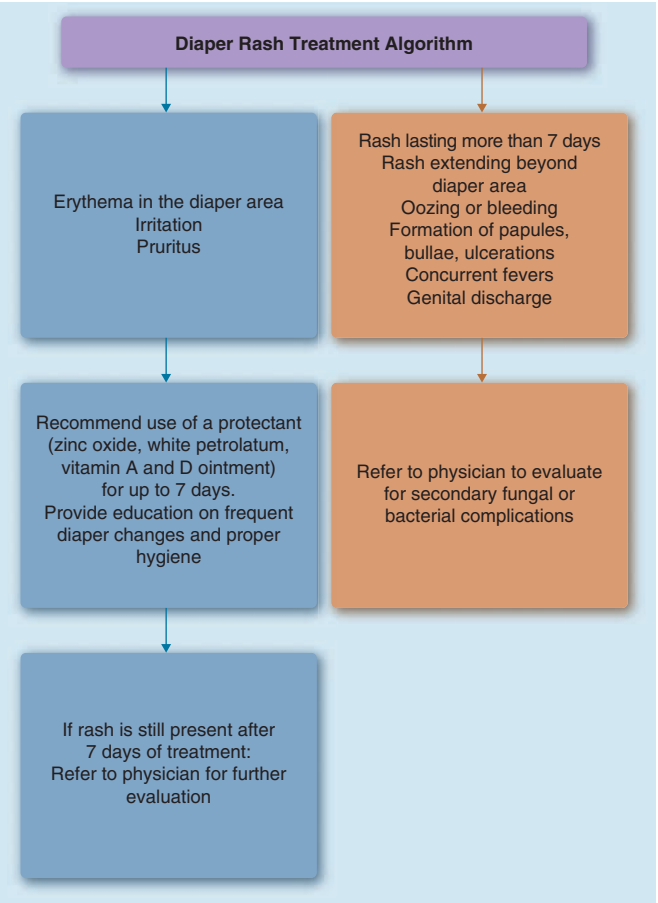

FIGURE 65–6. Diaper dermatitis treatment algorithm.

Patient Care Process: Diaper Dermatitis

Collect Information:

- Gather information related to rash symptoms, characteristics, location, and onset.
- Inquire about the patient's history, including similar rashes in the past, and any previous treatment.
- Obtain patient's allergy status.

Assess the Information:

- Determine the level of severity—is there a possibility of a secondary fungal or bacterial infection?
- Identify any signs and symptoms that require immediate physician referral.
- Determine what treatment options, if any, have been tried and if they were successful.
- Discuss labs that may be necessary if a secondary infection is suspected (cultures, biopsies).

Develop a Care Plan:

- Discuss available barrier treatment options with the caregiver.
- Identify appropriate preventative and treatment measures.

Implement the Care Plan:

- Provide caregiver education that includes proper usage instructions and potential side effects.
- Educate the caregiver on the importance of frequent diaper changes and proper hygiene.
- Emphasize importance of treatment compliance and use of preventative measures.

Follow-up: Monitor and Evaluate:

- Discuss symptoms to report to a physician (blistering, oozing, bleeding, changes in rash, or no improvement in symptoms within 2–3 days).

Outcome Evaluation

LO 6

KEY CONCEPT Most diaper rashes can be effectively treated in less than 1 week. If symptoms do not resolve or begin to worsen, advise caregivers to seek medical attention to determine the presence of secondary fungal or bacterial infections. In addition, provide educational information on proper diaper hygiene techniques in order to prevent the development of future diaper rashes.

Abbreviations Introduced in This Chapter

ACD	Allergic contact dermatitis
FDA	Food and Drug Administration
ICD	Irritant contact dermatitis

REFERENCES

1. Meier, MM, McCalmont TH. Diseases of the skin. In: McPhee SJ, Hammer GD. Pathophysiology of Diseases: An Introduction to Clinical Medicine, 7th ed. New-York, NY: McGraw-Hill; 2013.
2. Thiboutot D, Gollnick H. New insights into the management of acne: an update from the global alliance to improve outcomes in acne group. J Am Acad Dermatol. 2009;60:S1–S50.
3. White GM. Recent findings in the epidemiologic evidence, classification, and subtypes of acne vulgaris. J Am Acad Dermatol. 1998;39(2 pt 3):S34–S37.
4. Bhate K, Williams HC. Epidemiology of acne vulgaris. BJD. 2013;168:474–485.
5. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgairs. J Am Acad Dermatol 2016;74:945–973.
6. Bowe WP, Joshi SS, Shalita AR. Diet and acne. J Am Acad Dermatol. 2010;63:124–141.
7. Sibbald D. Acne vulgaris. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiological Approach, 10th ed. New York, NY: McGraw-Hill; 2017.
8. Foster KT, Coffey CW. Acne. In: Krinsky DL, Ferreri SP, Hemstreet B, et al., eds. The Handbook of Nonprescription Drugs, 18th ed. Washington, DC: American Pharmaceutical Association; 2015.
9. Eichenfield LF, Krakowski AC, Piggott C, et al.; American Acne and Rosacea Society. Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics. 2013;131:S163.9.
10. Decker A, Graber EM. Over-the-counter acne treatments. J Clin Aesthet Dermatol. 2012;5(5):32–40.
11. Guidance for Industry. Acne vulgaris: developing drugs for treatment. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER). Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071292.pdf. Accessed September 1, 2017.
12. Nast A, Dreno B, Bettoli V, et al. Guidelines for the treatment of acne. J Eur Acad Dermatol Venereol. 2012;26(suppl 1):1–29.
13. Thielitz A, Abdel-Naser MB, Fluhr JW, Zouboulis CC, Gollnick H. Topical retinoids in acne—an evidence based overview. J Dtsch Dermatol Ges. 2008;6:1023–1031.
14. Thielitz A, Gollnick H. Topical retinoids in acne vulgaris: update on safety and efficacy. Am J Clin Dermatol. 2008;9(6):369–381.
15. Akhavan A, Bershad S. Topical acne drugs: review of clinical properties, systemic exposure, and safety. Am J Clin Dermatol. 2003;4(7):473–492.
16. Gamble R, Dunn J, Petersen B, et al. Topical antimicrobial treatment of acne vulgaris: an evidence based review. Am J Clin Demnotol. 2012;13(3):141–162.
17. Fakhouri T, Yentzer BA, Feldman SR. Advancement in benzoyl peroxide-based acne treatment: methods to increase both efficacy and tolerability. J Drugs Dermatol. 2009;8(7):657–661.
18. Kircik, LH. Efficacy and safety of azelaic acid (AzA) gel 15% in the treatment of post-inflammatory hyperpigmentation and acne: a 16-week, baseline-controlled study. J Drugs Dermatol. 2011;10(6):586–590.
19. Stotland M, Shalita AR, Kissling RF. Dapsone 5% gel. A review of its efficacy and safety in the treatment of acne vulgaris. Am J Clin Dermatol. 2008;10(4):221–227.
20. Allergan. Aczone Package Insert. Irvine, CA: Allergan; 2012.
21. Tan HH. Antibacterial therapy for acne: a guide to selection and use of systemic agents. Am J Clin Dermatol. 2003;4(5):307–314.
22. Arowojolu AO, Gallo MF, Lopez LM. Combined oral contraceptive pills for the treatment of acne. Cochrane Database Syst Rev. 2009;7:CD004425.
23. Plake KS, Darbishire PL. Contact dermatitis. In: Krinsky DL, Ferreri SP, Hemstreet B, et al., eds. Handbook of Nonprescription Drugs, 18th ed. Washington, DC: American Pharmaceutical Association; 2015.
24. Rustemeyer T. van Hoogstraten IMW, von Blomberg BME, Gibbs S, Scheper RJ. Mechanisms of irritant and allergic contact dermatitis. In: Johansen JD, ed. Contact Dermatitis, 5th ed. 2011:43–90.
25. Parker F. Skin diseases of general importance. In: Goldman L, Bennett JC, eds. Cecil Textbook of Medicine, 21st ed. Philadelphia, PA: WB Saunders; 2000:2276–2298.
26. Whitmore SE. Dermatitis and psoriasis. In: Barker LB, Burton JR, Zieve PD, et al., eds. Principles of Ambulatory Medicine, 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:1905–1913.
27. Fonacier LS, Sher JM. Allergic contact dermatitis. Ann Allergy Asthma Immunol. 2014;113:9–12.
28. Tan C, Rasool S, Johnston GA. Contact dermatitis: allergic and irritant. Clin Dermatol. 2014;32:116–124.
29. Nicholson PJ, Llewellyn D, English JS. Evidence-based guidelines for the prevention, identification and management of occupation contact dermatitis and urticarial. Contact Dermatitis. 2010;63:177–186.
30. Fonacier L, Bernstein DI, Pacheco K, et al. Contact dermatitis: a practice parameter—update 2015. J Allergy Clin Immunol Pract. 2015;3:S1–S39.
31. Law RM, Law DS. Dermatologic drug reactions and common skin conditions. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiological Approach, 10th ed. New York, NY: McGraw-Hill; 2017.
32. Ale IS, Maibach HI. Irritant contact dermatitis. Rev Environ Health. 2014;29:195–206.
33. Cohen DE, Heidary N. Treatment of irritant and allergic contact dermatitis. Dermatol Ther. 2004;17:334–340.
34. Lee NP, Arriola ER. Poison ivy, oak, and sumac dermatitis. West J Med. 1999;171:354–355.
35. Law RM, Kwa P. Atopic dermatitis. In: Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: A Pathophysiological Approach, 10th ed. New York, NY: McGraw-Hill; 2017.
36. Burkhart C, Morrell D, Goldsmith L. Dermatological pharmacology. In: Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gillman's: The Pharmacological Basis of Therapeutics, 12th ed. New York, NY: McGraw-Hill; 2011: 1803–1832.
37. Borkowski S. Diaper rash care and management. Pediatr Nurs. 2004;30(6):467–470.
38. Atherton JD. A review of the pathophysiology, prevention and treatment of irritant diaper dermatitis. Curr Med Res Opin. 2004;20(5):645–649.

39. Stamatas GN, Tierney NK. Diaper dermatitis: etiology, manifestations, prevention, and management. Pediatr Dermatol. 2014;31:1–7.
40. Hagemeier NE. Diaper dermatitis and prickly heat. In: Krinsky DL, Ferreri SP, Hemstreet B, et al., eds. Handbook of Nonprescription Drugs, 18th ed. Washington, DC: American Pharmaceutical Association; 2015.
41. Klunk C, Domingues E, Wiss K. An update on diaper dermatitis. Clin Dermatol. 2014;32:477–487.
42. Ward DB, Fleischer AB, Feldman SR, Krowchuk DP. Characterization of diaper dermatitis in the United States. Arch Pediatr Adolesc Med. 2000;154:943–946.
43. Gupta AK, Skinner AR. Management of diaper dermatitis. Int J Dermatol. 2004;43:830–834.

66 Anemia

Maribel A. Pereiras

LEARNING OBJECTIVES

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

1. Discuss common causes of anemia.
2. Identify common signs and symptoms of anemia.
3. Describe diagnostic evaluation required to determine the etiology of anemia.
4. Develop a treatment regimen considering the underlying cause and patient-specific variables.
5. Compare and contrast oral and parenteral iron preparations.
6. Explain the optimal use of folic acid and vitamin B_{12} in patients with macrocytic anemia.
7. Evaluate the proper use of epoetin and darbepoetin in patients with anemia caused by cancer chemotherapy or chronic kidney disease.
8. Develop a plan to monitor the outcomes of pharmacotherapy for the treatment of anemia.

INTRODUCTION

KEY CONCEPT

Anemia is a deficiency of erythrocytes with a corresponding reduction in the concentration of hemoglobin (Hgb) that results in reduced oxygen-carrying capacity of the blood. Some patients with anemia may be asymptomatic initially, but eventually, the lack of oxygen to tissues results in fatigue, lethargy, shortness of breath, headache, edema, and tachycardia. Common causes include blood loss, decreased functional red blood cell (RBC) production, and increased RBC destruction. Determination of the underlying cause of anemia is essential for successful management.

LO 1 LO 2

EPIDEMIOLOGY AND ETIOLOGY

Anemia is a common diagnosis with a prevalence that varies widely based on age, gender, and race/ethnicity (Table 66–1).[1,2] Patients with specific comorbidities such as cancer and chronic kidney disease (CKD) have significantly higher rates of anemia. The incidence of anemia in cancer patients ranges from 30% to 90%. Contributing factors include the underlying malignancy and myelosuppressive antineoplastic therapy.[3] The prevalence of anemia in patients with CKD ranges from 15% to 20% in patients with CKD stages 1 through 3 and up to 70% in patients with stage 5.[4]

LO 1

A decrease in erythrocyte production can be multifactorial. Nutritional deficiencies (iron, vitamin B_{12}, and folic acid) are common causes and often easily treatable. Patients with cancer or CKD are at risk for developing anemia caused by dysregulation of iron and erythropoietin (EPO) hemostasis. Patients with chronic immune-related diseases such as rheumatoid arthritis and systemic lupus erythematosus are also at increased risk to develop anemia as a complication of their disease. Anemia related to chronic inflammatory conditions is termed anemia of chronic disease (ACD).[5]

Drug therapy is the mainstay of treatment for anemias caused by reduced RBC production and is the focus of this chapter. Anemia due to the destruction of erythrocytes, such as with blood loss or hemolytic anemia, will not be discussed.[6]

PATHOPHYSIOLOGY

Erythropoiesis

Erythropoiesis begins with a pluripotent stem cell in the bone marrow undergoing differentiation and ends with the appearance of RBCs in peripheral blood. The production of RBCs is stimulated by EPO, a hormone secreted by the kidney in response to cellular hypoxia. EPO stimulates RBC production by inducing differentiation of RBC precursors in the bone marrow to become reticulocytes (Figure 66–1). Reticulocytes become erythrocytes after 1 to 2 days in the bloodstream.[7]

Decreased-Production Anemias

▶ *Nutritional Deficiencies*

Deficiencies in folic acid and vitamin B_{12} may hinder the process of erythrocyte maturation. Folic acid and vitamin B_{12} are required for the formation of DNA. Significant decreases in the amount of either folic acid or B_{12} inhibit DNA synthesis and consequently RBC production.[7,8] Poor diet can contribute to folic acid and vitamin B_{12} deficiencies. Pernicious anemia describes a severe anemia caused by the malabsorption of vitamin B_{12} due to the absence of intrinsic factor, a glycoprotein produced by gastric parietal cells that binds to vitamin B_{12} and facilitates its absorption in the ileum. This condition results in B_{12} deficiency despite adequate dietary B_{12} intake.[9]

Iron is also essential for RBC production. It is required in the formation of Hgb. Lack of iron leads to a decrease in Hgb synthesis and decreased RBC production. Normal homeostasis of iron transport and metabolism is depicted in Figure 66–2.[10]

Table 66–1

Prevalence of Anemia[1,2]

Children (1–5 years)	43%
Males (17–84 years)	29%
Males (85+ years)	26%
Females (15–49 years, pregnant)	38%
Females (15–49 years, nonpregnant)	29%
Females (85+ years)	20%

Approximately 1 to 2 mg of iron is absorbed through the duodenum daily, and the same amount is lost via blood loss, desquamation of mucosal cells, or menstruation.

Iron-deficiency anemia (IDA) typically occurs because of inadequate absorption of iron or excessive blood loss. Inadequate absorption may occur in patients who have congenital or acquired intestinal conditions, such as inflammatory bowel disease, celiac disease, or bowel resection. Achlorhydria and diets poor in iron may also contribute to iron-deficient states. Iron deficiency may also occur following excessive iron loss. Common etiologies include excessive menstruation, ulcers, neoplastic lesions, and excessive bleeding following surgery or trauma.[10,11]

▶ *Dysregulation of Iron Homeostasis and Impaired Marrow Production*

Chronic diseases associated with ACD include infection, autoimmune disease, CKD, and cancer. A major contributing factor for development of ACD is disturbance of iron homeostasis related to activation of the immune system. Hepcidin is an acute-phase protein expressed in response to the upregulation of inflammatory cytokines. Increased expression of hepcidin causes decreased iron absorption from the gastrointestinal (GI) tract and inhibition of iron release from macrophages. In addition, immune activation can cause upregulation of cytokines that impair the proliferation and differentiation of erythroid precursors. Decreased production and blunted responsiveness to EPO can also contribute to ACD; this is best documented in patients with CKD. Finally, disruption of erythropoiesis secondary to infiltration of the bone marrow by cancer can lead to anemia.[3,5,10–12]

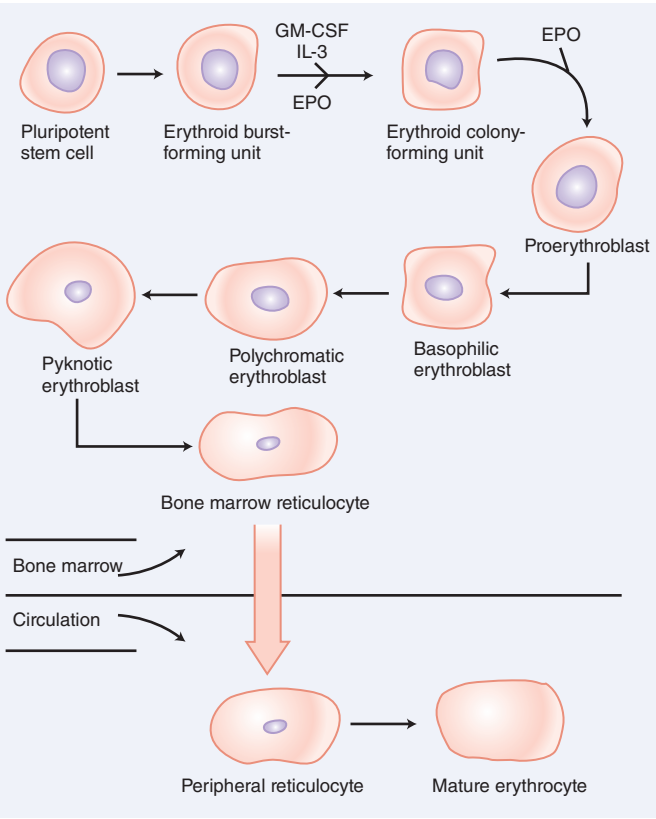

FIGURE 66–1. The process of erythropoiesis.

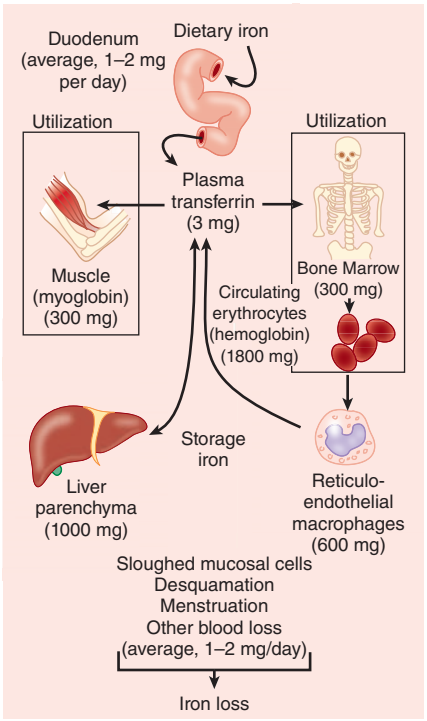

FIGURE 66–2. The distribution of iron use in adults. (From Andrews NC. Disorders of iron metabolism. N Engl J Med. 1999;341:1986–1995.)

TREATMENT

Desired Outcomes

KEY CONCEPT The goal of anemia therapy is to increase Hgb to levels that improve red cell oxygen-carrying capacity, alleviate symptoms, and prevent complications from anemia. Normal Hgb values are 14.0 to 17.5 g/dL (140–175 g/L or 8.69–10.9 mmol/L) for males and 12.3 to 15.3 g/dL (123–153 g/L or 7.63–9.50 mmol/L) for females. It is important to note that continuation of therapy should be assessed primarily by resolution of clinical symptoms. Patients who experience a resolution in their symptoms (eg, shortness of breath, tachycardia, fatigue, dizziness,) may not require aggressive therapy to maintain their Hgb values within normal limits. Hypoxia and cardiovascular sequelae due to anemia can be avoided if Hgb levels are greater than 7.0 g/dL (70 g/L or 4.34 mmol/L).[11]

General Approach to the Anemic Patient

KEY CONCEPT The underlying cause of anemia must be determined and used to guide therapy. A complete blood count (CBC) is the laboratory evaluation that provides objective characteristics of RBCs useful in determining etiology and appropriate treatment. The mean corpuscular volume and determination of iron, ferritin, folate, and vitamin B_{12} levels are required to correctly diagnose a

Patient Encounter 1, Part 1

A 58-year-old African American man was admitted to the emergency department secondary to dyspnea and fatigue or asthenia. He has also been having some paresthesias in his hands for the past 2 months. No other significant past medical history. Past surgical history includes gastric bypass surgery, 3 years ago.

What aspects of this patient's history suggest he may be anemic?

What laboratory assessments are required to make an appropriate diagnosis and therapeutic plan?

How would the requested laboratory parameter(s) aid your decision making?

patient's anemia. Figure 66–3 and Table 66–2 illustrate how laboratory test results determine the correct diagnosis.

Nonpharmacologic Therapy

The primary nonpharmacologic treatment of anemia is transfusion of RBCs. Safety concerns, cost, and the limited availability of this therapy support efforts to establish the "optimum" threshold for administering RBC transfusions. A Cochrane review concluded it is appropriate to use "restrictive transfusion triggers in patients free of serious cardiac disease." The authors concluded a reasonable "trigger for transfusion" for patients without significant cardiovascular disease is 7.0 g/dL (70 g/L or 4.34 mmol/L).[13] The Transfusion Requirements In Critical Care trial reported no significant differences in in-hospital mortality between patients randomly assigned to maintain Hgb levels of 7.0 to 9.0 g/dL (70–90 g/L or 4.34–5.59 mmol/L) and

Clinical Presentation and Diagnosis of Anemia

LO 2

Signs and Symptoms

Generally, the signs and symptoms of anemia are nonspecific and may include the following:

- Fatigue, lethargy, dizziness
- Shortness of breath
- Headache
- Edema
- Tachycardia

Other findings that may be present in some patients include:

- Dry skin, chapped lips
- Nail brittleness
- Hunger for ice, starch, or clay (termed pica)

Past Medical History

Inquire about the following conditions:

- History of blood loss, such as hemorrhoids, melena, or menorrhagia (IDA)
- Malnourished or recent weight loss (vitamin B_{12} or folate deficiency)
- Alcoholism (folate deficiency)
- Cancer or CKD
- Chronic autoimmune disorders or infections, such as HIV infection or rheumatoid arthritis (anemia of chronic disease)

Physical Examination

These findings aid the clinician in determining the severity of the anemia:

- Orthostatic hypotension and tachycardia secondary to volume depletion
- Cutaneous changes such as pallor, jaundice, and nail brittleness

LO 3

Laboratory Evaluation

Table 66–2 describes common tests used to determine the etiology of anemia. A diagnostic and treatment algorithm for anemia is outlined in Figure 66–3.

1. A CBC is a necessary first step in evaluating a patient with anemia. If the Hgb and Hct are less than the normal range, the patient is anemic. Subsequent evaluations of RBC indices and the peripheral smear often are necessary to determine the etiology (and ultimately, the treatment) of the anemia.
2. Evaluating the mean corpuscular volume (MCV) is the next step in an anemia workup. It is classified as microcytic, normocytic, or macrocytic if the MCV is below, within, or above the normal range of 80 to 96 fL/cell, respectively.

Microcytic Anemia and Iron Evaluation

Iron studies (see Table 66–2) should be evaluated in the setting of a low MCV. These include:

- Serum iron
- Serum ferritin—the best indirect determinant of body iron stores. It is commonly decreased in patients with IDA
- Total iron-binding capacity (TIBC)—quantifies the iron-binding capacity of transferrin and is increased in IDA
- Transferrin saturation (serum iron/TIBC)—indicates the amount of transferrin that is bound with iron; it is lower in IDA

Macrocytic Anemia

- Evaluate folic acid and vitamin B_{12} levels in the setting of an elevated MCV
- Further investigation by administering radiolabeled B_{12} (ie, Schilling test) to determine if lack of intrinsic factor

Normocytic Anemia

- Evaluate reticulocytes and CBC
- High reticulocyte counts may indicate RBCs loss via acute blood loss, hemolysis, or splenic sequestration
- Low serum iron with normal to increased ferritin consistent with ACD

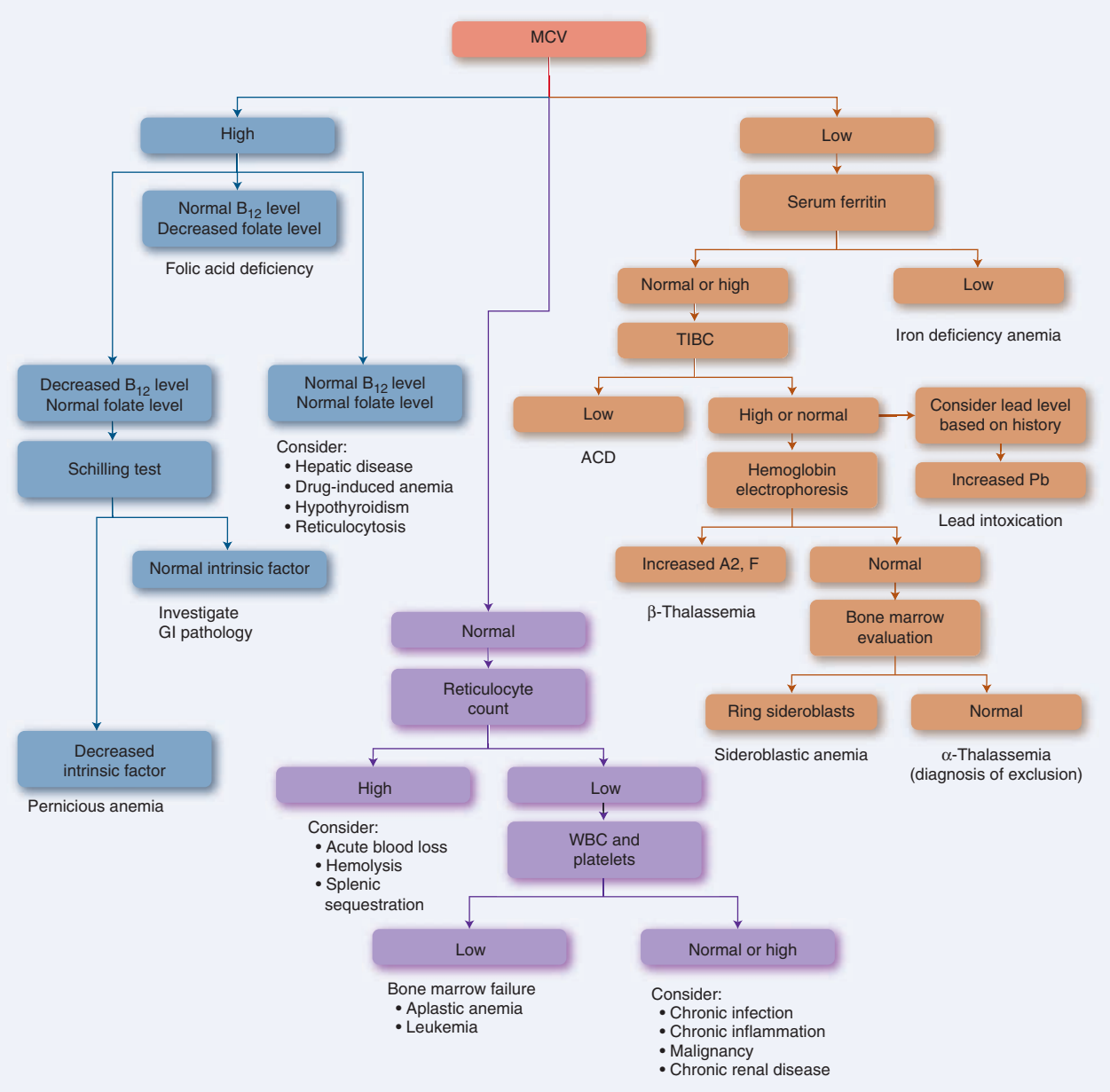

FIGURE 66–3. The anemia evaluation process. (ACD, anemia of chronic disease; A2, hemoglobin A2 type; F, hemoglobin F type; MCV, mean corpuscular volume; Pb, lead; TIBC, total iron-binding capacity.)

10.0 to 12.0 g/dL (100–120 g/L or 6.21–7.45 mmol/L).[14] Typically, only patients with acute symptoms (ie, dyspnea, chest pain) and Hgb concentrations in the range of 7.0 to 9.0 g/dL (70–90 g/L or 4.34–5.59 mmol/L) require blood transfusions.

Anemia can be attributed to diets poor in iron, folic acid, or vitamin B_{12}. However, in the United States, nutrient-poor diets rarely cause anemia. Therefore, ingesting a diet that is rich in iron, folic acid, or vitamin B_{12} should be encouraged, but is rarely the sole modality of treatment. Food sources of iron, folic acid, and vitamin B_{12} are listed in Table 66–3.

Pharmacologic Therapy

▶ *Iron-Deficiency Anemia*

KEY CONCEPT The gold standard treatment of IDA is oral iron therapy that provides 150 to 200 mg of elemental iron daily in divided doses. Many different iron products and salt forms are available.

LO 5

Typically, iron sulfate is the most commonly used formulation. Table 66–4 lists commonly prescribed oral iron products and the amount of elemental iron provided by each.

Iron supplementation resolves anemia by replenishing iron stores to levels necessary for RBC production and maturation. Reticulocytosis should occur in 7 to 10 days, and Hgb values should rise by about 1.0 g/dL (10 g/L or 0.62 mmol/L) per week. Patients should be reassessed if Hgb does not increase by 2.0 g/dL (20 g/L or 1.24 mmol/L) in 3 weeks.[15]

The preferred regimen for oral iron is 50 to 65 mg of elemental iron two to three doses daily on an empty stomach. Administration on an empty stomach (1 hour before or 2 hours after a meal) is preferred for maximal absorption. If patients develop intolerable GI side effects (ie, heartburn, nausea, bloating) after taking iron on an empty stomach, they should be advised to take it with meals. After absorption, iron binds to transferrin in

Table 66–2

Pertinent Laboratory Tests in the Evaluation of Anemia

Test Name	Normal Range	Description/Significance
CBC		
Hgb	Males: 14.0–17.5 g/dL (140–175 g/L or 8.69–10.9 mmol/L) Females: 12.3–15.3 g/dL (123–153 g/L or 7.63–9.50 mmol/L)	Amount of Hgb in the blood; signifies oxygen-carrying capacity of the blood and determines whether a patient is anemic
Hct	Males: 40.7%–50.3% (0.407–0.503) Females: 36.1%–44.3% (0.361–0.44.3)	The percent of blood that the erythrocytes encompass; also indicates anemia; the Hgb is measured, and the Hct is calculated
RBC	Males: 4.5–5.9 × 10^6 cells/μL (4.5–5.9 × 10^{12} cells/L) Females: 4.1–5.1 × 10^6 cells/μL (4.1–5.1 × 10^{12} cells/L)	The number of erythrocytes in a volume of blood; also indicates anemia, but seldom used
RBC Indices		
MCV	80–97.6 μm^3/cell (80–97.6 fL/cell)	A widely used laboratory value to measure RBC "size"; higher values indicate macrocytosis and lower values indicate microcytosis
MCH	27–33 pg/cell	Amount of Hgb per RBC; may be decreased in IDA
MCHC	32–36 g/dL (320–360 g/L)	Hgb divided by the Hct; also low in IDA
Iron Studies		
Serum iron		
Males	45–160 mcg/dL (8.1–28.6 μmol/L)	Measures amount of iron bound to transferrin; low in IDA
Females	30–160 mcg/dL (5.4–28.6 μmol/L)	
Serum ferritin		
Males	20–250 ng/mL (20–250 mcg/L; 45–562 pmol/L)	Ferritin is the protein–iron complex found in macrophages used for iron storage; low in IDA
Females	10–150 ng/mL (10–150 mcg/L; 22–337 pmol/L)	
TIBC	220–420 mcg/dL (39.4–75.2 μmol/L)	Measures the capacity of transferrin to bind iron; high in IDA
TSAT	15%–50% (0.15–0.50)	TSAT (%) = (serum iron/TIBC) × 100; a saturation of less than 15% (0.15) is common in IDA
Other Tests		
RBC distribution width (RDW)	11.5%–14.5% (0.115–0.145)	A higher value means the presence of many different sizes of RBCs; the MCV is therefore less reliable when RDW is larger
Reticulocyte count (Erythrocyte precursors)		Should be elevated in patients who are responding to treatment
Males	0.5%–1.5% of RBCs (0.005–0.015)	
Females	0.5%–2.5% of RBCs (0.005–0.025)	
Folic acid (plasma)	3.1–12.4 ng/mL or mcg/L (7.0–28.1 nmol/L)	Used to determine folic acid deficiency
Folic acid (RBC)	125–600 ng/mL (283–1360 nmol/L)	Used to determine folic acid deficiency
Vitamin B_{12}	180–1000 pg/mL (133–738 pmol/L)	Used to determine vitamin B_{12} deficiency
EPO level	2–25 mIU/mL (2–25 IU/L)	Patients may benefit from EPO therapy if they are anemic and EPO levels are normal or mildly elevated

EPO, erythropoietin; Hct, hematocrit; Hgb, hemoglobin; IDA, iron-deficiency anemia; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; RDW, RBC distribution width; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

the plasma and is transported to the muscles (for myoglobin), liver (for storage), or bone marrow (for red cell production). Common toxicities associated with oral iron include abdominal pain, nausea, heartburn, constipation, and dark stools.[16] New data is emerging regarding the optimal dosing schema for iron supplementation based on additional information regarding iron absorption and the effect on hepcidin. A study by Motretti and colleagues suggests that lower doses and less frequent dosing may improve the amount of iron absorbed. This data requires further evaluation but may offer a more convenient dosing schedule while minimizing side effects.[17,18]

Potentially clinically significant drug–drug interactions involving iron products include fluoroquinolones, tetracyclines, eltrombopag, and mycophenolate mofetil. Iron decreases the absorption of these drugs. The absorption of iron is influenced by gastric acidity. Limited data support drugs that decrease gastric acidity (antacids, proton pump inhibitors, and H_2-receptor antagonists) may impair the absorption of iron. If concurrent administration cannot be avoided, to minimize this interaction, oral iron should be administered at least several hours before or after the affected drug. The absorption can also be affected by certain disease states that may limit the absorption, such as celiac disease, inflammatory bowel disease or patients who have had gastric surgeries.[11]

Table 66–3

Food Sources of Iron, Folic Acid, or Vitamin B_{12}[41]

Nutrient	Food Sources
Iron	Red meat, organ meats, wheat germ, egg yolks, oysters
Folic acid	Green vegetables, liver, fruits, fortified cereals, chickpeas, enriched pasta
Vitamin B_{12}	Animal by-products, milk, yogurt

Patient Encounter 1, Part 2

Laboratory parameters are ordered, and the following is reported

CBC

- WBC: 6.50 × 10^3/μL (6.50 × 10^9/L)
- Hgb: 8.3 g/dL (83 g/L; 5.15 mmol/L)
- Hct: 24.8% (0.248)
- Plt: 121 × 10^3/μL (121 × 10^9/L)

Red Blood Cell Indices

- MCV: 120.4 μm^3 (120.4 fL)
- MCH: 28.4 pg/cell
- MCHC: 35.3 g/dL (353 g/L; 21.9 mmol/L)

Others

- RBC count: 3.6 × 10^6/μL (3.6 × 10^{12}/L)
- RDW: 22% (0.22)

Iron Studies

- Serum iron: 100 mcg/dL (17.9 μmol/L)
- Serum ferritin: 123 ng/L (123 mcg/L; 276 pmol/L)
- TIBC: 300 mcg/dL (53.7 μmol/L)
- Transferrin saturation: 36% (0.36)

B_{12} and Folate

- Serum folate: 5.3 ng/mL (12.0 nmol/L)
- Serum B_{12}: 127 pg/mL (93.7 pmol/L)

Is this a macrocytic or microcytic anemia?

Specifically, what is the etiology of the anemia?

Recommend the most appropriate drug regimen (drug, dosage form, and schedule).

Parenteral iron therapy is indicated when patients cannot tolerate oral formulations, have decreased intestinal absorption or are noncompliant. Five parenteral iron formulations are available in the United States.[19–24] Table 66–5[20–24] provides details pertinent to the use of these products. Iron dextran was available in two formulations, as a high and low molecular weight iron product. Dexferrum (the high-molecular-weight [HMW] product) is associated with a much higher incidence of life-threatening adverse effects, typically anaphylactic-like reactions, and this formulation has been discontinued.[25] Although total dose infusion (TDI), where the total replacement dose of iron is administered in one dose is not an approved method of administration in the United States, low-molecular-weight ID is approved for TDI in Europe. TDI administration achieves similar patient outcomes while lowering costs. Sodium ferric gluconate complex, iron sucrose, ferumoxytol, and ferric carboxymaltose received FDA labeling for the treatment of patients with anemia and CKD in the last decade.[19–24] Although the occurrence of life-threatening adverse events caused by parenteral iron is extremely low, the absolute rate of life-threatening events is substantially higher for HMW ID.[21]

The dose of iron dextran is calculated by the following equation: dose (mL) = 0.0442 (desired Hgb – observed Hgb) × body weight + (0.26 × body weight). The body weight that should be used is lean body weight for adults and children weighing more than 15 kg and actual body weight for children weighing 5 to 15 kg. Hemoglobin should be expressed in units of g/dL (hemoglobin expressed in g/L × 0.10, or mmol/L × 1.61). The dose in milligrams can be calculated based on a standard concentration of 50 mg of elemental iron per milliliter.[19] Prescribing information recommends administering iron dextran in 100-mg aliquots daily until the total dose is achieved. However, anecdotal evidence reports that the total calculated dose can be administered safely over 4 to 6 hours on 1 day. Because of the risk of anaphylaxis, a test dose of iron dextran (0.5 mL over at least 30 seconds) must be administered to patients before their first dose of iron dextran. Patients should be monitored for signs of anaphylaxis for at least 1 hour before administering the remaining total dose. Other adverse effects include arthralgias, arrhythmias, hypotension, flushing, and pruritus.[19]

▶ *Vitamin B_{12} and Folic Acid Anemia*

KEY CONCEPT Anemia from vitamin B_{12} (also known as pernicious anemia) or folic acid deficiency is treated by replacing the missing nutrient. Both folic acid and vitamin B_{12} are essential for erythrocyte production and maturation.

Table 66–4

Oral Iron Products and Elemental Iron Content[37–40]

Salt Form	Brand Name(s)	Percent of Elemental Iron	Formulation types
Ferrous sulfate	FeroSul Fer-In-Sol Slow Fe	~20	Elixir, liquid, solution Tablet—slow and extended release
Ferrous sulfate, anhydrous	N/A	~30	Tablet
Ferrous gluconate	Ferate	~12	Tablets
Ferrous fumarate	Ferretts Ferrimin Hemocyte	33	Tablets
Polysaccharide–iron complex	Niferex Ferrex NovaFerrum	Dose expressed as elemental iron	Liquid Capsule

Table 66–5

Parenteral US Iron Products

Product (Brand Name)	Iron dextran (INFeD)	Sodium ferric gluconate (Ferrlecit)	Iron sucrose (Venofer)	Ferumoxytol (Feraheme)	Ferric carboxymaltose (Injectafer)
Carbohydrate type	Dextran polysaccharide	Gluconate	Sucrose	Polyglucose sorbitol carboxymethylether	Carboxymaltose
Molecular weight (Daltons)	165,000	289,000–444,000	34,000–60,000	750,000	150,000
Maximum dose approved (mg)	100	125	200	510	750
Total Dose Infusion	Yes	No	No	No	No
Test Dose needed?	Yes	Yes	No	No	No
Premedications	Yes for TDI only	Yes for TDI only	No	No	No
Black Box warning	Yes	Yes	No	No	No
Rate of infusion undiluted[a]	50 mg/min	12.5 mg/min	40 mg/min	30 mg/sec	100 mg/min

[a]From FDA product labeling.

Data from Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol. 2016;91:31–38.

LO 6

Oral and parenteral vitamin B_{12} (cyanocobalamin) replacement therapies are equally effective in patients able to absorb B_{12}. Vitamin B_{12} is absorbed completely following parenteral administration, whereas oral vitamin B_{12} is absorbed poorly via the GI tract. Consequently, cyanocobalamin is commonly administered as an intramuscular or subcutaneous injection of 1000 mcg/day for 1 week, followed by 1000 mcg/week for a month or until the Hgb normalizes. Life-long maintenance therapy (1000 mcg/month) is required for patients with pernicious anemia or surgical resection of the terminal ileum. If the etiology was a dietary deficiency or reversible malabsorption syndrome, treatment can be discontinued after the underlying cause is corrected and vitamin B_{12} stores normalized. A common oral dosing regimen is from 1000 to 2000 mcg/day. If parenteral cyanocobalamin is used initially, oral vitamin B_{12} can be useful as maintenance therapy. Typically, resolution of neurologic symptoms, disappearance of megaloblastic RBCs, and increased Hgb levels occur within a week of therapy.[26] Vitamin B_{12} is well tolerated. Reported adverse effects include injection-site pain, pruritus, and rash.[27]

LO 6

The effective dose of folic acid is 1 mg/day by mouth. Absorption of folic acid is rapid and complete. However, patients with malabsorption syndromes may require doses up to 5 mg/day. Reticulocytosis occurs within days of commencing therapy. Typically, a patient's Hgb will start to rise after 2 weeks of therapy and normalize after 2 to 4 months of therapy. Folic acid is well tolerated. Nonspecific adverse effects include allergic reactions, flushing, and rash. A small study evaluating the effect of folic acid doses of 10 mg/day on phenytoin levels reported decreased phenytoin levels in 3 of 4 subjects. However, the occurrence of this interaction at folic acid doses of 1 mg/day has not been reported.[27]

Patient Encounter 1, Part 3

The patient is diagnosed with vitamin B_{12} deficiency anemia and is started on parenteral cyanocobalamin for 1 month followed by 1000 mcg of oral cobalamin taken daily. At his first weekly visit the patient reports no shortness of breath and feels better overall. A follow-up CBC 2 months later reveals a Hgb of 10 g/dL (100 g/L or 6.2 mmol/L), previously 8.3 g/dL (83 g/L or 5.15 mmol/L). He states he has noticed improvement in his paresthesias and he occasionally misses doses due to his hectic days.

What hemoglobin level would constitute a therapeutic response in this patient?

How can compliance be improved in this patient?

▶ *Anemia of Chronic Disease*

KEY CONCEPT Decreased RBC transfusion requirements is a goal of therapy in patients with ACD treated with the erythropoietin stimulating agent (ESAs). However, in 2007, the FDA product labeling for epoetin and darbepoetin were revised to include new data documenting safety concerns. Subsequently, the Centers for Medicare and Medicaid Services (CMS) implemented more restrictive ESA coverage determination guidelines. In 2010, the FDA implemented a risk evaluation and mitigation strategy (REMS) for ESAs administered to treat patients with cancer who are undergoing chemotherapy but in 2017 the FDA decided the REMS program was no longer needed.[28] Table 66–6 summarizes the FDA-labeled dosing regimens for patients whose anemia is related to cancer chemotherapy, CKD, or zidovudine treatment.

Anemia Due to Chemotherapy in Patients with Cancer Epoetin, a recombinant human EPO, and darbepoetin, a synthetic EPO analog, bind to the EPO receptors on RBC precursor cells in the bone marrow and result in increased RBC production. Darbepoetin differs from epoetin in that it is a glycosylated protein and exhibits a longer half-life, allowing for a longer dosing interval. Clinical practice guidelines consider epoetin and darbepoetin to be therapeutic equivalents.[3,29]

LO 7

KEY CONCEPT ESAs should only be used to prevent a transfusion and should not be initiated unless the hemoglobin is less than 10.0 g/dL (100 g/L, 6.21 mmol/L) and chemotherapy is planned for a minimum of two additional months. ESA-labeled dosing regimens for treatment of patients receiving chemotherapy are summarized in Table 66–6.

Postmarketing outcome data documented that cancer patients administered ESAs had an increased risk of thrombotic events, shorter progression-free and overall survival.[30] ESAs increased mortality of patients while on study (combined hazard ratio [cHR] 1.17; 95% confidence interval [CI] 1.06–1.30)

Table 66–6

ESA Products and Usual Doses for Anemia from Cancer/Chemotherapy, CKD, and Zidovudine/HIV Infection in Adult Patients[a]

	Epoetin-α (Epogen, Procrit)	Darbepoetin-α (Aranesp)
Cancer/chemotherapy dosing regimens	150 units/kg SC or IV three times per week 40,000 units SC or IV once every week	2.25 mcg/kg SC or IV once every week 500 mcg SC or IV fixed dose every 3 weeks
CKD dosing regimens	50–100 units/kg SC or IV three times per week	0.45 mcg/kg SC or IV once every week[b] 0.75 mcg/kg SC or IV once every 2 weeks[b] 0.45 mcg/kg SC or IV once every 4 weeks[c]
Zidovudine/HIV dosing regimen[d]	100 units/kg IV or SC three times per week	Not recommended

[a]Indications and dosage regimens per FDA product labeling.

[b]For patients on dialysis.

[c]For patients not on dialysis.

[d]FDA labeled indication for Procrit (epoetin-α), not Epogen (epoetin-α) or darbepoetin.

and worsened overall survival (cHR 1.06; 95% CI 1.00–1.12). This corresponds to a 17% increased risk of mortality for patients treated with ESAs while on study and a 6% increase of mortality overall. Based on these data, the FDA revised ESA product labeling, restricting their administration to patients with chemotherapy-induced anemia without curative intent. The 2010 update of the American Society of Clinical Oncology/American Society of Hematology clinical practice guideline on the use of ESAs in patients with cancer adopted FDA recommendations for more restrictive use of ESA in patients with cancer.[29]

In 2008, CMS published more restrictive coverage criteria for ESA treatment of chemotherapy-associated anemia. Patients should be monitored every 4 weeks. If Hgb has not increased by 1.0 g/dL (10 g/L, 0.62 mmol/L) after 4 weeks and remains less than 10.0 g/dL (100 g/L, 6.21 mmol/L), a one-time dose escalation of 25% is appropriate. If Hgb increases by more than 1.0 g/dL (10 g/L, 0.62 mmol/L), or is more than 10.0 g/dL (100 g/L, 6.21 mmol/L), the ESA should be discontinued. At 8 weeks if Hgb has increased by 1 g/dL (10 g/L, 0.62 mmol/L) but remains less than 10.0 g/dL(100 g/L, 6.21 mmol/L), continued ESA administration is covered. However, if after 8 weeks Hgb fails to increase by 1 g/dL (10 g/L, 0.62 mmol/L), CMS payment of therapy is not covered. CMS covers ESA therapy for up to 8 weeks after completion of chemotherapy for patients achieving respones.[3,31]

Patient Encounter 2, Part 1

A 4-year-old girl, along with her mother, presents to her pediatrician complaining of lack of energy that has become more noticeable over the past month. The daughter is also very "moody" throughout the day. She has also been exhibiting strange behaviors, such as eating dirt when playing in the yard. Her physical examination was notable for pallor. Past medical history is negative. Patient was born at 33 weeks 5 days via emergent cesarean, spent 44 days in NICU and suffered from necrotizing enterocolitis and underwent a small bowel surgical procedure. Mother states that her child is a very "picky" eater.

What aspects of this patient's history suggest she may be anemic?

What laboratory assessments are required to make an appropriate diagnosis and therapeutic plan?

Patient Encounter 2, Part 2

Laboratory results:

CBC

- WBC: 6.7 × 10^3/mm^3 (6.7 × 109/L)
- Hgb: 6.2 g/dL (62 g/L; 3.84 mmol/L)
- Hct: 20.8% (0.208)
- Plt: 210 × 103/μL (210 × 109/L)

Red Blood Cell Indices

- MCV: 71 μm^3 (71 fL)
- MCH: 23 pg/cell
- MCHC: 28.3 g/dL (283 g/L; 17.6 mmol/L)

Iron Studies

- Serum iron: 27 mcg/dL (4.8 μmol/L)
- Serum ferritin: 6.9 ng/mL (6.9 mcg/L; 16 pmol/L)
- TIBC: 459 mcg/dL (82.2 μmol/L)
- Transferrin saturation: 11% (0.11)

B_{12} and Folate

- Serum B_{12}: 707 pg/mL (522 pmol/L)
- Serum folate: 10 ng/mL (22.7 nmol/L)

Is this a macrocytic or microcytic anemia?

Specifically, what is the etiology of the anemia?

What would be the preferred drug regimen (drug, dosage form, and schedule)?

Patient Encounter 2, Part 3

The patient is diagnosed with iron-deficiency anemia (IDA) and is started on FeroSul (liquid iron sulfater) 2.5 mL (44 mg Fe/220 mg/5 mL) orally three times daily to be taken on an empty stomach. Follow-up CBC 1 month later reveals Hgb of 9.5 g/dL (95 g/L; 5.89 mmol/L), previously 6.2 g/dL (62 g/L; 3.84 mmol/L). The mother reports an improvement in mood and more energy. Pica has also decreased significantly. However, the mother struggles to give the medication three times a day explaining that her child is not fond of the taste and has developed constipation.

What hemoglobin level would constitute a therapeutic response in this patient?

What recommendation would you make regarding the compliance and to help with constipation?

"Functional" iron deficiency exists when total iron stores are normal or increased but disruption of iron homeostasis prevents utilization of the stored iron for erythropoiesis. "Functional" iron deficiency has been described in patients with ACD. Therefore, it is imperative that patients starting ESA therapy have laboratory studies performed to assess iron stores. If results document that a patient has suboptimal iron stores, iron replacement therapy is indicated prior to initiation of ESA therapy.

Anemia Due to CKD Anemia is common in patients with CKD. Early treatment of anemia in patients with CKD on dialysis has been associated with slower disease progression and lower risk of death. It is essential to evaluate and treat anemia in patients before they progress to stage 5 CKD (glomerular filtration rate [GFR] of less than 15 mL/min/1.73 m^2 [0.14 mL/s/m^2]).[32]

Patients with CKD typically develop normocytic, normochromic anemia as a result of EPO deficiency. However, a thorough workup of anemia should be performed to rule out other etiologies.[32] The 2012 KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease recommends that ESA therapy be started when the hemoglobin is between 9.0 and 10.0 g/dL (90–100 g/L) in dialysis patients. For those CKD patients not on dialysis, the guidelines recommend that ESAs be started when the Hgb is less than 10.0 g/dL (10 g/L) and should also be based on patient specific scenarios—if the rate of Hgb decline predicts the need for an RBC transfusion and if a goal of therapy is to either reduce the risk of RBC transfusion-related risks or reduce the chance of alloim-munization.[32,33] This dosing strategy was adopted to decrease the risk of serious adverse cardiovascular events. ESA-labeled dosing regimens for patients with CKD are summarized in Table 66–6.[34–36]

LO 7

Although EPO deficiency is the primary cause of CKD anemia, iron deficiency may also exist. Iron stores in patients with CKD should be maintained so that transferrin saturation is greater than 20% (0.20) and serum ferritin is greater than 100 ng/mL (100 mcg/L or 225 pmol/L). If iron stores are not maintained appropriately, epoetin or darbepoetin will not be effective. Most CKD patients will require iron supplementation.[32]

Anemia Due to Zidovudine in HIV-Infected Patients Early clinical trials evaluating the efficacy of zidovudine in patients with HIV documented that nearly 50% of patients treated with zidovudine developed anemia requiring RBC transfusions. Subsequently, results from numerous clinical trials reported that epoetin resulted in statistically significant decreases in transfusion requirements for patients with HIV who have serum EPO levels less than 500 mUnits/mL (500 U/L). Currently, epoetin has a labeled indication for the treatment of anemia in patients with EPO levels less than 500 mUnits/mL (500 U/L) and administered zidovudine doses less than 4200 mg/week.[34]

OUTCOME EVALUATION

KEY CONCEPT Patients should be monitored for Hgb response, symptom resolution, and adverse effects at appropriate intervals, and treatment regimens adjusted accordingly. The goal of anemia therapy is to correct the underlying etiology of the anemia, normalize the Hgb, and alleviate associated symptoms.

LO 4

- To ensure response for patients with IDA, monitor CBC with special attention to occurrence of reticulocytosis and iron studies.
- A 1.0-g/dL (10 g/L or 0.62 mmol/L) per week increase in Hgb is desirable in patients with IDA. Reevaluate patients with increases less than 2.0 g/dL (20 g/L or 1.24 mmol/L) in 3 weeks.
- For patients with folic acid deficiency, monitor Hgb periodically and reevaluate patients who fail to normalize Hgb levels after 2 months of therapy.
- For patients with vitamin B_{12} deficiency, monitor for resolution of neurologic symptoms (ie, confusion and paresthesias), if applicable, and Hgb levels weekly until the levels normalize.
- For cancer patients treated with chemotherapy without curative intent, initiate ESA treatment when Hgb levels are less than 10.0 g/dL (100 g/L or 6.21 mmol/L) and monitor Hgb levels weekly. If Hgb increases exceed 1.0 g/dL (10 g/L or 0.62 mmol/L) or if Hgb levels exceed 10.0 g/dL (100 g/L or 6.21 mmol/L), hold therapy until the Hgb level drops below 10.0 g/dL (100 g/L or 6.21 mmol/L). Restart the ESA at the lowest dose sufficient to reduce transfusions.
- For patients with CKD on dialysis, initiate ESA treatment when Hgb levels are less than 10.0 g/dL (100 g/L or 6.21 mmol/L) and monitor Hgb levels weekly. If Hgb levels approach or exceed 11.0 g/dL (110 g/L or 6.83 mmol/L), reduce or hold further doses until the level drops below 10.0 g/dL (100 g/L or 6.21 mmol/L). Restart the ESA at the lowest dose sufficient to reduce transfusions.
- For patients with CKD not on dialysis, initiate ESA treatment when Hgb levels are less than 10.0 g/dL (100 g/L or 6.21 mmol/L) and when the following additional criteria apply:
  - The rate of hemoglobin decline indicates the likelihood of a transfusion AND
  - Reducing the risk of alloimmunization and/or RBC transfusion-related risks are/is a goal. Monitor Hgb levels weekly. If Hgb levels exceed 10.0 g/dL (100 g/L or 6.21 mmol/L), reduce or hold further doses until the level drops below 10.0 g/dL (100 g/L or 6.21 mmol/L). Restart the ESA at the lowest dose sufficient to reduce transfusions.

Patient Care Process

Collect Information:

- Review the medical and surgical history in conjunction with any physical assessment findings
- Speak with the patient/family member to evaluate lifestyle habits, particularly dietary preferences, beliefs, health goals, and socioeconomic factors

Assess the Information:

- Based on physical examination and review of systems, determine if the patient exhibits signs or symptoms of anemia
- Review current medications and assess if they could be contributing to anemia
- Evaluate CBC, if anemia is present, assess RBC indices to determine if the anemia is microcytic, normocytic, or macrocytic
- Assess iron, folic acid, and vitamin B_{12} studies to determine etiology of anemia

Develop a Care Plan:

- Determine whether a transfusion or pharmacotherapy is indicated. If pharmacotherapy is needed, decide whether oral or intravenous therapy is indicated
- When initiating ESAs, assess the patient's iron status
- Discuss the importance of medication adherence with oral therapy
- Choose oral medications and doses that are optimal for the patient
- Select lifestyle and diet modifications that are likely to be effective and safe for the patient

Implement the Care Plan:

- Educate the patient on medication administration, potential new adverse effects, and how to report adverse effects
- Review signs and symptoms of anemia with the patient and address any concerns about anemia and its management
- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary

LO 8

Follow-up: Monitor and Evaluate:

- Follow-up monthly to assess efficacy and tolerance of therapy until resolution of symptoms and Hgb goal achieved
- Monitor for resolution of symptoms such as fatigue, shortness of breath, lethargy, headache, edema, and tachycardia
- Monitor the CBC monthly
- Monitor compliance of prescribed therapy and for side effects, such as:
  - Oral iron: nausea, vomiting, abdominal pain, heartburn, constipation, and dark stools
  - Parenteral iron: anaphylaxis (test dose required for iron dextran and observe for 1 hour after), injection-site pain/irritation, arthralgias, myalgias, flushing, malaise, and fever
  - Folic acid: bad taste, nausea, rash, and allergic reactions
  - Vitamin B_{12}: pain and erythema at injection site
  - ESAs: hypertension (monitor blood pressure), thrombosis (eg, deep vein thrombosis/pulmonary embolism, myocardial infarction, cerebrovascular accident, and transient ischemic attack), arthralgias, and headache

Abbreviations Introduced in This Chapter

CKD	Chronic kidney disease
EPO	Erythropoietin
ESA	Erythropoietin stimulating agent
GFR	Glomerular filtration rate
Hct	Hematocrit
Hgb	Hemoglobin
IDA	Iron-deficiency anemia
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
TIBC	Total iron-binding capacity

REFERENCES

1. World Health Organization. The Global Prevalence of Anaemia in 2011. Geneva: World Health Organization; 2015.
2. Guralnik JM, Eisenstaedt RS, Ferrucci L, et al. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004;104(8):2263–2268.
3. Cancer- and chemotherapy-induced anemia. NCCN Practice Guidelines in Oncology-V.1.2018. National Comprehensive Cancer Network. Available from: http://www.nccn.org/professionals/physician_gls/pdf/anemia.pdf. Accessed August 12, 2017.
4. McFarlane SI, Chen SC, Whaley-Connell AT, et al. Prevalence and associations of anemia of CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis. 2008:51(suppl 2): S46–S55.
5. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005;352(10):1011–1023.
6. Hudnall SD. Hematology: A Pathophysiologic Approach, 1st ed. Philadelphia, PA: Mosby; 2012:21.
7. Guyton AC, Hall JE. Red blood cells, anemia, and polycythemia. In: Guyton AC, Hall JE, eds. Textbook of Medical Physiology, 11th ed. Philadelphia, PA: WB Saunders; 2006:419–428.
8. Hesdorffer CS, Longo DL. Drug-induced megaloblastic anemia. N Engl J Med. 2015;373:1649–1658.
9. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017;129:2603–2611.
10. Andrews NC. Disorders of iron metabolism. N Engl J Med. 1999;341(26):1986–1995.
11. Camaschella C. New insights into iron deficiency and iron deficiency anemia. Blood Reviews. 2017;31:225–233.
12. Vyoral D, Petrak J. Therapeutic potential of hepcidin—the master regulator of iron metabolism. Pharmacological Research. 2017;115:242–254.
13. Carless PA, Henry DA, Carson JL, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochran Database Syst Rev. 2010;6:CD002042.

14. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med. 1999;340:409–417.
15. Brittenham GM. Disorders of iron metabolism: iron deficiency and iron overload. In: Hoff R, ed. Hematology: Basic Principles and Practice, 6th ed. Philadelphia, PA: Elsevier Saunders; 2013:437–449.
16. Alleyne M, Horne MK, Miller JL. Individualized treatment for iron-deficiency anemia in adults. Am J Med. 2008;121:943–948.
17. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice daily doses in iron-depleted young women. Blood. 2015;126(17):1981–1989.
18. Schrier SL. So you know how to treat iron deficiency anemia. Blood. 2015;126(17):1971.
19. INFed (iron dextran) prescribing information. Parsippany, NJ: Actavis Pharma, Inc; January 2014.
20. Dexferrum (iron dextran) prescribing information. Shirley, NY: American Regent; August 2008.
21. Ferrlecit (sodium ferric gluconate complex in sucrose injection) prescribing information. Bridgewater, NJ: Sanofi-Aventis; 2015.
22. Venofer (iron sucrose injection) prescribing information. Shirley, NY: American Regent; June 2016.
23. Feraheme (ferumoxytol injection) prescribing information. Lexington, MA: AMAG Pharmaceuticals; March 2015.
24. Injectafer (ferric carboxymaltose injection) prescribing information. Shirley, NY: American Regent, Inc.; July 2013.
25. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy and safety. Hematology Am Soc Hematol Educ Program. 2010;2010:338–347.
26. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017;129(19):2603–2611.
27. Zucchero FJ, Hogan MJ, Sommer CD, eds. Evaluations of Drug Interactions. San Bruno, CA: First DataBank; 2007.
28. Information on Erythropoiesis-Stimulating Agents (ESA) Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa (marketed as Aranesp). US Food and Drug Administration. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm109375.htm. Accessed August 24, 2017.
29. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol. 2010;28:4996–5010.
30. Bohlius J, Schmidlin K, Brillant C, et al. Erythropoietin or darbepoetin for patients with cancer—meta-analysis based on individual patient data. Cochrane Database Syst Rev. 2009;8:CD007303.
31. National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (110.21). Centers for Medicare and Medicaid Services. Available from: https://www.cms.gov/medicare-coverage-database/details/ncd-dtails.aspx?NCDId=322&ncdver=1&DocID=110.21&kq=true&bc=gAAAAAgAAAAAAA%3d%3d&. Accessed August 24, 2017.
32. NKF/DOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2012 update. Am J Kid Dis. 2012;82(4):1–64.
33. FDA Drug Safety Communication: modified dosing recommendations to improve the safe us of erythropoiesis-stimulating agents (ESAs) in chronic kidney disease. U.S. Food and Drug Administration. Available from: http://www.fda.gov/drugs/drugsafety/ucm259639.htm. Accessed August 22, 2017.
34. Procrit (epoetin alfa) prescribing information. Thousand Oaks, CA: Amgen; April 2017.
35. Aranesp (darbepoetin alfa) prescribing information. Thousand Oaks, CA: Amgen; April 2017.
36. Epogen (epoetin alfa) prescribing information. Centocor Ortho Biotech Products, April 2017.
37. Ferrous Sulfate. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; January 29, 2015.
38. Ferrous gluconate. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; January 29, 2015.
39. Ferrous fumarate. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; January 29, 2015.
40. Polysaccharide-iron complex. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; January 29, 2015.
41. Cook K. Anemias. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill; 2017.

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67 Coagulation and Platelet Disorders

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LEARNING OBJECTIVES

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

1. Describe the basics of the regulation of hemostasis and thrombosis.
2. Select appropriate nonpharmacological and pharmacological therapy for a patient with hemophilia in a given clinical situation.
3. Calculate an appropriate factor-concentrate dose for a product, given the percentage correction desired based on clinical situation.
4. List possible complications from hemophilia bleeding episodes.
5. Choose an appropriate treatment strategy for patients with factor VIII or IX inhibitors.
6. Devise a treatment plan for a patient with a specific variant of von Willebrand disease.
7. Describe various recessively inherited coagulation disorders (RICDs) and role of specific factor replacement in RICD management.
8. Recommend first-line and second-line treatment approaches for immune thrombocytopenia (ITP).
9. Identify basic clinical features, causes, and management of select thrombotic microangiopathies (TMAs).

INTRODUCTION

Components of the Hemostatic System

Following endothelial injury, vessel-wall response involves vasoconstriction, platelet plug formation, coagulation, and fibrinolysis regulation. In normal circumstances, platelets circulate in the blood in an inactive form. After injury, platelets undergo activation, which consists of (a) adhesion to the subendothelium, (b) secretion of granules containing chemical mediators (eg, adenosine diphosphate, thromboxane A2, thrombin, etc), and (c) aggregation. Chemical factors released from the injured tissue and platelets stimulate the coagulation cascade and thrombin formation. In turn, thrombin catalyzes the conversion of fibrinogen to fibrin and its subsequent incorporation into the platelet plug.

The coagulation system consists of intrinsic and extrinsic pathways. Both pathways are composed of a series of enzymatic reactions that ultimately produce thrombin, fibrin, and a stable clot. In parallel with the coagulation, the fibrinolytic system is activated locally. Plasminogen is converted to plasmin, which dissolves the fibrin mesh (Figure 67–1).[1]

INHERITED COAGULATION DISORDERS

HEMOPHILIA

Epidemiology and Etiology

Hemophilia A and B are coagulation disorders that result from defects in the genes encoding for plasma coagulation proteins. Hemophilia A (classic hemophilia) is caused by the deficiency of factor VIII, and hemophilia B (Christmas disease) is caused by the deficiency of factor IX. The incidences of hemophilia A and B are estimated at 1 in 5000 and 1 in 30,000 male births, respectively. Both types of hemophilia are evenly distributed across all ethnic and racial groups.[1]

Pathophysiology

The pathophysiology of hemophilia is based on the deficiency of factor VIII or IX resulting in inadequate thrombin generation and an impaired intrinsic pathway coagulation cascade (see Figure 67–1). Factor VIII and IX genes are located on the X-chromosome. Hemophilias are recessive X-linked diseases. Generally, affected males carrying a defective allele for either factor VIII or IX on their X-chromosome do not transmit the gene to their sons. However, their daughters are obligate carriers. More than 1000 mutations in factor VIII and IX genes have been identified to cause clinical hemophilia.[2] Consequently, hemophilia is not a result of a single genetic mutation. However, inversion at intron 22 of the factor VIII gene accounts for 40% of severe hemophilia A cases and this mutation is assessed during carrier and prenatal testing.[3]

Complications of Hemophilia

The severity of bleeding associated with hemophilia correlates with the degree of factor VIII or factor IX deficiency as measured against the normal plasma standard. Table 67–1 summarizes the age at onset and laboratory and clinical manifestations of hemophilia A and B.[4]

Treatment

▶ *Desired Outcomes*

Currently, there is no cure for hemophilia A or B. The life expectancy of hemophiliacs was only 8 to 11 years in the

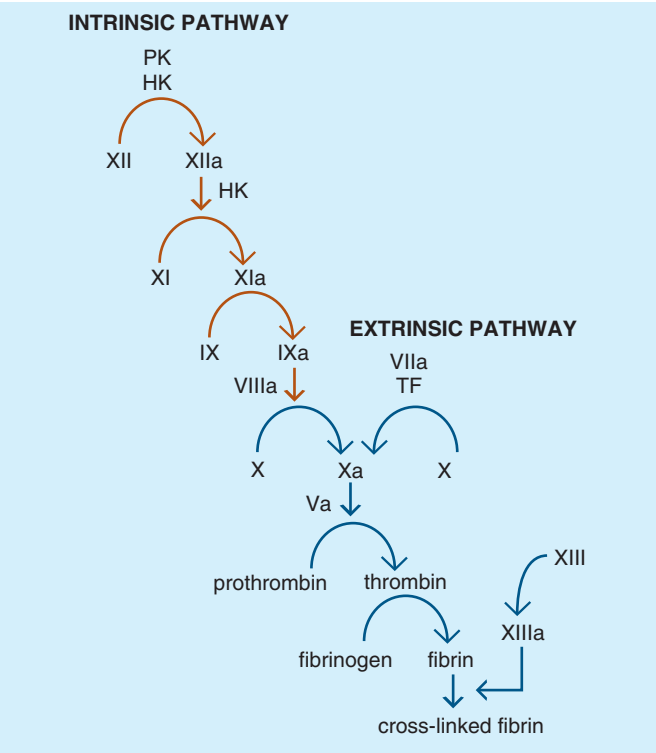

FIGURE 67–1. Cascade model of coagulation demonstrates activation via the intrinsic or extrinsic pathway. This model shows successive activation of coagulation factors proceeding from the top to the bottom where thrombin and fibrin are generated. (PK, prekallikrein; HK, high–molecular weight kininogen; TF, tissue factor.) (From Roberts HR et al. Molecular biology and biochemistry of the coagulation factors and pathways of hemostasis. In: Lichtman MA, Beutler E, Coller BS et al, eds. Williams Hematology, 7th ed. New York, NY: McGraw-Hill, 2006:1665–1694.)

1920s and 1930s. With the development of effective treatment strategies, life expectancy is currently about 63 to 75 years, or nearly that of the normal population.[5]

The short-term goals of hemophilia treatment include the following:

- Decrease the number of bleeding episodes per year or bleeding frequency
- Normalize or improve clotting factor concentrate levels

The long-term goals of hemophilia treatment include the following:

- Maintain clinical joint function
- Normalize orthopedic joint score
- Normalize radiologic joint score
- Maintain quality-of-life measurements

▶ *General Approach to Treatment*

KEY CONCEPT Intravenous factor replacement with recombinant or plasma-derived products to treat or prevent bleeding is the primary treatment of hemophilia. Primary prophylaxis is defined as the regular administration of factor concentrates in the absence of documented joint disease and initiated before the age of 3.[6] Primary prophylaxis is recommended for individuals who have not had a bleeding episode but have severe factor deficiency (factor VIII or IX activity levels < 1%) as it is efficacious in preventing bleeding and associated complications.[7]

Several studies have shown the benefit of prophylaxis in reducing morbidity in severe hemophilia A and B in both children and adults.[8]

▶ *Nonpharmacologic Therapy*

LO 2 **Supportive Care** Rest, ice, compression, elevation (RICE) can be used during the bleeding episode, following with casts, splints, and crutches after the bleeding has been controlled.

LO 2 **Surgery** Surgical arthroscopic synovectomy reduces replacement therapy–resistant disease and repetitive hemarthrosis of a single joint. This procedure removes inflamed joint tissue. Patients may have decreased range of motion after the surgery.

LO 2 **Orthotics** Joint prostheses do not deal with the deformities directly. Orthotics in hemophilia serves as an important supportive measure before or after surgery.

▶ *Pharmacologic Therapy*

Hemophilia A

LO 2 ***DDAVP*** Primary therapy is based on disease severity and type of hemorrhage.[9] Most patients with mild to moderate disease and a minor bleeding episode can be treated with 1-desamino-8-D-arginine vasopressin (desmopressin acetate [DDAVP]), a synthetic analogue of the antidiuretic hormone, vasopressin. DDAVP causes

Table 67–1

Laboratory and Clinical Manifestations of Hemophilia

	Severe (< 0.01 IU/mL [10 IU/L])[a]	Moderate (0.01–0.05 IU/mL [10–50 IU/L])[a]	Mild (> 0.05 IU/mL [50 IU/L])[a]
Age at onset	1 year or younger	1–2 years	2 years–adult
Neonatal symptoms			
PCB	Usual	Usual	Rare
ICH	Occasional	Uncommon	Rare
Muscle/joint hemorrhage	Spontaneous	Minor trauma	Minor trauma
CNS hemorrhage	High risk	Moderate risk	Rare
Postsurgical hemorrhage (without prophylaxis)	Frank bleeding, severe	Wound bleeding, common	Wound bleeding
Oral hemorrhage following trauma, tooth extraction	Usual	Common	Common

[a]0.01 IU/mL = 10 IU/L; 0.05 IU/mL = 50 IU/L; 0.5 IU/mL = 500 IU/L; 1 unit/mL = 1 IU/mL = 1000 IU/L; 1.5 IU/mL = 1500 IU/L.

CNS, central nervous system; ICH, intracranial hemorrhage; PCB, postcircumcisional bleeding.

Normal range of factor VIII/IX activity level is 0.5–1.5 IU/mL (50–150 IU/L). 1 IU/mL (1000 IU/L) corresponds to 100% of the factor found in 1 mL of normal plasma.

Clinical Presentation and Diagnosis of Hemophilia A and B

Hemophilia A and B are clinically indistinguishable.

Symptoms

- Ecchymoses
- Hemarthrosis—bleeding into joint spaces[a] (especially knee, elbow, and ankle)
  - Joint pain, swelling, and erythema
  - Cutaneous warmth
  - Decreased range of motion
- Muscle hemorrhage
  - Swelling
  - Pain with motion of affected muscle
  - Signs of nerve compression
  - Potential life-threatening blood loss, especially with thigh bleeding
- Mouth bleeding with dental extractions or trauma
- Genitourinary bleeding
- Gastrointestinal (GI) bleeding
- Hematuria
- Intracranial hemorrhage (spontaneous or following trauma), with headache, vomiting, change in mental status, and focal neurologic signs
- Excessive bleeding with surgery

Diagnostic Parameters/Laboratory Testing

- Family history
- Normal prothrombin time (PT)
- Normal platelet count
- Prolonged activated partial thromboplastin time (aPTT)
- Low factor VIII level (hemophilia A)
- Low factor IX level (hemophilia B)

[a]Hallmark of hemophilia; recurrent inadequately managed hemarthrosis leads to deformity and chronic pain (hemophilic arthropathy).

release of von Willebrand factor (vWF) and factor VIII from endothelial storage sites. DDAVP increases plasma factor VIII levels by twofold to fourfold within 60 minutes after an infusion or 90 minutes after an intranasal dose.[10] The recommended dose is 0.3 mcg/kg IV (infused over 15–30 minutes) or subcutaneously (if < 1.5 mL) or 150 mcg (in patients weighing < 50 kg) to 300 mcg (in patients weighing > 50 kg) intranasally via concentrated nasal spray, may repeat after 24 hours.[9] Desmopressin infusion may be administered daily for up to 2 to 3 days. Facial flushing, hypertension or hypotension, gastrointestinal upset, and headache are common side effects of desmopressin. Water retention and hyponatremia may occur; patients should be instructed to limit water intake while taking desmopressin. Serious side effects include seizures related to hyponatremia and myocardial infarction. Due to higher incidence of hyponatremia-related seizures in patients less than 2 years old, use of desmopressin is not recommended in this population. Tachyphylaxis, an attenuated response with repeated administration, may occur after several doses.[11] DDAVP should not be used in severe life-threatening bleeding because the response is delayed and the increase in factor VIII may not be sufficient for proper clotting. It is usually used to treat mild hemophilia A.

According to the manufacturer, use of DDAVP is contraindicated in patients with creatinine clearance less than 50 mL/min (0.83 mL/s); however, it has been used off label in patients with impaired renal function.

LO 2

Antifibrinolytic Therapy Aminocaproic acid and tranexamic acid are antifibrinolytic agents that reduce plasminogen activity leading to inhibition of clot lysis and clot stabilization. These agents are usually used as adjuncts in dental procedures or in difficult-to-control and menorrhagia episodes and have to be administered with appropriate factor concentrates to form a clot.[9]

LO 2

Factor VIII Replacement Patients with severe hemophilia may receive primary (before the first major bleed) or secondary (after the first major bleed) prophylaxis. All hemophiliacs with a major bleed require factor VIII replacement.[12] The therapy may include recombinant (produced via transfection of mammalian cells with the human factor VIII gene) or plasma-derived (concentrate from pooled plasma) factor VIII (Table 67–2). The choice of product and dose is based on the overall clinical scenario because the efficacy of various preparations does not differ significantly.[13] Newer generation plasma-derived coagulation factor concentrates are considerably safer owing to advancements in viral testing and inactivation technology. New-generation recombinant factor VIII products are stabilized with sucrose or produced in human cell lines, eliminating the concern for viral transmission.[9]

The severity of hemorrhage and its location are major determinants of percentage correction to target, as well as duration of therapy (Table 67–3). The normal range of factor VIII activity level is 1 IU/mL (1000 IU/L), which corresponds to 100% of the factor found in 1 mL of normal plasma. Minor bleeding may be treated with a goal of 25% to 30% (0.25–0.30 IU/mL [250–300 IU/L]) of normal activity, whereas serious or life-threatening bleeding requires greater than 80% of normal activity. Factor VIII is a large molecule that remains in the intravascular space, and its estimated volume of distribution is approximately 50 mL/kg. Generally, factor VIII levels increase by 2% (0.02 IU/mL [20 IU/L]) for every 1 unit/kg of factor VIII concentrate infused. To calculate factor VIII replacement dose, the following equation can be used:

LO 3

$$\text{Dose of factor VIII (units)} = \text{weight (kg)} \times \text{(desired percentage increase)} \times 0.5$$

Thus, to increase factor VIII levels by 50% (eg, from 0% to 50%) in a 70-kg (154-lb) patient, an IV dose of 1750 units is required. The median half-life of factor VIII ranges from 9.4 hours (in 1–6 year olds) to 10.4 hours (in 10–65 year olds).[14,15] Half the initial dose is given every half-life (every 8–12 hours) to maintain the desired factor VIII level. Although intermittent bolus infusions of factor VIII concentrates have been used successfully, continuous-infusion protocols can be used in patients requiring prolonged treatment of acute hemorrhage to avoid dangerously low trough levels and decrease the overall cost of therapy. Factor VIII can be administered as a continuous infusion at 2 to 4 units/kg/hour with daily factor level monitoring to ensure appropriate rate of infusion.[16,17]

Table 67–2

Factor Concentrates

Brand Name	Half-life	Other Contents
Factor VIII Concentrates		
Recombinant		
Advate	12.0 ± 4.2	Mannitol, trehalose
Adynovate	14.69 ± 3.79	Mannitol, trehalose
Afstyla	14.2 (26)	Sucrose
Eloctate	19.7 (17.4, 22.0)	Sucrose
Helixate FS	14.6 ± 4.38	Sucrose
Kogenate FS	14.6 ± 4.38	Sucrose
Kovaltry	14.3 ± 3.7	Sucrose
NovoEight	12.0 ± 9.3	Sucrose
Nuwiq	17.1 ± 11.2	Sucrose
Obizur		Sucrose
Recombinate	14.6 ± 4.9	Albumin
Xyntha	11.2 ± 5.0	Sucrose
Plasma-derived		
Alphanate	17.9 ± 9.6	Albumin, heparin, vWF
Hemofil M	14.7 ± 5.1	Albumin
Humate-P	11 (median)	Albumin, vWF
Koāte-DVI	16.12	Albumin, vWF
Monoclate-P	17.5	Albumin
Wilate	15.8 ± 11.0	Sucrose, vWF
Factor IX Concentrates		
Recombinant		
Alprolix	86.52 (37.2)	Sucrose, mannitol
Benefix	18.8 ± 5.4	Sucrose
Idelvion	104 (25)	Sucrose, mannitol
Ixinity	24 ± 7	Mannitol, Trehalose
Rixubis	26.7 ± 9.6	Sucrose, mannitol
Plasma-derived		
AlphaNine SD	21	Heparin
Mononine	25.3	
APCC		
Feiba VH or NF		II, VIIa, IX, X, factor VIII coagulant antigen
PCC		
Bebulin		Heparin, II, IX, X
Profilnine		II, VII, IX, X
Proplex T		Heparin, II, VII, IX, X
Other		
NovoSeven RT	3.54	Sucrose, mannitol

APCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; vWF, von Willebrand factor.

Table 67–3

Guidelines for Replacement Dosing with Factor VIII and Factor IX

Type of Hemorrhage	Desired Plasma Factor VIII Level (% of Normal)	Desired Plasma Factor XI Level (% of Normal)
CNS, intracranial, retropharyngeal, retroperitoneal, surgical prophylaxis	80–100	80–100
Mild hemarthrosis, mucosal (eg, epistaxis), superficial hematoma	30	20–30

Hemophilia B

LO 5

Factor IX Replacement Hemophilia B therapy may include recombinant (produced via transfection of mammalian cells with the human factor IX gene) or plasma-derived (concentrate from pooled plasma) factor IX (see Table 67–2). Guidelines for choosing the factor-concentrate formulation for hemophilia B are similar to the guidelines for hemophilia A. However, older generation factor IX concentrates containing other vitamin K–dependent proteins, called prothrombin complex concentrates (PCCs), have been associated with thrombogenic side effects and these products are not first-line treatment for hemophilia B. Because it is a small protein, the factor IX molecule passes into both the intravascular and the extravascular spaces. Therefore, the volume of distribution of recombinant factor IX is twice that of factor VIII. Consequently, 1 unit of factor IX administered per kilogram of body weight yields a 1% rise in the plasma factor IX level (0.01 IU/mL [10 IU/L]). To calculate the factor IX replacement dose, the following equation can be used:

LO 3

$$\text{Dose of factor IX (units)} = \text{weight (kg)} \times \text{(desired percentage increase)} \times F$$

where F = 1 for human plasma-derived products; F = 1.1 for Rixubis; F = 1.4 for Benefix in adults and 1.2 in children.

Thus, to increase factor IX levels by 50% (eg, from 0% to 50%) in a 70-kg (154-lb) patient, the required dose of factor IX is 4900 units IV (using Benefix). The half-life of factor IX ranges from 16 to 17 hours; therefore, doses are given every 18 to 24 hours. Factor IX fusion protein can be given every 1 to 2 weeks.[18]

Gene therapy for the treatment of hemophilia is currently under investigation. A recent clinical trial has shown long-term therapeutic levels of factor IX in ten subjects with severe hemophilia B receiving a single infusion of a factor IX transgene vector.[19,20]

► *Treatment of Patients with Factor VIII or IX Inhibitors*

Factor VIII and IX inhibitors are antibodies that develop in approximately 30% and 5% of hemophilia A and hemophilia B patients, respectively, in response to replacement therapy. There is no difference between plasma-derived and recombinant products in their potential for inhibitor development. These antibodies bind to and neutralize the activity of infused factor concentrates. Other complications include anaphylaxis.[21] Although the inhibitors do not increase hemorrhage frequency, their existence challenges the treatment of bleeding episodes. Titers of inhibitors are measured and reported in Bethesda units (BU), and this measurement is used to guide therapy (Figure 67–2). Management options for acute bleeding in patients with factor inhibitors include the administration of factor VIII concentrates, PCCs, aPCC, recombinant factor VIIa (rFVIIa), and recombinant porcine factor VIII (Obizur).[22] Immune tolerance induction can be attempted to prevent future bleeding episodes.

LO 5

Factor VIII concentrates can be used in patients with low inhibitor levels to control acute bleeding episodes. The dose of factor VIII is determined based on clinical response (see Figure 67–2).

PCCs contain the vitamin K–dependent factors II, VII, IX, and X. These agents bypass factor VIII at which the antibody is directed (see Figure 67–2). However, PCCs carry the risk of serious thrombotic complications. The only aPCC agent available, FEIBA® (Factor Eight Inhibitor Bypassing Activity), has a higher concentration of activated factors.

Factor VIIa (rFVIIa) is a bypassing agent designed to generate thrombin only at tissue injury sites, where it binds tissue factor.

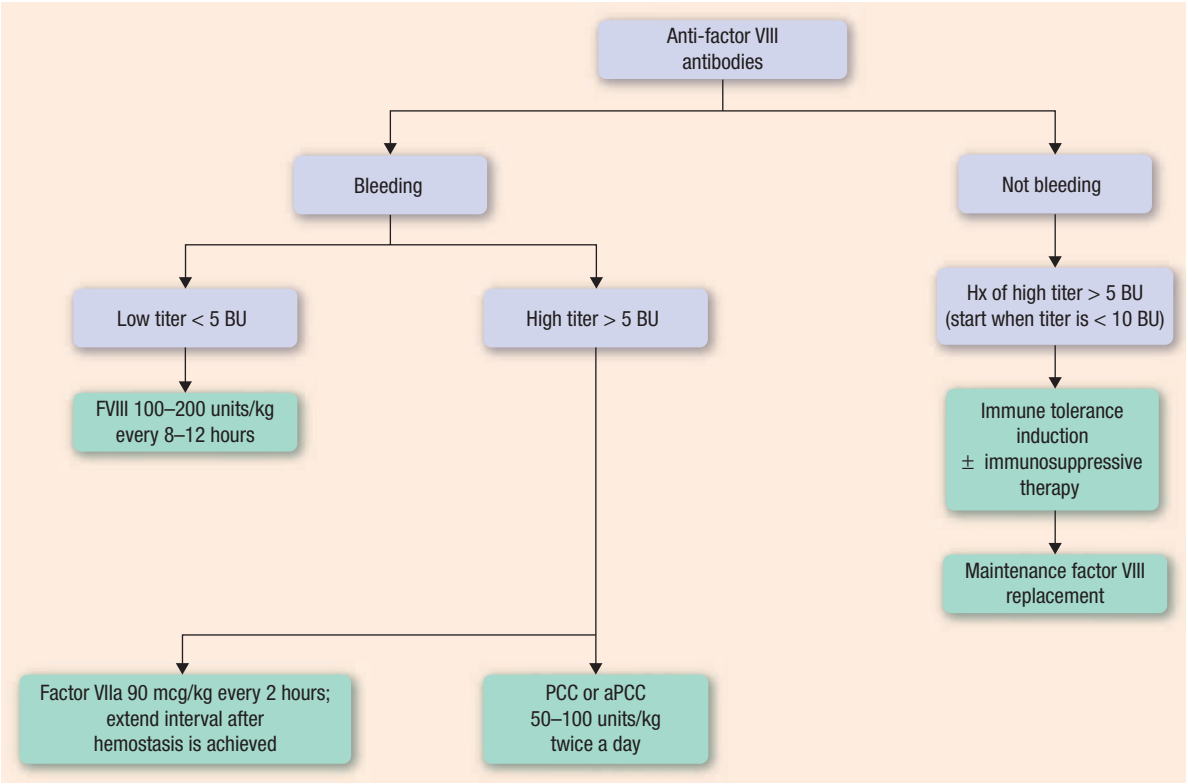

FIGURE 67–2. Treatment algorithm for the management of patients with hemophilia A and factor VIII antibodies. (aPCC, activated prothrombin complex concentrate; BU, Bethesda unit.) (From Trinkman H, Beam D, Hagemann T. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017, Figure 101–1.)

Due to its local action, rFVIIa is associated with fewer systemic thrombotic events than PCC. rFVIIa is used effectively in surgeries and spontaneous bleeds.[23]

Recombinant porcine factor VIII serves as a third-line agent (only after factor VIIa and aPCC have failed) due to the relatively high incidence of cross-reactivity with factor VIII inhibitors.

Induction of immune tolerance, which is often performed with the goal of eliminating the inhibitor, is accomplished by the administration of repetitive doses of factor VIII or IX with or without immunosuppressive therapy. It is effective in 70% of patients with hemophilia A and 30% of patients with hemophilia B.

Pain Associated with Hemophilia

Pain commonly occurs in patients with hemophilia. Acute bleeding episodes and long-term joint destruction are common sources of pain. Acetaminophen and opioid analgesics are recommended to control mild to moderate and severe pain, respectively. Nonsteroidal anti-inflammatory drugs and aspirin should be avoided if possible, because these drugs bind to platelets and increase the risk of bleeding episodes. Cyclooxygenase-2 (COX-2) inhibitors can be used with caution.[24]

Outcome Evaluation

The main goal of hemophilia treatment is to prevent bleeding episodes and their long-term complications. Clinicians should evaluate patients for the following:

- Musculoskeletal status, including joint range of motion and radiologic assessment, as indicated.
- Number and type of bleeding episodes to assess adequacy of prophylactic treatment and home therapy.
- Use of clotting-factor concentrates to check for the development of inhibitors, especially in patients with severe disease and poor treatment responders.
- Age-appropriate immunizations following standard vaccination schedules are recommended in all hemophiliacs without evidence of immunity.

VON WILLEBRAND DISEASE

Epidemiology and Etiology

Von Willebrand disease (vWD) is the most common inherited bleeding disorder caused by a deficiency or dysfunction of vWF. It is classified based on the quantitative deficiency of vWF or qualitative abnormalities of vWF. Based on population studies, the prevalence of vWD is 0.6% to 1.3%. In contrast to hemophilia, the majority of vWD cases are inherited as an autosomal dominant disorder, suggesting equal frequency in males and females.[25,26]

Pathophysiology

vWF is a large multimeric glycoprotein with two main functions in hemostasis: to aid platelet adhesion to injured blood vessel walls and to carry and stabilize factor VIII in plasma. Table 67–4 represents three main vWD phenotypes, their frequency, and genetic transmission.[27]

Treatment

▶ *Desired Outcomes*

Unlike hemophilia, the bleeding tendency in vWD is less frequent and generally less severe. Consequently, chronic prophylaxis

Patient Encounter 1, Part 1: vWD

A 15-year-old girl without significant past medical history is referred to hematology clinic with a complaint of having heavy menstrual bleeds with normal menstrual cycle but with clots, size of about a quarter and soaking through a pad within an hour. The bleeds usually last for 10 days. Her mother reports history of spontaneous nosebleeds and easy bruising in male and female members of the family.

What are this patient's risk factors for vWD?

What additional information for developing a treatment plan do you need to collect?

is usually unwarranted. The goal of two mainstay therapeutic options in vWD is:

- To stop spontaneous bleeding as necessary
- To prevent surgical and postpartum bleeding

▶ *Nonpharmacologic Therapy*

Local measures, including pressure and ice, may be used to control superficial bleeding.

▶ *Pharmacologic Therapy*

Systemic therapy is used to prevent bleeding associated with surgery, childbirth, and dental extractions and to treat bleeding that cannot be controlled with local measures. The two systemic approaches involve using desmopressin, which stimulates the release of endogenous vWF, or administering products that contain vWF. The general approach to the treatment of vWD is depicted in Figure 67–3. In 2008, The National Heart, Lung, and Blood Institute issued comprehensive evidence-based guidelines for the diagnosis and management of vWD.[26]

LO 6

DDAVP Most patients with type 1 vWD (functionally normal vWF) and a minor bleeding episode can be treated successfully with desmopressin, which induces release of factor VIII and vWF from endothelial cells through interaction with vasopressin V2 receptors. The recommended dose is the same as that used to treat mild factor VIII deficiency (0.3 mcg/kg IV infused over 15–30 min or 150–300 mcg intranasally via concentrated nasal spray, may repeat after 24 hours). This therapy is generally ineffective in type 2A patients, who secrete abnormal vWF. It is recommended in type 2B patients who respond to it. DDAVP may increase the risk of postinfusion thrombocytopenia, in which case a concomitant platelet infusion is administered. Type 3 vWD patients who lack releasable stores of vWF do not respond to DDAVP therapy.[28]

The individual responsiveness to desmopressin is consistent, and a test dose administered at the time of diagnosis or prior to therapy is the best predictor of response. Generally, DDAVP is more effective in vWD than in hemophilia patients, with an average twofold to fivefold increase in vWF and factor VIII levels over baseline. In patients with an adequate response, desmopressin is first-line therapy because it allows for once-daily administration (elevates plasma levels for 8–10 hours), does not pose a threat in terms of viral transmission, and costs substantially less than the plasma-derived products.

Antifibrinolytic Therapy Fibrinolysis inhibitors and oral contraceptives are used successfully in the management of epistaxis and menorrhagia or as adjuvant treatments.[29] Fibrinolysis inhibitors include aminocaproic acid (25–60 mg/kg orally or IV [or 4–5 g] every 4–6 hours, to a maximum dose of 24 g/day) and tranexamic acid (10 mg/kg IV every 8 hours). Oral tranexamic acid recently received FDA approval for the treatment of cyclic heavy menstrual bleeding; its use is currently not approved for vWD patients. The IV form of tranexamic acid given as swish and swallow or spit every 6 to 8 hours has been used as bleeding prophylaxis in dental surgery. Both aminocaproic acid and tranexamic acid are dose adjusted for patients with renal insufficiency.

Replacement Therapy KEY CONCEPT Type 1 vWD patients unresponsive to desmopressin, patients with types 2 and 3 vWD, and major surgery patients require replacement therapy with plasma-derived, intermediate- and high-purity virus-inactivated factor VIII concentrates containing vWF.

Table 67–5 provides typical dosing guidelines and target levels of replacement therapy–concentrates to control various types of hemorrhage. Ultra-high-purity (monoclonal) plasma-derived and recombinant factor VIII concentrates do not contain vWF and should not be used in the treatment of vWD.

Outcome Evaluation

The main goal of vWF treatment is to prevent bleeding with surgery or dental procedures. Clinicians should evaluate patients every 6 to 12 months for the following:

- Number and type of bleeding episodes to assess the need for prophylactic treatment.

Table 67–4

Classification of vWD

Phenotype	Mechanism of Disease	Percentage of Cases	Genetic Transmission
Type 1 vWD	Partial (mild to moderate) quantitative deficiency of vWF and factor VIII	70–80	Autosomal dominant
Type 2 vWD	Qualitative abnormalities of vWF	10–30	
2A	Decreased platelet-dependent vWF function owing to lack of larger multimers	10–20	Autosomal dominant (or recessive)
2B	Decreased platelet-dependent vWF function owing to lack of larger multimers	5	Autosomal dominant
2M	Defective platelet-dependent vWF functions not associated with multimer defects	Uncommon	Autosomal dominant (or recessive)
2N	Defective vWF binding to factor VIII	Uncommon	Autosomal recessive
Type 3 vWD	Severe quantitative deficiency of vWF	Rare	Autosomal recessive

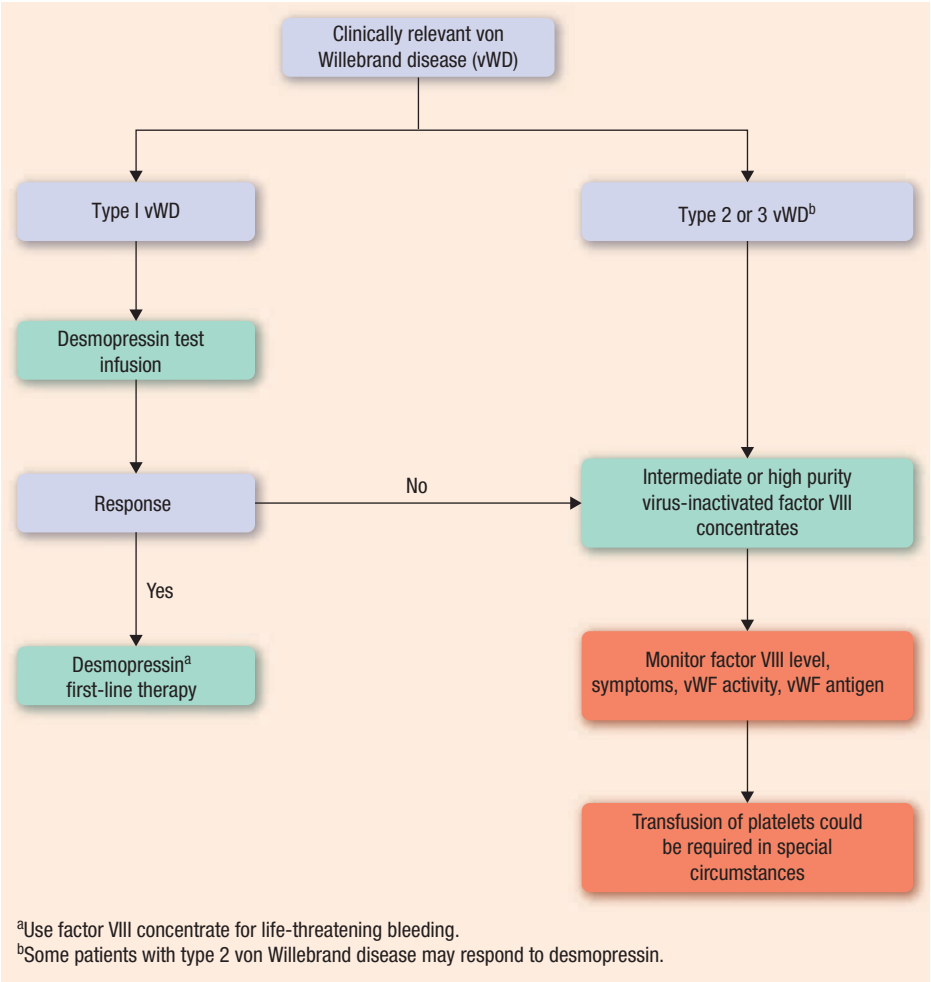

FIGURE 67–3. Guidelines for the treatment of vWD. (From Trinkman H, Beam D, Hagemann T. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York, NY: McGraw-Hill; 2017, Figure 101–2.)

- Ensure adequate levels of vWF and factor VIII prior to minor and major surgical procedures and for the treatment of bleeding.
- Vaccination against hepatitis A and B is recommended in all patients with vWF deficiency with no evidence of immunity.

OTHER CLOTTING FACTOR DEFICIENCIES

Etiology and Epidemiology

LO 7

Recessively inherited coagulation disorders (RICDs) refer to relatively rare deficiencies in factors II, V, VII, and X to XIII resulting in either decreased clotting factor production or production of a dysfunctional molecule with reduced activity.[30]

Clinical Presentation and Diagnosis of vWD

Clinical manifestations vary depending on the subtype. Patients with mild disease may be asymptomatic into adulthood.

Symptoms

- Bruising
- Mucocutaneous bleeding
- Epistaxis
- Oral cavity bleeding
- Menorrhagia
- GI bleeding
- Joint and deep tissue bleeding
- Postoperative bleeding

Laboratory Testing

- Low or normal vWF antigen concentration in plasma (vWF:Ag)
- Low or normal factor VIII coagulation assay (FVIII:C)[a]
- Low ristocetin cofactor activity (vWF:RCo)[b]

[a]Factor VIII coagulation assay measures the ability of vWF to bind and maintain adequate levels of factor VIII.

[b]Ristocetin cofactor activity (vWF:RCo) assay measures the ability of vWF to interact with intact platelets (normal 50–200 IU/dL [500–2000 IU/L]).

Table 67–5

Replacement Therapy in vWD

Condition	Therapy	Recommended Dosage
Major surgery	Maintain vWF:RCo and factor VIII levels at least 100 IU/dL (1000 IU/L) followed by 50 IU/dL (500 IU/L) for 7–14 days To minimize risk of thrombosis: vWF:RCo levels should not exceed 200 IU/dL (2000 IU/L), and factor VIII levels should not exceed 250 IU/dL (2500 IU/L)	40–60 units/kg[a] loading dose, followed by 20–40 units/kg every 12–24 hours DDAVP may be added after a few days
Minor surgery	Prophylaxis: maintain vWF:RCo and factor VIII levels at least 30 IU/dL (300 IU/L) (preferably > 50 IU/dL [> 500 IU/L]) Minor surgery: maintain vWF:RCo and factor VIII levels at least 30 IU/dL (300 IU/L) (preferably > 50 IU/dL [> 500 IU/L]) for 3–5 days	30–60 units/kg loading dose, followed by 20–40 units/kg every 12–48 hours DDAVP may be added after a few days

[a]vWF concentrates are dosed based on vWF:RCo units concentration in the preparation to achieve the desired vWF:RCo levels.

LO 7 The clinical severity of bleeding varies and generally is poorly correlated with the factor blood levels. Table 67–6 illustrates these clotting factor deficiencies and some of their characteristics.

Pathophysiology

The RICDs are rare genetic disorders. Mutations in the genes responsible for the respective clotting factors result in impaired functionality or production of the factor.

Treatment

▶ *Desired Outcomes*

LO 7 Therapeutic interventions for RICDs improve hemostasis via replacement of deficient blood coagulation factors while minimizing the development of immune tolerance.[31]

Hemostatic levels should be maintained for the following conditions:

- Spontaneous bleeding—until bleeding stops
- Minor surgery—for 2 to 3 days
- Major surgery—until incision site has healed

▶ *Nonpharmacologic Therapy*

Transfusional Therapies KEY CONCEPT The primary treatment of RICDs is single-donor fresh-frozen plasma (FFP) that contains all coagulation factors. Disadvantages of FFP treatment include the risk of the patient becoming volume overloaded, especially when repeated infusions are administered to improve and maintain hemostasis; risk of infections; and risk of inhibitor development. PCCs licensed for the treatment of hemophilia B also contain significant levels of vitamin K–dependent factors and may be used for treatment of RICD. Table 67–7 lists the recommended RICD treatment schedules in different clinical scenarios.

▶ *Pharmacologic Therapy*

Less severe hemorrhages may be treated successfully with antifibrinolytic amino acids alone or in combination with factor replacement therapy. Tranexamic acid and aminocaproic acid may be administered IV or orally (for doses, see vWD, Pharmacologic Therapy mentioned earlier).

Table 67–6

Clotting Factor Deficiency Characteristics

Factor Deficient	Inheritance Pattern	Estimated Incidence	Laboratory Abnormalities	Severity and Site of Bleeding
II	Autosomal dominant or recessive	Extremely rare	Prolonged PT and aPTT	Mild to moderate umbilical cord, joint, and mucosal tract
V	Autosomal recessive	1:1,000,000	Prolonged PT and aPTT	Mild to moderate mucosal tract
VII	Autosomal recessive	1:500,000	Prolonged PT	Mild to severe mucosal tract and joint
X	Autosomal recessive	1:1,000,000	Prolonged PT and aPTT	Mild to severe umbilical cord, joint, and muscle
XI	Autosomal recessive	4% of Ashkenazi Jews: otherwise rare	Prolonged aPTT	Mild to moderate posttraumatic bleeding
XII	Unknown	Unknown	Prolonged aPTT	No bleeding
XIII	Autosomal recessive	< 1:2,000,000	Normal PT and aPTT	Moderate to severe umbilical cord, intracranial, and joint bleeding; recurrent miscarriages, impaired wound healing

aPTT, activated partial thromboplastin time; PT, prothrombin time.

Table 67–7

Treatment of Factor Deficiencies

Factor Deficient	Major Surgery	Spontaneous Bleeding
II	1. PCC: 20–30 units/kg 2. FFP: 15–20 mL/kg	1. FFP: 15–20 mL/kg
V	1. FFP: 15–20 mL/kg	1. FFP: 15–20 mL/kg
VII	1. rFVIIa: 15–30 mcg/kg every 4–6 hours	1. rFVIIa: 15–30 mcg/kg every 4–6 hours
X	1. PCC: 20–30 units/kg 2. FFP: 15–20 mL/kg	1. PCC: 20–30 units/kg 2. FFP: 15–20 mL/kg
XI	1. FFP: 15–20 mL/kg	1. FFP: 15–20 mL/kg
XIII	1. Pasteurized plasma concentrate: 10–20 units/kg 2. FFP: 15–20 mL/kg 3. Cryoprecipitate (1 bag per 10 kg)	1. FFP: 3–5 mL/kg

Numbers indicate lines of therapy.

FFP, fresh-frozen plasma; PCC, prothrombin complex concentrates.

PLATELET DISORDERS

Platelets, in combination with several other factors such as blood vessel wall and coagulation factors, play key role in hemostasis. Normal platelet count is 150–450 × 10^3/mm^3 (150–450 × 10^9/L). Thrombopoietin, a hormone synthesized in the liver, regulates platelet production. Several congenital and iatrogenic disorders may result in low platelet count; among them, drug-induced thrombocytopenia, infection-induced thrombocytopenia, disseminated intravascular coagulation (DIC), congenital thrombocytopenia, and idiopathic immune thrombocytopenia (ITP). Two types of thrombocytopenic disorders and their treatments are discussed below.

Patient Encounter 1, Part 2: vWD

Medications: None

Allergies: NKA

PE/ROS:

Well-nourished, well-developed (WNWD) female, otherwise healthy. Wt 52 kg.

Labs:

Platelet count: 205 × 10^3/mm^3 (205 × 10^9/L) (normal 140–440 × 10^3/mm^3 [140–440 × 10^9/L])

aPTT: 40 seconds (normal 25–40 seconds)

PT: 14 seconds (normal 11–15 seconds)

FVIII-C: 51% (normal 50%–150%)

vWF: RCo: 25 IU/dL or 250 IU/L (normal 50–200 IU/dL or 500–2000 IU/L)

vWF-Ag: 28 IU/dL or 280 IU/L (normal 50–200 IU/dL or 500–2000 IU/L)

Given this additional information, is this patient's presentation consistent with vWD?

Define treatment goals for this patient.

Patient Care Process: Hemophilia A/B, vWD, and RICD

Collect Information:

- Obtain a complete medical and medication history.
- Evaluate CBC, vital signs, and coagulation studies. If a bleeding disorder is diagnosed, evaluate specific coagulation assays to determine the etiology of the bleeding disorder.

Assess the Information:

- Identify appropriate goals of therapy based on patient's presentation.
- Based on patient data, determine if patient has contraindications to any potential therapeutic options.

Develop a Care Plan:

- Institute nonpharmacological therapy to minimize minor bleeding.
- Depending on the specific diagnosis and disease severity, select appropriate therapy with desmopressin, antifibrinolytic medications, and/or disease-specific factor replacement therapies.
- Recommend prophylactic therapies before major and minor surgical procedures based on bleeding risk assessment.
- Evaluate pain and treat if necessary, selecting medications that do not increase the risk of bleeding.

Implement the Care Plan:

- Educate the patient and/or patient's caregivers about coagulation disorder, efficacy/safety of replacement therapies, and medication/activities to avoid.
- Address any patient concerns about coagulation disorder and its management.
- Discuss importance of medication adherence and follow-up monitoring to achieve optimal outcomes. Determine whether there are any barriers to adherence.
- Review vaccination history and recommend appropriate vaccinations.
- Determine patient's ability to afford prescribed pharmacotherapy.

Follow-up: Monitor and Evaluate:

- If clotting factor replacement is utilized, continuously evaluate its efficacy and test for inhibitors development if loss of efficacy is observed.
- Monitor number/severity of bleeding episodes, joint count/joint destruction, and pain associated with some coagulation/bleeding disorders.
- Determine whether the patient is experiencing any adverse reactions or drug interactions.

Patient Encounter 1, Part 3: vWD: Creating a Care Plan

Based on the information presented, create a care plan for this patient.

What additional pharmacologic interventions can be considered for this patient if first line fails?

IMMUNE THROMBOCYTOPENIA

Epidemiology and Etiology

ITP is one of the most common causes of acquired thrombocytopenia. The estimated incidence is 1.9 to 6.4 cases per 100,000 persons in children and 3.3 cases per 100,000 in adults.[32] ITP is an acquired disorder caused by immune-mediated destruction of platelets, resulting in shortened platelet life span.

Childhood-onset and adult-onset ITP present very differently. Adult-onset ITP is generally chronic (> 6 months) and affects women two to three times more often than men. By contrast, childhood-onset ITP is acute in onset and usually follows an infectious illness, and both sexes are equally affected. Childhood ITP typically resolves on its own within 4 to 6 weeks without major sequelae. ITP occurs in about 1 of every 1000 pregnancies. In pregnant women with preexisting ITP, both maternal and fetal complications may occur, requiring separate management.

Clinical Presentation and Diagnosis of ITP

General

The typical patient is well with the exception of bleeding.

Symptoms

- Petechiae
- Purpura, wet purpura
- Ecchymoses
- Cutaneous bleeding
- Mucosal site bleeding
- Epistaxis
- Gingival bleeding
- Hematuria
- Menorrhagia
- Intracranial hemorrhage (rare)

Diagnostic Criteria

- Platelet count less than $100 \times 10^3/mm^3$ ($100 \times 10^9/L$)
- Otherwise normal complete blood count with differential
- Normal reticulocyte count
- Normal peripheral blood smear (no hemolysis or blast cells)
- History and physical examination ruling out other possible causes of thrombocytopenia[30]

Other Laboratory Testing

Laboratory testing to evaluate other courses of that can lead to secondary ITP, such as HCV, HIV, *H. pylori*.

Pathophysiology

ITP can be primary or secondary. Primary ITP can occur due to formation of autoimmune IgG antibodies directed at patient's platelets' surface glycoproteins, GPIIb/IIIa and GP1b/IX/V; abnormal production of megakaryocytes in the bone marrow; or T-cell defects that lead to destruction of platelets. The majority of adult ITP cases are due to primary causes.

Secondary ITP occurs due to an underlying disorder, such as autoimmune (eg, rheumatoid arthritis, systemic lupus erythematosus [SLE]) or infections diseases (eg, human immunodeficiency virus [HIV], hepatitis C virus [HCV], or *Helicobacter pylori* infections).[33] Platelet survival time is significantly shorter in patients with ITP (from minutes to 2–3 days compared with normal 7–10 days). Sequestration in spleen, liver, and bone marrow is partially responsible for decreased platelet survival.

Treatment

▶ *Desired Outcomes*

In children, the main goal of ITP treatment is to maintain the platelet count associated with sufficient hemostasis, while awaiting spontaneous or treatment-induced remission. In adults, the main goal is to maintain platelet count greater than $30 \times 10^3/mm^3$ ($30 \times 10^9/L$), because below this count, the incidence of bleeding is increased.[34]

▶ *General Approach to Treatment*

KEY CONCEPT The treatment of ITP is determined by the presence of bleeding and platelet count. In some cases, no therapy is needed (Table 67–8). The initial treatment of children with ITP is controversial because greater than 75% to 80% of cases resolve spontaneously irrespective of pharmacologic intervention, although children with severe hemorrhage should be treated. Therapy may be considered in children meeting one of the following criteria: platelet counts less than $10 \times 10^3/mm^3$

Table 67–8

Guidelines for the Management of Adult ITP

Greater than 30×10^3 platelets/mm^3 (30×10^9/L), no bleeding	No treatment
First line therapies	
Less than 30×10^3 platelets/mm^3 (30×10^9/L), bleeding symptoms	Prednisone (1 mg/kg/day) or high-dose dexamethasone Anti-D immune globulin (50–75 mcg/kg/day, × one dose) if corticosteroids contraindicated IVIg (1 g/kg/day × one dose, repeat as necessary) if corticosteroids contraindicated
Second line therapies	
Reserved for patients with bleeding symptoms and platelets < 30×10^3 platelets/mm^3 (30×10^9/L) after an adequate trial of first-line agents	Splenectomy Rituximab (375 mg/m^2 once weekly for four doses) Eltrombopag (25–75 mg daily) Romiplostim (1–10 mcg/kg) Immunosuppressants
Hemorrhage	Platelet transfusion IVIg (1 g/kg/day × one dose, repeat as necessary) Methylprednisolone (1 g/day for 3 days)

Patient Encounter 2, Part 1: ITP

A 23-year-old female with history of a short respiratory illness presented with gingival bleeding, requiring swishing with icy water and nonitchy ecchymotic rash on her left forearm. Patient denied any history of hematemesis, epistaxis, hemoptysis, hematuria, melena, or trauma.

What patient information is suggestive of ITP?

What additional information for developing a treatment plan do you need to collect?

(10 × 10^9/L) and mucocutaneous bleeding; platelet counts less than 30 × 10^3/mm^3 (30 × 10^9/L) and moderate systemic or mucosal bleeding; or factors that may increase the risk of bleeding (such as participation in active contact sports increasing risk of head injury).[35] In adults, treatment is indicated when platelet counts are less than 30 × 10^3/mm^3 (30 × 10^9/L) or severe bleeding is present.[34]

▶ *Nonpharmacologic Therapy*

LO 8

Splenectomy In adults, splenectomy is generally considered after 3 to 6 months if the patient continues to require 10 to 20 mg/day of prednisone to maintain the platelet count greater than 30 × 10^3/mm^3 (30 × 10^9/L). Splenectomy may also be considered for urgent treatment of neurologic symptoms or for managing relapse despite an adequate trial of corticosteroids, IV immunoglobulin (IVIg), or anti-Rh(D). Even though individual patient response cannot be predicted, the majority (66%–88%) of refractory adult patients have a favorable response to splenectomy within several days; however, some patients will have no response or will experience a relapse sometime after splenectomy.

In children, splenectomy is usually reserved due to the self-limited nature of ITP and fear of infectious complications following splenectomy. However, splenectomy is recommended in children with ITP duration greater than 1 year with significant bleeding symptoms and unresponsive or intolerant of pharmacological therapies. Between 70% and 80% of children attain complete remission following splenectomy. Laparoscopic splenectomy is preferable to open splenectomy because it speeds the recovery and shortens the duration of hospitalization. The major drawback of splenectomy is bacterial sepsis, occurring at incidence rates of approximately 1%. Immunizations with *Haemophilus influenzae* type b, pneumococcal, and meningococcal vaccines are indicated in all patients 2 weeks prior to splenectomy.[36] Additional complications include thrombosis and pulmonary hypertension.

Platelet Transfusions Platelet transfusions are indicated if a patient has severe life-threatening bleeding, such as intracranial hemorrhage. In such situations, platelet transfusions are administered along with IVIg and glucocorticoids (discussed later).[35]

Additional Consideratons Patients with severe thrombocytopenia may need to restrict their participation in extreme contact sports. Medications that inhibit platelet aggregation (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) should be avoided.

▶ *Pharmacologic Therapy*

The general approach to management of ITP in adults is summarized in Table 67–8.

Patient Encounter 2, Part 2: ITP

PE/ROS:

Wt 60 kg; vital signs within normal limits.

Skin: round, macular, bluish in color, ecchymotic rash, 4 cm in diameter, located on left forearm. Oral cavity: bleeding gingival surfaces noted.

The rest of the examination is unremarkable.

Medications: None

Allergies: NKA

Labs:

WBC: 5.8 × 10^3/mm^3 (5.8 × 10^9/L) (normal 3.5–10.5 × 10^3/mm^3 [3.5–10.5 × 10^9/L])

Platelet count: 9 × 10^3/mm^3 (9 × 10^9/L); manual count: 15 × 10^3/mm^3 (15 × 10^9/L) (normal 140–440 × 10^3/mm^3 [140–440 × 10^9/L])

Platelet count 2 months prior: 240 × 10^3/mm^3 (240 × 10^9/L)

aPTT: 35 seconds (normal 25–40 seconds)

PT: 11 seconds (normal 10–12 seconds)

Hgb: 12.1 g/dL (121 g/L or 7.5 mmol/L) (normal 12.0–15.5 g/dL or 120–155 g/L or 7.50–9.61 mmol/L)

Hct: 35% (normal 34.9%–44.5%)

Peripheral blood smear:

WBC: few activated lymphocytes and neutrophils with left shift

RBC: normocytic and normochromic

Platelets: giant platelets seen

Disseminated intravascular coagulation ruled out based on laboratory test and blood film

HCV: negative

HIV: negative

H. pylori antibody: negative

Pregnancy: negative

Given this additional information, is this patient's presentation consistent with ITP?

Define treatment goals for this patient.

Glucocorticoids Glucocorticoids may decrease splenic sequestration of antibody-coated platelets, diminish antibody generation, and increase platelet output by the bone marrow. In adults, the response rate to oral prednisone (1 mg/kg/day) is 50% to 75%, with patients usually responding within the first 1 to 2 weeks. The duration of therapy depends on the platelet count response; guidelines advocate for a longer course of prednisone therapy (21 days), followed by a taper. High-dose dexamethasone (40 mg orally or intravenously daily) administered for 4 days in 14- to 28-day cycles has also been used successfully and may be superior to prednisone.[37] In children, oral or parenteral corticosteroids (prednisone, dexamethasone, methylprednisolone) can be used; various dosage regimens have been studied with no specific drug or dosage regimen showing superiority.[34]

LO 8

LO 8

IV Immunoglobulin (IVIg) IVIg impairs the clearance of platelets coated with IgG by activating inhibitory receptor

FcRγIIb. Roughly 80% of adults will respond to IVIg, but remission usually is not sustained. In adults, use of IVIg (1 g/kg/day given as a single dose, repeated if necessary) is reserved for situations in which rapid increase in platelet count is necessary, such as life-threatening bleeding and very low platelet count, or for patients who have contraindications to glucocorticoids. If treatment is indicated in children, a single dose of IVIg (0.8–1 g/kg) is usually effective. IVIg use is complicated by many serious adverse effects and high cost.

LO 8

Anti-Rh(D) Anti-Rh(D) can be used only in Rh(D)-positive patients who have not had splenectomy. It is as efficacious as IVIg and is generally less expensive. The indications for use of anti-Rh(D) are identical to those for IVIg. Anti-Rh(D) is a desirable form of treatment in chronic ITP when the goal is to circumvent long-term exposure to corticosteroids. Initial dose is 50 mcg/kg intravenously, with dosage adjustment recommended based on hemoglobin levels. Administration of anti-Rh(D) may increase the platelet count in about 70% to 80% of children with ITP. Response to anti-Rh(D) lasts about 3 to 5 weeks, and substantial numbers of patients treated repetitively with anti-Rh(D) can postpone or avoid splenectomy. Rare fatal intravascular hemolysis has been reported with use of anti-Rh(D); close monitoring for 8 hours after drug administration is recommended.

LO 8

Immunosuppressants Immunosuppressant therapy is generally utilized for patients who are refractory to or intolerant of all other ITP treatments. Rituximab, an anti-CD20 antibody, at a dose of 375 mg/m^2 once weekly for four doses, can induce long-term response in 21% to 27% of patients.[34] Progressive multifocal leukoencephalopathy (PML) has been rarely reported with rituximab use. Rituximab can be considered as a second- or third-line therapy in patients who have experienced treatment failure with corticosteroids, IVIg, or splenectomy. Screening for hepatitis B infection is required prior to rituximab initiation.

Azathioprine and cyclophosphamide produce response rates of 20% to 40% in adult patients who are treated for 2 to 6 months. Other medications used in ITP include vincristine, vinblastine, cyclosporine, danazol, and mycophenolate mofetil; due to major toxicities and lack of adequate evidence-based recommendations, their use is reserved for refractory ITP. All immunizations should be up to date prior initiating immunosuppressant therapy because these medications increase susceptibility to infections.

Thrombopoietic Growth Factors Additional treatment options for ITP include a thrombopoiesis-stimulating protein and a small-molecule thrombopoietin (TPO) receptor agonist. These agents stimulate the bone marrow to make enough platelets to overcome the body's premature destruction of platelets. Romiplostim and eltrombopag are two TPO mimetics that have been approved by the FDA for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag is approved for managing of childhood ITP.

LO 8

Romiplostim is a TPO peptide mimetic that binds to and activates the human TPO receptor. Romiplostim works by stimulating megakaryopoiesis, which results in enhanced platelet production. Initial dose of romiplostim is 1 mcg/kg subcutaneously once weekly based on the actual body weight. Dose can be adjusted weekly by increments of 1 mcg/kg until the patient achieves a platelet count greater than or equal to 50×10^3/mm^3 (50×10^9/L) as necessary to reduce the risk for bleeding. The maximum dose is 10 mcg/kg/week. Studies demonstrate long-term efficacy of romiplostim over treatment periods of 5 years.[38]

Eltrombopag is a nonpeptide thrombopoietin receptor agonist with a low immunogenic potential that stimulates megakaryocyte proliferation and differentiation. Eltrombopag has been shown to increase platelet counts and decrease bleeding eposides in patients with ITP.[39] The usual daily dose is 50 mg by mouth once daily; it is subsequently adjusted to a maximum dose of 75 mg daily in order to achieve and maintain a platelet count greater than or equal to 50×10^3/mm^3 (50×10^9/L) in order to reduce the risk for bleeding. Studies demonstrate long-term efficacy over treatment periods of 3 years.[38,40]

Both agents need to be discontinued if platelet counts do not increase after 4 weeks at a maximum dose.

Romiplostim and eltrombopag are effective in increasing platelet counts in patients with ITP and can be used in combination with therapies that inhibit platelet destruction. Although usually well tolerated, a number of rare but serious risks have been reported, including changes in the bone marrow, worsened thrombocytopenia and the risk of bleeding after cessation of the medication, thrombotic/thromboembolic complications (including portal vein thrombosis with eltrombopag), and worsening of blood cancers. Eltrombopag carries a "black box warning" regarding increased risk of hepatotoxicity. Monitoring of hepatic enzymes every 2 weeks initially, followed by every 4 weeks thereafter, is recommended. In patients with hepatitis C treated with interferon and ribavirin, eltrombopag increases the risk of hepatic decompensation. It is also associated with development of cataracts and has several significant drug–drug interactions.

TPO-mimetic agents are expensive. Their use is generally reserved for patients who have treatment-resistant ITP after trying splenectomy and rituximab. These agents can also be tried in patients intolerant to other therapies, or in combination with other therapies.

Fostamatinib is a tyrosine kinase inhibitor that received FDA approval for ITP in adults who have insufficient response to a previous treatment (approved April 2018). Place in therapy for this new medication remains to be determined.

Outcome Evaluation

- Monitor platelet counts as indicated clinically.
- In adults, the goal of therapy is to maintain platelet count greater than or equal to 30×10^3/mm^3 (30×10^9/L).
- Monitor for signs and symptoms of bleeding.

THROMBOTIC MICROANGIOPATHIES

Epidemiology and Etiology

TMAs include a diverse variety of disorders with different pathophysiological features. Typical presentation includes small vessel (microangiopathic) hemolytic anemia with thrombocytopenia. Microvascular thrombosis occurs due to defects in the endothelium of small vessels, such as arterioles and capillaries.[41]

Patient Encounter 2, Part 3: ITP: Creating a Care Plan

Based on the information presented, create a care plan for this patient. If pharmacologic therapy is indicated, list first-line and alternative therapies.

Patient Care Process ITP

Collect Information:

- Conduct physical examination evaluating sites of bleeding. Obtain a complete medical and medication history.
- Evaluate CBC, peripheral blood smear, and Rh(D) status; order tests to rule out other diseases commonly associated with thrombocytopenia.

Assess the Information:

- Determine whether ITP is likely due to primary or secondary causes (this may change treatment focus).
- Evaluate platelet count, occupational risks of bleeding, and actual bleeding severity to determine the initial treatment approach.
- Identify relevant goals of therapy based on patient's platelet counts and presence or absence of bleeding.
- Based on patient data, determine if patient has contraindications to any potential ITP therapeutic options.

Develop a Care Plan:

- Choose medications and doses that are optimal for the patient.
- First-line treatment for patients meeting criteria for pharmacotherapy is corticosteroids for up to 21 days. Anti-Rh(D) or IVIg can be considered if corticosteroids are contraindicated or rapid rise in platelet count is necessary. Alternatives to first-line agents include immunosuppressants and TPO mimetics, which are reserved for patients failing to respond after adequate trial of first-line agents. Surgical splenectomy is reserved for refractory ITP.

Implement the Care Plan:

- Educate the patient about new medications in their regimen, discuss drug administration and side effects, especially focusing on serious effects and their management.
- Address any patient concerns about ITP and its management.
- Discuss importance of medication adherence and follow-up monitoring to achieve optimal outcomes. Determine whether there are any barriers to adherence. Educate patient's caregivers, if applicable.
- Review vaccination history and recommend appropriate vaccinations.
- Determine patient's ability to afford prescribed pharmacotherapy.

Follow-up: Monitor and Evaluate:

- Adhere to prescriber's recommendations on appropriate frequency of follow-up (depends on severity at presentation and pharmacotherapy chosen).
- Review platelet response and bleeding to assess changes in clinical status and evaluate pharmacotherapy for efficacy and safety. In adults, once response is achieved, monitor regularly to ensure platelet counts stay above $30 \times 10^3/mm^3$ ($30 \times 10^9/L$).
- Determine whether the patient is experiencing any adverse reactions or drug interactions.

LO 9

Primary TMAs include thrombotic thrombocytopenic purpura (TTP), shiga toxin-mediated hemolytic uremic syndrome (ST-HUS), immune or dose-related drug-induced TMA, complement-mediated TMA, metabolism-mediated TMA, and coagulation-mediated TMA. Classification and causes of primary TMA are summarized in Table 67–9. Here, we will focus on TTP and complement-mediated TMAs.

Table 67–9

Thrombotic Microangiopathy Syndromes

Name	Notes
TTP (ADAMTS13 deficiency)	Hereditary presents in children, acquired usually presents in adults.
Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS)	Triggered by *Shigella dysenteriae* or *Escherichia coli* Shiga-toxin producing infection.
Drug-induced	Can be mediated by immune reaction (eg, quinine) or related to the increased dose (eg, bevacizumab, sunitinib).
Complement-mediated	Mutations in complement factor H (CFH), CD46, complement factors I (CFI), B (CBF).
Coagulation-mediated	Genetic abnormalities in proteins mediating coagulation (eg, thrombomodulin gene [THBD], diacylglycerol kinase epsilon [DGKE]).

Thrombotic Thrombocytopenic Purpura

TTP is a severe systemic disorder characterized by thrombi formation within the circulation that results in the platelet consumption and subsequent thrombocytopenia.[41] TTP can occur in all ages, and can be hereditary or acquired. Both types of TTP are very rare; the estimated annual incidence of acquired TTP is three cases per million adults.[42]

▶ *Pathophysiology*

LO 9

Endothelial cells normally synthesize vWF in the form of a high-molecular-weight multimer composed of smaller identical monomers. Each monomer is able to bind platelets, and the number of monomers on the vWF multimer is directly proportional to its platelet-binding capacity. Consequently, particularly adherent ultra-large molecules of vWF (ULvWF) are broken down to smaller size by vWF-cleaving proteases such as ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats) to avoid undesired clot formation. TTP results from inherited deficiency in the vWF-cleaving protease ADAMTS13 activity, or development of autoimmune inhibitors to ADAMTS13. This, in turn, elevates circulating levels of ULvWF, leading to inappropriate platelet agglutination. Thrombocytopenia develops because the rate of aggregated platelet consumption is faster than megakaryocyte bone marrow production. Microangiopathic hemolytic anemia generally follows as a consequence of red blood cell damage by platelet clumps occluding the microcirculation. Occlusive ischemia of the brain or GI tract

is common. TTP is distiguished from other TMAs for rarely causing renal abnormalities.

▶ *Desired Outcomes*

The main goal of TTP treatment is to prevent end-organ damage.

▶ *Nonpharmacologic Therapy*

LO 9 KEY CONCEPT The present standard of treatment for hereditary TTP is plasma infusion containing ADAMTS13 protease. For acquired TTP, urgent plasma exchange (PEX) is needed to remove ADAMTS13 inhibitor. If PEX is unavailable, treatment with plasma infusion and glucocorticoids is indicated until PEX is available.[43]

LO 9 **Plasma Exchange** The procedure involves removal of the patient's plasma and its substitution with donor plasma. In this manner, circulating antibody inhibitor to ADAMTS13 is removed and enzyme is replenished. PEX involves placement of two IV lines (cannulae) into two separate veins. Blood removed through one cannula is centrifuged to separate the blood cells from the plasma. The blood cells are mixed subsequently with donor plasma and returned to the patient via the second cannula. The goal is to exchange 1 to 1.5 plasma volumes (40–60 mL/kg). The procedure generally is repeated daily until neurologic symptoms resolve and normal lactate dehydrogenase (LDH) and platelet counts are maintained for several days. After complete remission is achieved, PEX frequency can be reduced to every other day for an additional few days, with subsequent PEX discontinuation and close patient follow-up. When PEX is started immediately upon diagnosis, remission and survival rates at 6 months are approximately 80%. Although generally considered safe, complications from catheter insertion or catheter infection may occur and include hemorrhage, pneumothorax, sepsis, and thrombosis. Allergic reactions to plasma can cause severe hypotension and hypoxia.[44]

LO 9 **Splenectomy** Splenectomy is reserved for patients with frequently relapsing disease who are refractory to PEX or immunosuppressive therapy.

▶ *Pharmacologic Therapy*

LO 9 **Glucocorticoids** Glucocorticoids can be used for their immunosuppressive effect in combination with PEX; however, they are not as efficacious as monotherapy in TTP. The most commonly used agents are methylprednisolone 250 mg/day IV for or prednisone 1 mg/kg/day orally for the duration of PEX therapy and 1 to 2 weeks after normalized platelet counts are maintained.

LO 9 **Immunosuppressants** TTP that fails to respond adequately to PEX can be treated with immunosuppressive agents. Cytotoxic immunosuppressive therapies with the most potential benefit in refractory TTP include cyclosporine and rituximab. Other agents that had been used include bortezomib, vincristine, cyclophosphamide, azathioprine, and mycophenolate mofetil.[43]

Complement-Mediated TMA

LO 9 This type of TMA results from a genetic mutations of various factors responsible for alternative pathway of complement activation. Generally thought to be triggered by an infectious episode in predisposed patients, uncontrolled complement activation leads to formation of membrane attack complexes that cause endothelial damage, TMA, and renal failure.[45]

▶ *Nonpharmacologic Therapy*

LO 9 Supportive therapy may include blood or platelet transfusions, maintenance of fluid balance to support adequate end-organ perfusion, and dialysis therapy. Liver-kidney transplantation provides cure for this type of TMA, but is associated with significant complications.

▶ *Pharmacologic Therapy*

LO 9 Eculizumab is a humanized monoclonal antibody that binds to complement component C5, thus preventing formation of C5b and subsequent formation of C5b-9 (membrane attack complex).[46] Complement genetic studies may be helpful in determining whether a patient is a good candidate to receive eculizumab (eg, patients with C5 mutations may not be best candidates). For best results, treatment should be started within 48 hours of presentation; the usual adult dose is 900 mg intravenous infusion once weekly for 4 doses, followed by 1200 mg on week 5 and

Clinical Presentation and Diagnosis of Thrombotic Microangiopathies[a]

Onset and typical features will vary depending on precipitating cause.

1. Thrombocytopenia
   - Thrombocytopenic purpura
   - Bleeding
2. Fever (sometimes)
3. Microangiopathic hemolytic anemia
4. Neurologic symptoms (sometimes)
   - Headache, confusion, difficulty speaking, transient paralysis, numbness
5. Renal abnormalities (rare with TTP, common with other TMA types)
   - Proteinuria, hematuria, mild or severe renal insufficiency

Laboratory Testing

- Decreased ADAMTS 13 activity (< 10% or normal)—TTP
- Decreased hemoglobin, hematocrit, and platelets
- Peripheral blood smear showing schistocytes
- Decreased serum haptoglobin
- Elevated LDH
- Elevated indirect bilirubin level
- Elevated reticulocyte count
- Normal PT and aPTT
- Elevated urine protein, red blood cells, and/or serum creatinine, decreased urine output

[a]Thrombotic microangiopathies diagnosis can be based on the presence of thrombocytopenia and microangiopathic hemolytic anemia in the absence of other possible causes.

Patient Encounter 3, Part 1: TTP

A 21-year-old African female was seen in the emergency room for severe headache, confusion, chills, nausea and vomiting, and purplish pin-point nonitchy rash and petechiae on the abdomen. Patient has no history of gingival bleeding, hematemesis, melena, hematochezia, or autoimmune diseases including SLE and is otherwise healthy.

What patient information is suggestive of TTP?

What additional information for developing a treatment plan do you need to collect?

Patient Encounter 3, Part 2: TTP

PE/ROS:

Young WNWD female in no distress

Wt 70 kg, T 101.3°F (38.5°C), BP 128/75 mm Hg, HR 80 beats/min, RR 18 breaths/min

Neuro: patient appears confused but oriented × 3

Skin: disseminated purplish pin-point nonitchy rash and bruises on the abdomen

The rest of the examination is unremarkable

No familial history of hematologic disorders

Medications: none

Allergies: NKA

Labs:

- Platelet count: $8 \times 10^3/mm^3$ ($8 \times 10^9/L$) (normal 140–440 × $10^3/mm^3$ [140–440 × $10^9/L$])
- aPTT: 35 seconds (normal 25–40 seconds)
- PT: 11 seconds (normal 10–12 seconds)
- Haptoglobin: 10 mg/dL (100 mg/L) (normal 30–200 mg/dL or 300–2000 mg/L)
- LDH: 1057 U/L (17.62 µkat/L) (normal 100–250 U/L, or 1.67–4.17 µkat/L)
- Hgb: 7.1 g/dL (71 g/L; 4.34 mmol/L) (normal 12.0–15.5 g/dL or 120–155 g/L or 7.50–9.61 mmol/L)
- Hct: 22% (normal 34.9%–44.5%)
- Blood peripheral smear: numerous schistocytes (10–15 per high power field)
- SCr: 0.8 mg/dL (71 µmol/L) (normal 0.6–1.2 mg/dL [53–106 µmol/L])
- ADAMTS13 activity: < 5% (normal ≥ 60%)
- Anti-ADAMTS13 IgG: 3.2 units/mL [normal ≤ 0.4 units/mL]
- Imaging studies: CT-scan head–unremarkable
- Pregnancy test: negative

Given this additional information, is this patient's presentation consistent with TTP?

What is the likely etiology of this patient's TTP?

Define treatment goals for this patient.

Patient Encounter 3, Part 3: TTP: Creating a Care Plan

Based on the information presented, create a care plan for this patient.

Patient Care Process for Thrombotic Microangiopathy

Collect Information:

- Obtain a complete medical and medication history.
- Evaluate CBC, vital signs, neurologic symptoms, chemistry 7 panel, and urinalysis for presence of thrombocytopenia, fever, anemia, and renal abnormalities. Evaluate neurologic symptoms and peripheral blood smear.

Assess the Information:

- Identify the primary cause of TMA to evaluate appropriate targeted treatment selection.
- Identify appropriate goals of therapy based on patient's presentation.
- Based on patient data, determine if patient has contraindications to any potential therapeutic options.

Develop a Care Plan:

- Choose medication and doses (if applicable) that are optimal for the patient.
- If patient meets clinical criteria for diagnosis of acquired TTP, start daily PEX as soon as possible. Glucocorticoids and other adjunctive therapies may be considered.

Implement the Care Plan:

- Educate the patient about new medications in their regimen, discuss drug administration and side effects, especially focusing on serious effects and their management.
- Address any patient concerns about specific TMA and its management.
- Discuss importance of medication adherence and follow-up monitoring to achieve optimal outcomes. Determine whether there are any barriers to adherence. Educate patient's caregivers, if applicable.
- Review vaccination history and recommend appropriate vaccinations.
- Determine patient's ability to afford prescribed pharmacotherapy.

Follow-up: Monitor and Evaluate:

- Adhere to prescriber's recommendations on appropriate frequency of follow-up (depends on severity at presentation and pharmacotherapy chosen). When platelet counts stay above $150 \times 10^3/mm^3$ ($150 \times 10^9/L$) for 2 days, PEX may be discontinued; glucocorticoids may be continued for additional 1 to 2 weeks.
- Determine whether the patient is experiencing any adverse reactions or drug interactions.
- Follow patients indefinitely with periodic CBC/LDH measurements to screen for possible relapse.

1200 mg every 2 weeks thereafter. All immunizations should be up to date in patients considered for this therapy, as it can increase the risk of serious infections, including meningiococcal infection. PEX or plasma infusion are alternative therapies, since eculizumab therapy is very expensive.

Abbreviations Introduced in This Chapter

ADAMTS13	A disintegrin and metalloprotease with thrombospondin type 1 repeats (vWF-cleaving metalloprotease)
BU	Bethesda units
DDAVP	1-Desamino-8-D-arginine vasopressin (desmopressin acetate)
DIC	Disseminated intravascular coagulation
FFP	Fresh-frozen plasma
HCV	Hepatitis C virus
ICH	Intracranial hemorrhage
ITP	Immune thrombocytopenia
IVIg	IV immunoglobulin
PCC	Prothrombin complex concentrate
PEX	Plasma exchange
rFVIIa	Recombinant factor VIIa
RICD	Recessively inherited coagulation disorder
TTP	Thrombotic thrombocytopenic purpura
ULvWF	Ultra-large molecules of vWF
vWD	von Willebrand disease
vWF	von Willebrand factor

REFERENCES

1. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. Am J Hematol. 1998;59(4):288–294.
2. Zimmerman B, Valentino LA. Hemophilia: in review. Pediatr Rev. 2013;34(7):289–294; quiz 295.
3. Swystun LL, James P. Using genetic diagnostics in hemophilia and von Willebrand disease. Hematol Am Soc Hematol Educ Program. 2015;2015:152–159.
4. Bhat R, Cabey W. Evaluation and management of congenital bleeding disorders. Emerg Med Clin North Am. 2014;32(3):673–690.
5. Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. Blood. 2007;110(3):815–825.
6. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost JTH. 2014;12(11):1935–1939.
7. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. Blood. 2015;125(13):2038–2044.
8. Ljung R. Aspects of prophylactic treatment of hemophilia. Thromb J. 2016;14(suppl 1):30.
9. MASAC. Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. MASAC Document # 249. 2017.
10. Castaman G, Mancuso ME, Giacomelli SH, et al. Molecular and phenotypic determinants of the response to desmopressin in adult patients with mild hemophilia A. J Thromb Haemost JTH. 2009;7(11):1824–1831.
11. Srivastava A. Optimizing clotting factor replacement therapy in hemophilia: a global need. Hematol Amst Neth. 2005;10(suppl 1): 229–230.
12. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19(1):e1–e47.
13. Mannucci PM, Mancuso ME, Santagostino E. How we choose factor VIII to treat hemophilia. Blood. 2012;119(18):4108–4114.
14. Collins PW, Björkman S, Fischer K, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. J Thromb Haemost JTH. 2010;8(2):269–275.
15. Kepa S, Horvath B, Reitter-Pfoertner S, et al. Parameters influencing FVIII pharmacokinetics in patients with severe and moderate haemophilia A. Haemoph Off J World Fed Hemoph. 2015;21(3):343–350.
16. Batorova A, Holme P, Gringeri A, et al. Continuous infusion in haemophilia: current practice in Europe. Haemoph Off J World Fed Hemoph. 2012;18(5):753–759.
17. Prelog T, Dolničar MB, Kitanovski L. Low-dose continuous infusion of factor VIII in patients with haemophilia A. Blood Transfus Trasfus Sangue. 2016;14(5):474–480.
18. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013;369(24):2313–2323.
19. Nathwani AC, Reiss UM, Tuddenham EGD, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. N Engl J Med. 2014;371(21):1994–2004.
20. Nienhuis AW, Nathwani AC, Davidoff AM. Gene Therapy for Hemophilia. Mol Ther J Am Soc Gene Ther. 2017;25(5):1163–1167.
21. Recht M, Pollmann H, Tagliaferri A, Musso R, Janco R, Neuman WR. A retrospective study to describe the incidence of moderate to severe allergic reactions to factor IX in subjects with haemophilia B. Haemoph Off J World Fed Hemoph. 2011;17(3):494–499.
22. Lillicrap D, Schiviz A, Apostol C, et al. Porcine recombinant factor VIII (Obizur; OBI-1; BAX801): product characteristics and preclinical profile. Haemophilia. 2015 Aug 17. [Epub ahead of print.]
23. Berntorp E, Shapiro AD. Modern haemophilia care. Lancet Lond Engl. 2012;379(9824):1447–1456.
24. MASAC. MASAC Recommendations on use of COX-2 Inhibitors in Persons with Bleeding Disorders. 2005.
25. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987;69(2):454–459.
26. Nichols WL, Hultin MB, James AH, et al. von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). Haemoph Off J World Fed Hemoph. 2008;14(2):171–232.
27. Sadler JE, Budde U, Eikenboom JCJ, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. J Thromb Haemost JTH. 2006;4(10):2103–2114.
28. Castaman G, Goodeve A, Eikenboom J. Principles of care for the diagnosis and treatment of von Willebrand disease. Haematologica. 2013;98(5):667–674.
29. Leebeek FWG, Eikenboom JCJ. Von Willebrand's Disease. N Engl J Med. 2016;375(21):2067–2080.
30. Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. Blood. 2004;104(5):1243–1252.
31. Escobar MA. Advances in the treatment of inherited coagulation disorders. Haemoph Off J World Fed Hemoph. 2013;19(5):648–659.
32. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in

children and adults: a critical review of published reports. Am J Hematol. 2010;85(3):174–180.
33. Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood. 2017;129(21):2829–2835.
34. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190–4207.
35. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168–186.
36. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis Off Publ Infect Dis Soc Am. 2014;58(3):e44–e100.
37. Mithoowani S, Gregory-Miller K, Goy J, et al. High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis. Lancet Haematol. 2016;3(10):e489–e496.
38. Kuter DJ, Bussel JB, Newland A, et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. Br J Haematol. 2013;161(3):411–423.
39. Elgebaly AS, Ashal GE, Elfil M, Menshawy A. Tolerability and efficacy of eltrombopag in chronic immune thrombocytopenia. Clin Appl Thromb Hemost. 2017;23(8):928–937.
40. Saleh MN, Bussel JB, Cheng G, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood. 2013;121(3):537–545.
41. George JN, Nester CM. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371(7):654–666.
42. Reese JA, Muthurajah DS, Kremer Hovinga JA, Vesely SK, Terrell DR, George JN. Children and adults with thrombotic thrombocytopenic purpura associated with severe, acquired Adamts13 deficiency: comparison of incidence, demographic and clinical features. Pediatr Blood Cancer. 2013;60(10):1676–1682.
43. Scully M, Hunt BJ, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158(3):323–335.
44. Som S, Deford CC, Kaiser ML, et al. Decreasing frequency of plasma exchange complications in patients treated for thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, 1996 to 2011. Transfusion (Paris). 2012;52(12):2525–2532; quiz 2524.
45. Goodship THJ, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017;91(3):539–551.
46. Cofiell R, Kukreja A, Bedard K, et al. Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS. Blood. 2015;125(21):3253–3262.

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68 Sickle Cell Disease

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LEARNING OBJECTIVES

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

1. Explain the underlying causes of sickle cell disease (SCD) and their relationship to patient signs and symptoms.
2. Identify the typical characteristics of SCD as well as symptoms that indicate complicated disease.
3. Identify the desired therapeutic outcomes for patients with SCD.
4. Recommend appropriate pharmacotherapy and nonpharmacotherapy interventions for patients with SCD.
5. Recognize when chronic maintenance therapy is indicated for a patient with SCD.
6. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for SCD.
7. Educate patients about the disease state, appropriate therapy, and drug therapy required for effective treatment and prevention of complications.

INTRODUCTION

KEY CONCEPT "Sickle cell syndrome" refers to a collection of autosomal recessive genetic disorders that are characterized by the presence of at least one sickle hemoglobin (HbS) gene.[1,2]

Sickle cell disease (SCD) is a chronic illness that is associated with frequent crisis episodes. Acute complications are unpredictable and potentially fatal. Common symptoms include excruciating musculoskeletal pain, life-threatening pneumonia-like illness, cerebrovascular accidents, and splenic and renal dysfunction.[2] As the disease progresses, patients may develop organ damage from the combination of hemolysis and infarction. Because of the complexity and severity of SCD, it is imperative that patients have access to comprehensive care with providers who have a good understanding of the countless clinical presentations and the management options of this disorder.

EPIDEMIOLOGY AND ETIOLOGY

LO 1 Sickle cell trait (SCT) is the heterozygous form (HbAS) of SCD in which a person inherits one normal adult hemoglobin (*HbA*) gene and one sickle hemoglobin (*HbS*) gene. These individuals are carriers of the SCT and are usually asymptomatic.[2] About 1 in 13 African American babies is born with SCT.[3] Symptomatic disease is seen in homozygous and compound heterozygous genotypes of SCD. Sickle cell anemia (SCA) is the homozygous (HbSS) state of SCD.[2] It is the most common and severe form of SCD. SCD affects both males and females equally because it is not a sex-linked disease.

KEY CONCEPT Around 100,000 Americans have SCD and it occurs in approximately 1 out of every 365 African American births.[3] HbSS (~75%) is the most common genotype, followed by HbSC (~18%), HbSβ^+-thalassemia (~5%), and HbSβ^0-thalassemia (~2%). Other variants account for fewer than 1% of patients.[2,4] For every infant diagnosed with SCD, 50 are identified as carriers.[4]

Having the *HbS* gene protects heterozygous carriers from succumbing to *Plasmodium falciparum* (malaria) infection.[1] The microorganism cannot parasitize abnormal red blood cells (RBCs) as easily as normal RBCs. Consequently, persons with heterozygous sickle gene (*SCT*) have a selective advantage in tropical regions where malaria is endemic.

The highest incidence of SCD is seen in those with African heritage, but SCD also affects persons of Indian, Saudi Arabian, Mediterranean, South and Central American, and Caribbean ancestry.[4]

Normal HbA is composed of two α-chains and two β-chains (α2β2).[1] A single substitution of the amino acid valine for glutamic acid at position 6 of the β-polypeptide chain is responsible for the production of a defective form of hemoglobin called HbS.[1] Different genetic mutations encode for other hemoglobin variants such as hemoglobin C (HbC).[1] The α-chains of HbS, HbA, and HbC are structurally identical. The chemical differences in the β-chain are responsible for RBC sickling and its associated sequelae.

The HbSS state of SCD occurs when individuals inherit the mutant *HbS* gene from both parents. The progeny of two carriers will have a 25% probability of having SCD and a 50% risk of being a carrier. β-Thalassemia can be found in conjunction with HbS. Patients with HbSS and HbSβ^0-thalassemia do not have normal β-globulin production and usually have a more severe course than those with HbSC and HbSβ^+-thalassemia.

LO 1 Impaired circulation, destruction of RBCs, and vascular stasis are three known problems that are primarily responsible for the clinical manifestations of SCD (Figure 68–1).

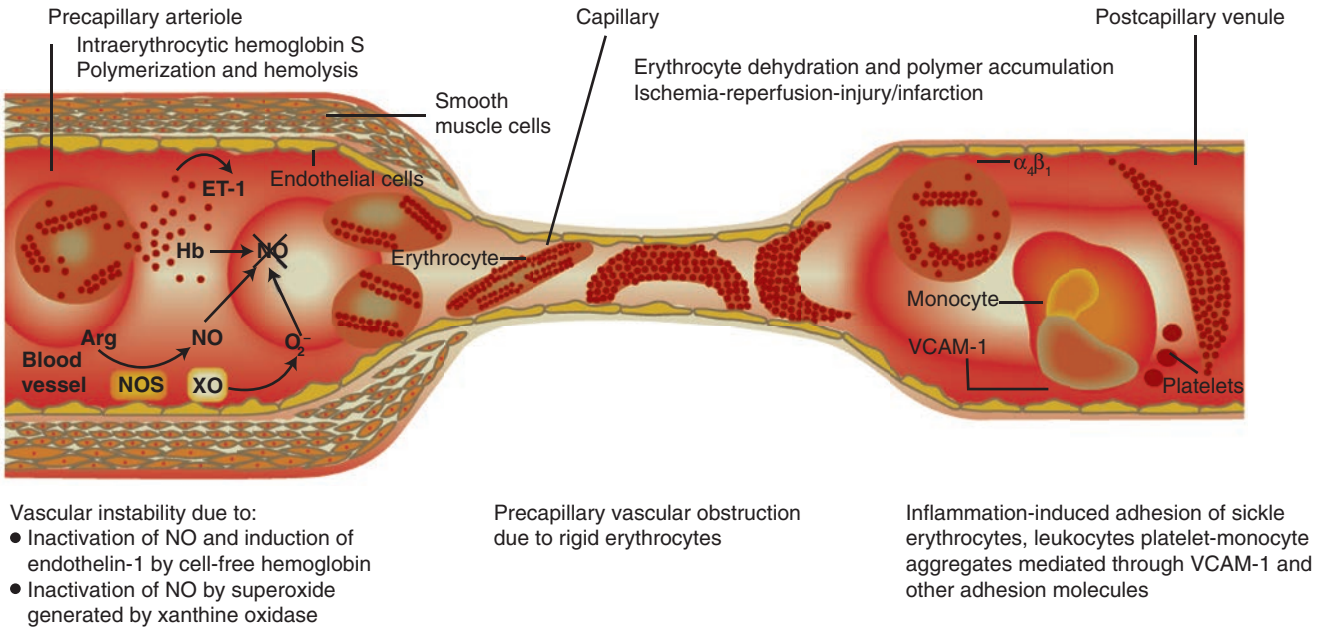

FIGURE 68–1. Pathophysiology of SCD. (Arg, arginine; ET-1, endothelin-1; Hb, hemoglobin; NO, nitric oxide; NOS, nitrous oxide synthase; VCAM-1, vascular cell adhesion molecule 1; XO, xanthine oxidase.) (From Kato GJ, Gladwin MT. Sickle cell disease. In: Hall JB, Schmidt GA, Wood LDH, eds. Principles of Critical Care, 3rd ed. New York, NY: McGraw-Hill; 2005:1658.)

PATHOPHYSIOLOGY

KEY CONCEPT SCD involves multiple organ systems, and its clinical manifestations vary greatly between and among genotypes.

Sickle Hemoglobin Polymerization

The primary event in the molecular pathogenesis of SCD involves polymerization of deoxygenated HbS. HbS carries oxygen normally, and when oxygenated, the solubility of HbS and HbA are the same. Once the oxygen is unloaded to the tissues, HbS solubility decreases. This promotes hydrophobic interactions between the hemoglobin molecules and polymerization, which leads to the distortion of the RBC into the characteristic crescent or sickle shape.[1]

Viscosity of Erythrocytes and Sickle Cell Adhesion

LO 2

When HbS becomes reoxygenated, the polymers within the RBCs disappear, and the cells eventually return to normal shape. Vasoocclussion is caused by a combination of factors. Repeated assaults on RBCs from sickling and unsickling can lead to cell membrane damage, loss of membrane flexibility, and rearrangement of surface phospholipids. The life span of sickled RBCs is markedly shorter (10–20 days) than that of normal RBCs (100–120 days). As intracellular membrane viscosity of HbS-containing RBCs increases, blood viscosity increases, which further contributes to vasoocclusion.[5] There is also increasing evidence that suggest sickle cells adhere to vascular endothelium.[1,5] The combined effects of decreased RBC deformability, slow transit through microcirculation, and adhesion to vascular endothelium contribute to obstruction of small and sometimes large blood vessels. The resulting local tissue hypoxia can accentuate the pathologic process of SCD.

Protective Hemoglobin Types

Fetal hemoglobin (HbF) binds oxygen more tightly than HbA, and it has a decreased propensity to sickling. HbA2 also possesses this characteristic but to a lesser extent. RBCs that contain HbF sickle less readily than cells without. HbF is composed of two α chains and two γ chains; therefore, it is not affected by point mutations on β chains. Irreversibly sickled cells (ISCs) are found to have low HbF concentrations. In some patients, higher HbF may ameliorate the disease.

Other Pathophysiologic Effects

LO 2

Other factors may be responsible for the pathogenesis of some of the clinical features of SCD. Sickle cells can obstruct blood flow to the spleen leading to functional asplenia. Impaired splenic function can increase the propensity to infection by encapsulated organisms, particularly *Streptococcus pneumoniae*.[1] Additionally, coagulation abnormalities are not uncommon since almost every component of hemostasis is altered in SCD.

Clinical Presentation and Diagnosis of SCT

General

- Generally asymptomatic

Symptoms

- Females may have frequent urinary tract infections

Signs

- Microscopic hematuria occurs rarely
- Gross hematuria may occur spontaneously or with heavy-intensity exercise

Laboratory Tests

- Normal Hgb values

Clinical Presentation and Diagnosis of SCD

General

- Identified by neonatal screening before 2 months of age in the United States

Symptoms

- Painful vasoocclusive crises are the hallmark of SCD
- Dactylitis (hand–foot syndrome) before age 1 year
- May develop infarction of the spleen, liver, bone marrow, kidney, brain, and lungs
- Gallstones
- Priapism in males
- Slow-healing lower extremity ulcers after trauma or infection
- Weakness, fatigue

Signs

- Chronic hemolytic anemia is common
- Enlargement of spleen and heart
- Scleral icterus

Laboratory Tests

- Hgb 7.0 to 10.0 g/dL (70–100 g/L or 4.34–.21 mmol/L)
- Low HgF and increased reticulocytes, platelets, and white blood cells (WBCs)
- Presence of sickled cells on blood smear
- Neonatal screening: hemoglobin electrophoresis, isoelectric focusing, or DNA analysis

TREATMENT

Desired Outcomes

LO 3 Multidisciplinary, regularly scheduled care is required over the lifetime of the SCD patient, with the goal of reduction of complications and hospitalizations. Comprehensive care should include medical, educational, and psychosocial aspects as well as genetic and medication counseling.

LO 3 Therapeutic interventions for SCD should be targeted at preventing and/or minimizing the symptoms related to the disease and its complications. The goals of treatment are to reduce or eliminate the patient's symptoms; decrease the frequency of sickle crises, including vasoocclusive pain crises; prevent the development of complications; and maintain or improve the quality of life through decreased hospitalizations and decreased morbidity. Specific therapeutic options may:

- Maintain or increase the hemoglobin level to the patient's baseline
- Increase the HbF concentration
- Decrease the HbS concentration
- Prevent infectious complications
- Prevent or effectively manage pain
- Prevent central nervous system (CNS) damage, including stroke

General Approach to Treatment

Patients should be educated to recognize the signs and symptoms of complications that would require urgent evaluation. Patients and parents of children with SCD should be educated to seek immediate medical care when a fever develops or signs of infection occur. With acute illnesses, prompt evaluation is important, as deterioration may occur rapidly. Fluid status should be monitored to avoid dehydration or overhydration, both of which may worsen complications of SCD. Patients in acute distress should maintain oxygen saturation at 92% (0.92) or at their baseline. Any supplemental oxygen requirements should be evaluated.[4]

Nonpharmacologic Therapy

LO 4 Patients should avoid smoking and excessive alcohol intake. Patients with SCD should maintain adequate hydration in order to help decrease blood viscosity and should be educated to avoid extreme temperature changes and to dress properly in hot and cold weather. Physical exertion that leads to complications should be avoided.[4] Regular examinations, including ophthalmic, dental, renal, pulmonary, and cardiac function, are required to monitor for organ damage. A treatment overview is shown in Table 68–1.

Pharmacologic Therapy

▶ *Health Maintenance*

Immunizations Children with SCD should receive the required immunizations as recommended by the American Academy of Pediatrics and the Advisory Committee on Immunization Practices, including vaccination for meningococcal disease.[6] Additionally, influenza vaccine should be administered yearly to SCD patients 6 months of age and older, including adult patients. All adult patients with SCD should also receive the vaccine for meningococcal disease as well as a one-time dose of *Haemophilus influenzae* type b vaccine. The quadrivalent conjugate meningococcal vaccine should be administered in two doses at least 2 months apart and should be revaccinated every 5 years.[7] In addition, adults should be vaccinated with the serogroup B meningococcal vaccine with either a 2-dose series of MenB-4C at least 1 month apart, or a 3-dose series of MenB-FHbp at 0, 1–2, and 6 months.[7]

Because patients with SCD have impaired splenic function, they are less adequately protected against encapsulated organisms such as *S. pneumoniae*, *H. influenzae,* and *Salmonella*. KEY CONCEPT

LO 4 The use of pneumococcal vaccine in combination with penicillin prophylaxis in SCD patients has dramatically decreased the rates of morbidity and mortality; however, there are still groups of SCD children who continue to have high rates of invasive pneumococcal infections.[8,9] Infection is the leading cause of death in children with SCD younger than 3 years of age.[9] Two pneumococcal vaccines are available. The 13-valent pneumococcal conjugate vaccine (PCV 13: Prevnar) is routinely administered to infants and children and provides good protection against the 13 most common isolates seen in this age range. Administer the first dose of PCV 13 between 6 weeks and 6 months of age, followed by two additional doses at 2-month intervals and a fourth dose at 12 to 15 months of age. The 23-valent polysaccharide vaccine (PPSV 23: Pneumovax 23) is indicated for children older than 2 years and adults. Because PPSV 23 is a polysaccharide vaccine, children younger than 2 years do not respond well. PPV 23 contains the 23 most common isolates of *S. pneumoniae* seen in older children and adults. Because of the different serotypes seen in the two vaccines, it is recommended that children with SCD receive both vaccines, with a dose of PPSV 23 administered after the child turns 2 years of age. The dose of PPSV 23 should be separated from the last dose of PCV 13 by at least 2 months.

Table 68–1

Management of SCD

Options and Comments	
Health Maintenance	
Infection prophylaxis	• Pneumococcal vaccines (PCV 13 and PPV 23) • Penicillin prophylaxis for children younger than 5 years of age • Annual influenza vaccine
Induction of fetal hemoglobin	• Hydroxyurea is the primary agent • Other agents are butyrates (arginine butyrate and sodium phenylbutyrate), decitabine, clotrimazole, and erythropoietin • Combination HbF inducers have been proposed
Chronic transfusion therapy	• Primary indication: stroke prevention in pediatric patients • May also reduce pain crisis and acute chest syndrome • Goal: maintain HbS < 30% (0.30)
Future Prospects	
Transplantation	• May potentially cure the disease • Most experience is with HLA-matched donors; umbilical cord blood transplantation is being evaluated
L-Glutamine	• Decreases complications • FDA approved 2017
Crises and Complications	
Fever and infection	• Broad-spectrum antibiotic: cefotaxime or ceftriaxone (clindamycin for cephalosporin allergy); vancomycin for staphylococcal and resistant pneumococcal organisms • Fluids • Acetaminophen or ibuprofen for fever
Stroke	• Exchange transfusion • Initiate chronic transfusion therapy to prevent recurrent strokes
Acute chest syndrome	• Broad-spectrum antibiotics (include Mycoplasma coverage) • Bronchodilator if wheezing or history of reactive airway disease • Fluids • Pain management • Transfusion
Pain crisis	• Hydration • Analgesics

An additional dose of PPSV 23 should be given to children 3 to 5 years of age to ensure antibody response. This second dose should be administered 5 years after the first PPSV 23 dose. All adults with SCD should be vaccinated with both PCV 13 as well as PPSV 23. Adults and children who have not previously received PCV13 or PPSV 23 should receive one dose of PCV 13 followed by a single dose of PPSV 23 at a minimum of 8 weeks later.[7] If an adult or child with SCD has already received at least one dose of PPSV 23, they should additionally receive one dose of PCV 13 at least 1 year after the dose of PPSV 23. When both vaccines are indicated in an unvaccinated patient with SCD, PCV 13 should be administered first, followed by a dose of PPSV 23 at least 8 weeks later.[7] A one-time revaccination with PPSV 23 should occur 5 years after the first dose of PPSV 23.[7] Because some children fall behind on their childhood vaccinations, a catch-up schedule is presented in Table 68–2.[6]

LO 4 LO 5 **Penicillin** KEY CONCEPT Children with SCD should receive prophylactic penicillin until at least the age of 5 years, even if they have been appropriately immunized against pneumococcal infections. Penicillin V potassium is typically initiated at age 2 months, with a dose of 125 mg orally twice daily until age 3 years, then 250 mg orally twice daily until 5 years of age. Amoxicillin 20 mg/kg/day divided every 12 hours (maximum of 250 mg/dose) can also be used. The intramuscular use of benzathine penicillin 600,000 units every 4 weeks from age 6 months to 6 years is also an option for nonadherent patients. Penicillin-allergic patients may receive erythromycin 10 mg/kg twice daily. Penicillin prophylaxis usually is not continued in children older than 6 years, but may be considered in patients with a history of invasive pneumococcal infection or surgical splenectomy.[4,10]

LO 4 **Folic Acid** Folic acid supplementation with 1 mg daily is generally recommended in adult SCD patients, women considering pregnancy, and any SCD patient with chronic hemolysis.[4] Because of accelerated erythropoiesis, these patients have an increased need for folic acid. There are conflicting studies in the SCD population, especially among infants and children, but if the child has chronic hemolysis, supplementation is recommended.[11]

Fetal Hemoglobin Inducers HbF induction in patients with SCD, especially those with frequent crises, has been shown to decrease RBC sickling and RBC adhesion. A direct relationship between HbF concentrations and the severity of disease has been demonstrated in studies.[2]

Hydroxyurea Hydroxyurea is a ribonucleotide reductase inhibitor that prevents DNA synthesis and traditionally has been used in chemotherapy regimens. Studies in the 1990s found that hydroxyurea increases HbF levels as well as increasing the number of HbF-containing reticulocytes and intracellular HbF. Other beneficial effects of hydroxyurea include antioxidant properties, reduction of neutrophils and monocytes, increased intracellular water content leading to increased red cell

Table 68–2

Pneumococcal Immunization for Children with SCD[6,8]

	Recommended Schedule
Previously Unvaccinated	
Age 2–6 months	PCV 13 (Prevnar): three doses 8 weeks apart; then one dose at 12–15 months
Age 7–11 months	PCV 13 (Prevnar): two doses 8 weeks apart; then one dose at 12–15 months
Age 12–23 months	PCV 13 (Prevnar): two doses 8 weeks apart
Age 24–71 months	PCV 13 (Prevnar): two doses 8 weeks apart PPV 23 (Pneumovax): two doses; first dose at least 8 weeks after last PCV 13 dose; second dose 5 years after the first PPV 23 dose
Age 5 years or older	PCV 13 (Prevnar): one dose PPV 23 (Pneumovax): one dose at least 8 weeks after last PCV 13 dose; second dose 5 years after the first PPV 23 dose
Previously Vaccinated	
Age 12–23 months, incomplete PCV 13 series	PCV 13 (Prevnar): two doses 8 weeks apart
Age 24–71 months, any incomplete schedule or completed less than three doses with PCV 13	PCV 13 (Prevnar): two doses 8 weeks apart PPV 23 (Pneumovax): two doses; first dose at least 6–8 weeks after last PCV 13 dose; second dose 5 years after the first PPV 23
Age 24–71 months, any incomplete schedule of three doses or four doses of PCV 13	PCV 13 (Prevnar): one dose at least 8 weeks after the most recent dose PPV 23 (Pneumovax): two doses; first dose at least 6–8 weeks after last PCV 13 dose; second dose 5 years after the first PPV 23
Age 24–71 months, one dose PPV 23 given	PCV 13 (Prevnar): one dose at least 8 weeks after PPV 23 dose
Age 5–18 years, received one dose PPV 23	PPV 23 (Pneumovax): second dose 5 years after first PPV 23 PCV 13 (Prevnar): one dose at least 8 weeks after PPV 23 If only received one dose of PPV 23 (Pneumovax): second dose 5 years after the first PPV 23 dose

deformability, decreased red cell adhesion to endothelium, and increased levels of nitric oxide, which is a regulator involved in physiologic disturbances.[12]

KEY CONCEPT Hydroxyurea reduced the frequency of hospitalizations and the incidences of pain, acute chest syndrome (ACS), and blood transfusions by almost 50% in a landmark trial in adult SCD patients with moderate to severe disease. Hemoglobin and HbF concentrations increased and hemolysis decreased.[12] A follow-up study demonstrated a 40% reduction in mortality over a 9-year period in patients continuing to receive hydroxyurea.[13] Not all patients responded equally; therefore, hydroxyurea may not be the best option for all patients.

The use of hydroxyurea in children and adolescents with SCD has been investigated, and similar results were reported as in adult trials, with no adverse effects on growth and development.[4,14,15] LO 4 Hydroxyurea is recommended as an option for children with moderate to severe SCD and can be used in children as young as 6 months of age.[16]

The most common adverse effect of hydroxyurea is myelosuppression. Long-term adverse effects are unknown, but myelodysplasia, acute leukemia, and chronic opportunistic infections have been reported.[12] Hydroxyurea is teratogenic in high doses in animal studies and this is a concern, which should be addressed with patients. Normal pregnancies with no birth defects have been reported in some women receiving hydroxyurea, but close monitoring and weighing risk versus benefit to the patient are vitally important. Hydroxyurea is excreted in breast milk and should be avoided in lactating mothers.[12]

LO 5 Hydroxyurea should be considered in SCD with frequent vasoocclusive crises, severe symptomatic anemia, repeated history of ACS, or other history of severe vasoocclusive crisis (VOC) complications.[4] The prevention of organ damage or reversal of previous damage has not been shown to occur with chronic use of hydroxyurea.[13] However, hydroxyurea treatment LO 5 should be considered in all infants 9 months of age and older, as well as children and adolescents with SCD regardless of their clinical severity, in order to reduce complications related to SCD.[17] The goals of therapy with hydroxyurea are to decrease the acute complications of SCD, improve quality of life, and reduce the number and severity of pain crises.

Hydroxyurea is available in 200-, 300-, 400-, and 500-mg capsules. Extemporaneous liquid preparations can be prepared for children who cannot swallow capsules. Doses should start at 10 to 15 mg/kg daily in a single oral dose, which can be increased after 8 to 12 weeks if blood counts are stable and there are no

Patient Encounter 1

A 3-year-old boy with SCD is currently taking penicillin V potassium 125 mg orally twice daily, acetaminophen as needed for pain, and a gummy multivitamin daily. He fully completed all his routine childhood vaccinations, including PCV 13 and is up to date. His only past hospitalization was at 9 months for dactylitis.

What are the general prophylaxis recommendations for children with SCD?

What interventions do you want to make today to his medication/immunization regimens?

Design an infection prevention plan for this patient.

Table 68–3

Dosage Adjustments for Renal and Hepatic Dysfunction

Medication	Renal Adjustment	Hepatic Adjustment
Decitabine (Decagon)	For Scr ≥ 2 mg/dL (177 μmol/L): hold therapy until values return to baseline	For serum alanine transaminase (ALT), serum glutamic pyruvic transaminase (SGPT), or total bilirubin values more than two times the upper limit of normal: hold therapy until values return to baseline
Deferoxamine (Desferal)	Cl_{cr} 10–50 mL/min (0.17–0.83 mL/s): administer 25%–50% of usual dose	No adjustment recommended
Deferasirox	Cl_{cr} < 10 mL/min (0.17 mL/s): do not use	Severe or persistent elevations in liver function tests: decrease the daily dose or discontinue therapy
Children	Greater than 33% increase in Scr (on two consecutive readings) and above the age-appropriate upper limits of normal: decrease daily dose by 10 mg/kg (Exjade) or 7 mg/kg (Jadenu) Scr ≥ 2 times age-appropriate upper limits of normal: discontinue treatment	
Adults	Greater than 33% increase in Scr above pretreatment values on two consecutive readings: decrease daily dose by 10 mg/kg (Exjade) or 7 mg/kg (Jadenu) CL < 40 mL/min (0.38 mL/s): discontinue treatment	Severe or persistent elevations in liver function tests: decrease the daily dose or discontinue therapy
Deferiprone	No adjustment necessary	No adjustment necessary
Folic acid	No adjustment necessary	No adjustment necessary
Hydroxyurea	Cl_{cr} < 60 mL/min (1.00 mL/s): initial dose of 7.5 mg/kg/day Cl_{cr} 10–50 mL/min (0.17–0.83 mL/s): reduce the daily dose by 50% Cl_{cr} < 10 mL/min (0.17 mL/s): administer 20% of the usual dose Hemodialysis: 7.5 mg/kg/day given after dialysis	Monitor patient for bone marrow toxicity

Data from Refs. 18–24.

LO 6 side effects. Individualize the dosage based on the patient's response and the toxicity seen. With close monitoring, doses can be increased 5 mg/kg/day up to 35 mg/kg daily.[12] In patients with renal failure, dosing of hydroxyurea will need to be adjusted according to the creatinine clearance, as shown in Table 68–3.

LO 6 Closely monitor patients for efficacy and toxicity while they are receiving hydroxyurea. Monitor mean corpuscular volume (MCV), since it typically increases as the level of HbF increases. If the MCV does not increase with hydroxyurea use, the marrow may be unable to respond, the dose may not be adequate, or the patient may be nonadherent.[12] However, lack of increase in MCV or in HbF is not an indication to discontinue therapy; the clinical response to therapy may take 3 to 6 months. A 6-month trial on the maximum tolerated dose is required prior to consideration of discontinuation due to treatment failure, whether secondary to lack of adherence or failure to respond to therapy. HbF levels can also be monitored to assess response LO 6 with a goal of increasing HbF to 15% to 20% (0.15–0.20). Assess blood counts every 2 weeks during dose titration and then every 4 to 6 weeks once the dose is stabilized. Temporary discontinuation of therapy is warranted if hemoglobin level is less than 4.5 g/dL (45 g/L or 2.79 mmol/L), absolute neutrophil count is less than $2 \times 10^3/mm^3$ ($2 \times 10^9/L$), platelets are less than $80 \times 10^3/mm^3$ ($80 \times 10^9/L$), or the reticulocytes are less than $80 \times 10^3/mm^3$ ($80 \times 10^9/L$). Monitor for increases in serum creatinine and transaminases. Once the patient's blood counts have returned to baseline, hydroxyurea may be restarted with a dose that is 2.5 to 5 mg/kg less than the dose associated with the patient's toxicity. Doses may then be increased by 2.5 to 5 mg/kg daily after 12 weeks with no toxicity.

Administer prophylactic folic acid supplementation to SCD patients receiving hydroxyurea, because folate deficiency may be masked by the use of hydroxyurea.

5-Aza-2′-Deoxycytine (Decitabine) For patients who do not respond to hydroxyurea, or cannot tolerate the side effects of hydroyurea, 5-azacytidine and 5-aza-2′-deoxycytidine (decitabine) may be useful. Both induce HbF by inhibiting methylation of DNA, preventing the switch from γ- to β-globin production. Decitabine appears to be safer and more potent than 5-azacytadine. In a small study in adults refractory to hydroxyurea, decitabine 0.2 mg/kg subcutaneously one to three times weekly was associated with an increase in HbF in all patients. Additionally, RBC adhesion was reduced. Neutropenia was the only significant toxicity reported.[25]

LO 4 **L-Glutamine Therapy** Recently FDA approved to reduce acute complications of SCD in adults and children 5 years of age and older, L-glutamine is available as an oral powder that is administered twice daily based on body weight. The dose should be mixed immediately prior to administration with 8 oz of cold or room temperature water, milk or apple juice, or can be mixed into 4 to 6 oz of soft food, such as applesause or yogurt. Clinical studies demonstrated significant decreases in the number of pain crises, vaso-occlusive crises hospitalizations, hospitalizations, ACS and time to first sickle cell crisis. Adverse effects seen in studies included constipation, nausea, headache, and abdominal pain. A majority of the patients in clinical trials were also receiving hydroxyurea.[26,27]

LO 5 **Chronic Transfusion Therapy** Chronic transfusion therapy is warranted to prevent serious complications from SCD, including stroke prevention and recurrence. KEY CONCEPT Especially in children, chronic transfusions have been shown to decrease stroke recurrence from approximately 50% to 10% over 3 years. Without chronic transfusions, approximately 70% of ischemic stroke patients will have another stroke. Chronic transfusion therapy also may be used to prevent vasoocclusive pain and ACS, as well as prevent progression of organ damage.[4]

Patient Encounter 2, Part 1

A 25-year-old African American man with SCD is admitted to the hospital for progressive shoulder and chest pain that began 2 days ago. The patient denies injury. He complains of a nonproductive cough.

PMH: Sickle cell disease (HbSS); admitted for vasoocclusive crises three times over the past year; acute chest syndrome at age 8, 9, 12, 18, 22, and 24; multiple blood transfusions

PSH: Cholecystectomy, splenectomy

FH: Father with SCD. Mother with SC trait.

Allergies: NKDA

SH: Occasional alcohol. Is sexually active

Home Meds: Hydrocodone/acetaminophen 7.5/325 mg, two tablets every 6 hours as needed for pain; folic acid 1 mg daily by mouth, hydroxyurea 2 gm orally once daily.

PE:

VS: T 39.1°C (102.4°F), BP 113/66 mm Hg, P 78 beats/min, RR 26 breaths/min, O_2 Sat 97% (0.97) on 2 L nasal cannula, Ht 173 cm (5′8″), Wt 71 kg (160 lb)

Gen: Awake, alert × 3, in some distress, and obviously in pain

HEENT: Normocephalic, atraumatic. PERRLA. No lymphadenopathy

Chest: Normal to inspection and palpation. Mild rales and wheezes

CV: RRR, no m/g/r

Abd: Soft, NT/ND

Ext: No clubbing, cyanosis, or edema. Shoulder pain with palpation

Neuro: Cranial nerves II through XII are grossly intact. Nonfocal

Labs: Hgb 7.3 g/dL (73 g/L or 4.53 mmol/L), Hct 23.1% (0.231 fraction), WBC 16 × 10^3/μL (16 × 10^9/L), BMP WNL

Chest x-ray shows pulmonary infiltrates.

What is your assessment of this patient's condition?

List treatment goals for this patient.

Devise a detailed therapeutic plan for this patient's hospital management.

The goal of chronic transfusion therapy is to maintain the HbS level at less than 30% (0.30) of total hemoglobin concentration. Transfusions are usually administered every 3 to 4 weeks depending on the HbS concentration. For secondary stroke prevention, current studies have indicated that lifelong transfusion may be required, with increased incidence of recurrence once transfusions are stopped.[4,17]

The benefits of transfusion should be weighed with the risks. Risks associated with transfusions include alloimmunization (sensitization to the blood received), hyperviscosity, viral transmission, volume overload, iron overload, and transfusion reactions. Although the risk of contracting AIDS has decreased dramatically, hepatitis C remains a concern. All SCD patients should be vaccinated for hepatitis A and B and should be serially monitored for hepatitis C and other infections. Parvovirus occurs in 1 of every 40,000 units of RBCs and can be associated with acute anemia and multiple sickle cell complications.[4] Iron overload is a risk for patients maintained on chronic transfusions for more than 1 year. Counsel patients to avoid excessive dietary iron, and monitor serum ferritin regularly. Chelation therapy with deferoxamine, deferasirox, or deferiprone should be considered when the serum ferritin level is greater than 1500 to 2000 ng/mL (1500–2000 mcg/L; 3400–4500 pmol/L).

LO6 LO7 LO4 LO6

Patient Encounter 2, Part 2

The patient recovers from his hospitalization and comes to clinic for follow-up 2 weeks after discharge. He was discharged on his home medications. He has been feeling pretty well, but routine laboratory tests indicate that his Cl_{Cr} is now 40 mL/min/1.73 m^2 (0.38 mL/s/m^2).

How should his medications be adjusted?

Deferoxamine should be initiated at 20 to 40 mg/kg daily (to a maximum of 1–2 g/day) over 8 to 12 hours subcutaneously and has been associated with growth failure.[4] Monitor children receiving deferoxamine for adequate growth and development on a regular basis. Additionally, patients receiving deferoxamine should receive supplemental ascorbic acid starting 1 month after deferoxamine initiation; the ascorbic acid will increase the availability of iron for chelation. Patients with preexisting cardiac conditions should not receive ascorbic acid supplementation. Deferasirox is available in three dosage forms: a tablet (Exjade) that should be dispersed in water, orange juice, or apple juice and taken orally 30 minutes before food, a tablet (Jadenu) that can be swallowed whole and granules (Jadenu Sprinkle) which are sprinkled on soft food.[28] Exjade should be initiated at 20 mg/kg once daily and titrated every 3 to 6 months by 5 to 10 mg/kg/day up to a maximum dose of 40 mg/kg/day. Jadenu and Jadenu Sprinkle should be initated at 14 mg/kg once daily and titrated every 3 to 6 months by 3.5 or 7 mg/kg/day to a maximum dose of 28 mg/kg/day. Exjade and Jadenu are not bioequivalent on an mg to mg basis because of bioavailability differences: when converting from one dosage form to the other, the dose for Jadenu should be about 30% less than the Exjade dose. For both products, the dose should be rounded to the whole tablet dosage form available. Exjade is available in 125 mg, 250 mg, and 500 mg dispersible tablets. Jadenu and Jadenue Sprinkles are available in 90 mg, 180 mg, and 360 mg tablets and packets. Deferiprone is approved for use in adults with thalassemia syndromes who have not responded adequately to other chelation therapies.[29] It is administered three times daily as an oral dosage form. Some recent studies have evaluated combination therapy for treatment of transfusion-associated iron overload. A synergistic effect has been demonstrated with the concomitant use of deferoxamine and deferiprone.[30] Monitor all chelation patients for auditory and ocular changes on a yearly basis. Exchange transfusions may also be helpful in cases of iron overload.

LO6

Sickle cell hemolytic transfusion reaction syndrome is a unique problem in SCD patients. Due to alloimmunization, an acute or delayed transfusion reaction may occur 5 to 20 days posttransfusion. Patients may develop symptoms suggestive of a pain crisis or worsening symptoms if they are already in crisis. A severe anemia after transfusion also may occur due to a rapid decrease in hemoglobin and hematocrit, along with a suppression of erythropoiesis. Further transfusions may worsen the clinical picture due to autoimmune antibodies. Recovery may occur only after ceasing all transfusions and is evidenced by a gradual increase in hemoglobin with reticulocytosis, which indicates the patient is now making their own RBCs.[4]

LO 4 **Allogeneic Hematopoietic Stem Cell Transplant** Allogeneic hematopoietic stem-cell transplantation (HSCT) is the only potential cure for SCD. The best candidates are children with SCD who are younger than 16 years of age with severe complications, who have an identical human leukocyte antigen (HLA)-matched donor, usually a sibling. The transplant-related mortality rate is between 5% and 10%, and graft rejection is approximately 10%. In a recent review, the overall survival rate was 95% and the event-free survival was 92% in children with SCD who received a transplant from an HLA-matched sibling.[31] Other risks include secondary malignancies, development of seizures or intracranial bleeding, and infection in the immediate posttransplant period.[4,32]

Experience with HSCT in adult patients with SCD is still somewhat limited. The use of less intense preparative regimens has made HSCT more available for the older patient with SCD. The best results have been seen in the use of progenitor cells (from bone marrow, cord blood, or peripheral blood stem cells) from matched sibling or related donors. The largest published trial to date in adults undergoing nonmyeloablative transplant involved 30 patients with an 87% rate of disease-free survival.[32]

► *Acute Complications*

LO 4 **Transfusions for Acute Complications** Red cell transfusion is indicated in patients with acute exacerbations of baseline anemia; in cases of severe vasoocclusive episodes, including ACS, stroke, and acute multiorgan failure; and in preparation for procedures that will require the use of general anesthesia or ionic contrast products. Transfusions also may be useful in patients with complicated obstetric problems, refractory leg ulcers, refractory and prolonged pain crises, or severe priapism. Hyperviscosity may occur if the hemoglobin level is increased to greater than 10.0 to 11.0 g/dL (100–110 g/L or 6.21–6.83 mmol/L). Volume overload leading to congestive heart failure is more likely to occur if the anemia is corrected too rapidly in patients with severe anemia and should be avoided.[4]

Infection and Fever KEY CONCEPT Any fever greater than 38.5°C (101.3°F) in an SCD patient should be immediately evaluated, and the patient should have a blood culture drawn and be started on antibiotics that provide empirical coverage for encapsulated organisms.[4]

Patients who should be hospitalized include the following:

- Infants younger than 1 year of age
- Patients with a previous sepsis or bacteremia episode
- Patients with temperatures in excess of 40°C (104°F)
- Patients with WBC counts greater than $30 \times 10^3/mm^3$ ($30 \times 10^9/L$) or less than $0.5 \times 10^3/mm^3$ ($0.5 \times 10^9/L$) and/or platelets less than $100 \times 10^3/mm^3$ ($100 \times 10^9/L$) with evidence of other acute complications
- Acutely ill-appearing individuals

LO 4 Broad IV antibiotic coverage for the encapsulated organisms can include ceftriaxone or cefotaxime. For patients with true cephalosporin allergy, clindamycin may be used. If staphylococcal infection is suspected due to previous history or the patient appears acutely ill, vancomycin should be initiated. Macrolide antibiotics, such as erythromycin or azithromycin, may be initiated if mycoplasma pneumonia is suspected. While the patient is receiving broad-spectrum antibiotics, their regular use of penicillin for prophylaxis can be suspended. Fever should be controlled with acetaminophen or ibuprofen. Because of the risk of dehydration during infection with fever, increased fluid may be needed.[1,4]

Bone infarcts or sickling in the periosteum usually is indicated by pain and swelling over an extremity. Osteomyelitis should also be considered. *Salmonella* species are the most common cause of osteomyelitis in children with SCD, followed by *Staphylococcus aureus*.[1] Select an appropriate antibiotic to cover the suspected organisms empirically.

LO 6 **Cerebrovascular Accidents** Acute neurologic events, such as stroke, will require hospitalization and close monitoring. Patients should have physical and neurologic examinations every 2 hours.[4] Acute treatment may include exchange transfusion or simple transfusion to maintain hemoglobin at approximately 10.0 g/dL (100 g/L or 6.21 mmol/L) and HbS concentration at less than 30% (0.30). Patients with a history of seizure may need anticonvulsants, and interventions for increased intracranial pressure should be initiated if necessary. Children with history of stroke should be initiated on chronic transfusion therapy.[4]

LO 6 Early detection of ischemic stroke can be done with the use of transcranial Doppler ultrasonography. In the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study, screening with this method followed by chronic transfusion therapy significantly reduced the incidence of stroke.[33-35] Screening is recommended in all patients older than 2 years.

Acute Chest Syndrome ACS will require hospitalization for appropriate management of symptoms and to avoid complications. Patients should be encouraged to use incentive spirometry at least every 2 hours. Incentive spirometry helps the patient take long, slow breaths to increase lung expansion. Appropriate management of pain is important, but analgesic-induced hypoventilation should be avoided. Patients should maintain appropriate fluid balance because overhydration can lead to pulmonary edema and respiratory distress. Infection with gram-negative, gram-positive, or atypical bacteria is common in ACS, and early use of broad-spectrum antibiotics, including a macrolide, quinolone, or cephalosporin is recommended. Fat emboli, from infarction of the long bones, may lead to ACS. Oxygen therapy should be utilized in any patient presenting with respiratory distress or hypoxia. Oxygen saturations, measured by pulse oximeter, should be maintained at 92% (0.92) or above. Exchanges transfusions are often indicated when there is a rapid progression of ACS symptoms, such as increased needs for supplemental oxygen, increased respiratory distress, or progression of pulmonary infiltrates, and patients who present with wheezing may require inhaled bronchodilators.[4,36]

LO 4

The use of corticosteroids is controversial. Although they may decrease the inflammation and endothelial cell adhesion seen with ACS, their use has also been associated with higher readmission rates for other complications.

Priapism By age 18, approximately 90% of males with SCD will have had at least one episode of priapism. Stuttering priapism, where erection episodes last anywhere from a few minutes to

Clinical Presentation and Diagnosis of ACS in SCD

General
- Occurs in 15% to 43% of patients and is responsible for 25% of deaths
- Risk factors include young age, low HbF level, high Hgb and WBCs, winter seasons, reactive airway disease
- Recurrences are up to 80% and can lead to chronic lung disease

Symptoms
- Patients may complain of cough, fever, dyspnea, chest pain

Signs
- Temperature greater than 38.5°C (101.3°F)
- Hypoxia
- New infiltrate on chest x-ray

Laboratory Tests
- CBC with reticulocyte count
- Blood gases
- Oxygen saturation
- Cultures (blood and sputum)

Other
- Closely monitor pulmonary status

less than 2 hours, resolves spontaneously. Erections lasting more than 2 hours should be evaluated promptly. Goals of therapy are to provide pain relief, reduce anxiety, provide detumescence, and preserve testicular function and fertility. Initial treatment should include aggressive hydration and analgesia. Transfusion may or may not be helpful, but should be considered in anemic patients. Avoid the use of ice packs due to the risk of tissue damage.[4]

LO 4

Both vasoconstrictors and vasodilators have been used in the treatment of priapism. Vasoconstrictors are thought to work by forcing blood out of the cavernosum and into the venous return. Aspiration of the penile blood followed by intracavernous irrigation with epinephrine (1:1,000,000 solution) has been effective with minimal complications.[37] In severe cases, surgical intervention to place penile shunts has been used, but there is a high failure rate, and the risk of complications, from skin sloughing to fistulas, limits its use.

LO 4

Pseudoephedrine dosed at 30 to 60 mg daily taken at bedtime has been used to prevent or decrease the number of episodes of priapism.[4] Terbutaline 5 mg has been used orally to prevent priapism, with mixed results.[37,38] Leuprolide, a gonadotropin-releasing hormone, also has been used for this indication. Hydroxyurea may be helpful in some patients.[37,39] The use of antiandrogens is under investigation.[4]

LO 4

▶ *Treatment of Acute Complications*

Aplastic Crisis Most patients in aplastic crisis will recover spontaneously and therefore treatment is supportive. If anemia is severe or symptomatic, transfusion may be indicated. Infection with human parvovirus B19 is the most common cause of aplastic crisis. Isolate infected patients because parvovirus is highly contagious. Pregnant individuals should avoid contact with infected patients because midtrimester infection with parvovirus may cause hydrops fetalis and still birth.[1,4]

Clinical Presentation and Diagnosis of Priapism in SCD

General
- Mean age of initial episode is 12 years of age
- Most males with SCD will have one episode by age 20
- Repeated episodes can lead to fibrosis and impotence

Symptoms
- Patients may complain of painful and unwanted erection lasting anywhere from less than 2 hours (stuttering type) to more than 2 hours (prolonged type)

Signs
- Urinary obstruction

Laboratory Tests
- CBC with reticulocyte count

Other
- Monitor for duration of episode
- Prolonged episodes should be considered medical emergencies

Sequestration Crisis RBC sequestration in the spleen in young children may lead to a rapid drop in hematocrit, resulting in hypovolemia, shock, and death. Treatment is RBC transfusion to

Clinical Presentation and Diagnosis of Acute Aplastic Crisis in SCD

General
- Transient suppression of RBC production in response to bacterial or viral infection
- Most commonly due to infection with parvovirus B19

Symptoms
- Patients may complain of headache, fatigue, dyspnea, pallor, or fever
- Patients may also complain of upper respiratory or GI infection symptoms

Signs
- Temperature greater than 38.5°C (101.3°F) may occur
- Hypoxia
- Tachycardia
- Acute decrease in Hgb with decreased reticulocyte count

Laboratory Tests
- CBC with reticulocyte count
- Chest x-ray
- Parvovirus titers
- Cultures (blood, urine, and throat)

Clinical Presentation and Diagnosis of Sequestration Crisis in SCD

General
- Acute exacerbation of anemia due to sequestration of large blood volume by the spleen
- More common in patients with functioning spleens
- Onset often associated with viral or bacterial infections
- Recurrence is common and can be fatal

Symptoms
- Sudden onset of fatigue, dyspnea, and distended abdomen
- Patients may present with vomiting and abdominal pain

Signs
- Rapid decrease in Hgb and Hct with elevated reticulocyte count
- Splenomegaly
- May exhibit hypotension and shock

Evaluation
- Vital signs
- Spleen size changes
- Oxygen saturations
- CBC with reticulocyte count
- Cultures (blood, urine, throat)

Clinical Presentation and Diagnosis of Vasoocclusive Crisis in SCD

General
- Most often involves the bones, liver, spleen, brain, lungs, and penis
- Precipitating factors include infection, extreme weather conditions, dehydration, and stresses
- Recurrent acute crises result in bone, joint, and organ damage and chronic pain

Symptoms
- Patients may complain of deep throbbing pain, local tenderness

Signs
- Erythema and swelling of painful area
- Dactylitis in young infants
- Temperature greater than 38.5°C (101.3°F)
- Leukocytosis

Laboratory tests
- CBC with reticulocyte count
- Urinalysis
- Abdominal studies (if symptoms exist)
- Cultures (blood and urine)
- Liver function tests and bilirubin
- Chest x-ray

correct the hypovolemia, as well as broad-spectrum antibiotics, because infections may precipitate the crisis.[1,4]

LO 4 Recurrent episodes are common and can be managed with chronic transfusion and splenectomy. Observation is used commonly in adults because their episodes are milder. Splenectomy is usually delayed until after 2 years of age to lessen the risk of postsplenectomy septicemia. Patients with chronic hypersplenism should be considered for splenectomy.[4,40]

LO 4 **Vasoocclusive Pain Crisis** The mainstay of treatment for vasoocclusive crisis includes hydration and analgesia (Table 68–4). Pain may involve the extremities, back, chest, and abdomen. KEY CONCEPT Patients with mild pain crisis may be treated as outpatients with rest, warm compresses to the affected (painful) area, increased fluid intake, and oral analgesia. Patients with moderate to severe crises should be hospitalized. Infection should be ruled out because it may trigger a pain crisis, and any patient presenting with fever or critical illness should be started on empirical broad-spectrum antibiotics. Patients who are anemic should be transfused to their baseline. IV or oral fluids at 1.5 times maintenance are recommended. Close monitoring of the patient's fluid status is important to avoid overhydration, which can lead to ACS, volume overload, or heart failure.[4]

LO 6 Aggressive pain management is required in patients presenting in pain crisis. Assess pain on a regular basis (every 2–4 hours), and individualize management to the patient. The use of pain scales may help with quantifying the pain rating. Obtain a good medication history of what has worked well for the patient in the past. Use acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) for treatment of mild to moderate pain. Patients with bone or joint pain who require IV medications may be helped by the use of ketorolac, an injectable NSAID. Because of the concern for side effects, including GI bleeding, ketorolac should be used only for a maximum of 5 consecutive days.

LO 6 Monitor for the total amount of acetaminophen given daily, because many products contain acetaminophen. Maximum daily dose of acetaminophen for adults is 3 g/day, and for children, five doses over a 24-hour period.[41] Add an opioid if pain persists or if pain is moderate to severe in nature. Combining an opioid with an NSAID can enhance the analgesic effects without increasing adverse effects.[42-45]

LO 4 Severe pain should be treated with an opioid such as morphine, hydromorphone, methadone, or fentanyl. Moderate pain can be effectively treated in most cases with a weak opioid such as codeine or hydrocodone, usually in combination with acetaminophen. Meperidine should be avoided because of its relatively short analgesic effect and its toxic metabolite, normeperidine. Normeperidine may accumulate with repeated dosing and can lead to CNS side effects including seizures.

IV opioids are recommended for use in treatment of severe pain because of their rapid onset of action and ease in titration. Intramuscular injection should be avoided. Analgesia should be individualized and titrated to effect, either by scheduled around-the-clock doses or continuous infusion. The use of continuous infusion will avoid the fluctuations in blood levels between doses that are seen with bolus dosing. As-needed dosing of analgesia is only appropriate for breakthrough pain or uncontrolled pain. Patient-controlled analgesia (PCA) is commonly used and allows the patient to have control over his or her analgesic breakthrough dosing. As the pain crisis resolves, the pain medications can be

Table 68–4

Management of Acute Pain of SCD

Principles

Treat underlying precipitating factors.
- Avoid delays in analgesia administration.
- Use pain scale to assess severity.
- Choice of initial analgesic should be based on previous pain crisis pattern, history of response, current status, and other medical conditions.
- Schedule pain medication; avoid as-needed dosing.
- Provide rescue dose for breakthrough pain.
- If adequate pain relief can be achieved with one or two doses of morphine, consider outpatient management with a weak opioid; otherwise hospitalization is needed for parenteral analgesics.
- Frequently assess to evaluate pain severity and side effects; titrate dose as needed.
- Treating adverse effects of opioids is part of pain management.
- Consider nonpharmacologic intervention.
- Transition to oral analgesics as the patient improves; choose an oral agent based on previous history, anticipated duration, and ability to swallow tablets; if sustained-release products are used, a fast-release product is also needed for breakthrough pain.

Analgesic Regimens

Mild to moderate pain:

Hydrocodone + acetaminophen:
- Dose based on hydrocodone—children: 0.2 mg/kg per dose every 6 hours; adults: 5–10 mg/dose

Anti-inflammatory agents:
- Use with caution in patients with renal failure (dehydration) and bleeding
- Ibuprofen (oral): children: 10 mg/kg every 6–8 hours; adults: 200–400 mg/dose
- Naproxen: 5 mg/kg every 12 hours; adults: 250–500 mg/dose
- Ibuprofen + hydrocodone: Each tablet contains 200 mg ibuprofen and 7.5 mg hydrocodone per tablet; only for older children who can swallow tablets

Moderate to severe pain:

Morphine—children:
- 0.1–0.15 mg/kg per dose every 3–4 hours; adults: 5–10 mg/dose
- Continuous infusion: 0.04–0.05 mg/kg/hour; titrate to effect

Hydromorphone—children:
- 0.015 mg/kg per dose every 3–4 hours; adults: 1.5–2 mg/dose
- Continuous infusion: 0.004 mg/kg/hour; titrate to effect

IV anti-inflammatory agents:
- Ketorolac: 0.5 mg/kg up to 30 mg/dose every 6 hours

Patient-controlled analgesics:
- Morphine: 0.01–0.03 mg/kg/hour basal; demand 0.01–0.03 mg/kg every 6–10 minutes; 4 hours lockout 0.04–0.06 mg/kg
- Hydromorphone: 0.003–0.005 mg/kg/hour basal; demand 0.003–0.05 mg/kg every 6–10 minutes; 4 hours lock out 0.4–0.6 mg/kg

tapered. Physical therapy and relaxation therapy can be helpful adjuvants to analgesia.[42–45]

Tolerance to opioids is seen when patients have had continuous long-term use of the medications and can be managed during acute crises by using a different potent opioid or using a larger dose of the same medication. Adverse effects associated with the use of opioids include respiratory depression, itching, nausea and vomiting, constipation, and drowsiness. Patients on continuous infusions of opioids should be on continuous pulse oximeter to assess oxygen saturations. Monitor the patient for oxygen saturations less than 92% (0.92). Oxygen should be administered as needed to keep the saturations above 92% (0.92). Itching can be managed with an antihistamine such as diphenhydramine. Nausea and vomiting can be treated and managed with the administration of antiemetics such as promethazine or the 5HT3 antagonists, but the use of promethazine is contraindicated in children younger than 2 years of age. Assess stool frequency in all patients on a continuous opioid, and start stool softeners or laxatives as needed. Excessive sedation is difficult to control, and the concurrent use of an opioid with diphenhydramine or other sedative medications can exacerbate the drowsiness, leading to hypoxemia. A continuous very low dose of naloxone, an opioid antagonist, has been used successfully when the adverse effects such as itching are unbearable.[46]

LO 6

As patients age and their SCD advances, most will present with some level of chronic pain, which should be treated with the lowest dose of oral analgesic, typically a combination of hydrocodone and acetaminophen on an as-needed basis. Neuropathic pain can result from repeated vaso-occlusive crises, and may require the regular use of medications such as gabapentin, amitriptyline, or pregabalin.

OUTCOME EVALUATION

SCD treatment and prevention are considered successful when complications are minimized. The major outcome parameters are a decrease in morbidity and mortality, measured by the number of hospitalizations, and the extent of end-organ damage seen over time. Today, with longer survival for SCD, chronic manifestations of the disease contribute to the morbidity later in life (Table 68–5). Thirty years ago, complications from SCD contributed to high mortality. It was estimated that approximately 50% of patients with SCD did not survive to reach adulthood.[1] Since that time, data suggest improvement in mortality rates for patients with SCD. The survival age for individuals with HbSS has increased to at least the fifth decade of life. Recent reports suggest 85% survival by 18 years of age.[4] SCD is a chronic disease and cannot be cured, except in some patients with transplant.

Table 68–5

Chronic Complications of SCD

System	Complications
Auditory	Sensorineural hearing loss due to sickling in cochlear vasculature with hair cell damage
Cardiovascular	Cardiomegaly, myocardial ischemia, murmurs, and abnormal ECG; patients with SCD have lower BP than the normal population; normal BP values for SCD should be used for diagnosis of hypertension ("relative" hypertension); heart failure usually is related to fluid overload
Dermatologic	Painful leg ulcers; failure to heal occurs in 50% of patients; recurrences are common
Genitourinary	Renal papillary necrosis, hematuria, hyposthenuria, proteinuria, nephrotic syndrome, tubular dysfunction, chronic renal failure, impotence, priapism
Growth and development	Delay in growth (weight and height) and sexual development; decreased fertility; increased complications during pregnancy; depression may be more prevalent than in general population, especially in patients with unstable disease
Hepatic and biliary	Cholelithiasis, biliary sludge, acute and chronic cholecystitis, and cholestasis (can be progressive and life-threatening)
Neurologic	"Silent" brain lesions on MRI are associated with poor cognitive and fine motor functions; pseudotumor cerebri (rare)
Ocular	Retinal or vitreous hemorrhage, retinal detachment, transient or permanent visual loss; central retinal vein occlusion
Pulmonary	Pulmonary fibrosis, pulmonary hypertension, cor pulmonale
Renal	Hematuria, hyposthenuria (inability to concentrate urine maximally), tubular dysfunction, enuresis during early childhood, acute renal failure can also occur
Skeletal	Aseptic necrosis of ball-and-socket joints (shoulder and hip); prostheses may be needed due to permanent damage; bone marrow hyperplasia resulting in growth disturbances of maxilla and vertebrae
Spleen	Asplenia (autosplenectomy or surgical splenectomy)

LO 7

Starting with birth, SCD patients should have regularly scheduled health assessments and interventions when necessary. Obtain a urine analysis, complete blood count, liver function tests, ferritin or serum iron level and total iron-binding capacity, blood urea nitrogen (BUN), and creatinine on at least a yearly basis and more often for children younger than 5 years of age to monitor for complications. All SCD patients should have regular screening of their hearing and vision.

All patients and parents of children with SCD should have a plan for what to do in the event of symptoms of infection or pain. Obtain a medication history when patients are admitted to the hospital. Assess adherence with prophylactic penicillin and childhood immunization schedules in all pediatric SCD patients.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.
- Review available laboratory tests.

Assess the Information:

- Based on physical examination and review of systems, determine whether the patient is experiencing any signs or symptoms of an acute or chronic SCD complication (Tables 68–1 and 68–5).
- Assess the safety, efficacy, and patient adherence of current pharmacotherapy.
- Identify any significant adverse drug effects or interactions.
- Assess the patient's medication history. Does the patient take any medications routinely for SCD? Which analgesics have been helpful to the patient in the past? Are they taking appropriate doses to achieve the desired effect? If not, why?
- Determine if the patient is up to date on their immunizations. Have they received their annual influenza vaccine? Are they missing any vaccines?

Develop a Care Plan:

- Choose medications and doses that are optimal for the patient.
- Select lifestyle modifications that are likely to be effective and safe for the patient.
- Determine whether drug doses are optimal.
- If the patient is having an acute complication of SCD, arrange for referral and/or admission to the hospital.

Implement the Care Plan:

- Educate the patient about changes in drug therapy, medication administration, potential new adverse effects, and how to manage and report adverse effects that occur.

(*Continued*)

Patient Care Process (*Continued*)

- Address any patient concerns about SCD and its management.
- Discuss the importance of medication adherence and lifestyle modifications to prevent complications of SCD.
- Determine if the patient has prescription coverage or whether recommended agents are included on the institution's formulary.
- Arrange for vaccination if the patient is not up to date with recommendations.
- Review medication history and physical examination findings, laboratory tests, and results of other diagnostic tests.
- Assess for adverse effects from medications that the patient is taking.
- Stress the importance of adherence with the therapeutic regimen. Adjust therapeutic regimens as needed based on patient response and adverse effects.

Follow-up: Montor and Evaluate:

- Follow-up at monthly intervals or more frequently to assess effectiveness and safety of therapy, to avoid complications from SCD and to improve quality of life for the patient.

Abbreviations Introduced in This Chapter

ACS	Acute chest syndrome
CNS	Central nervous system
HbA	Normal adult hemoglobin
HbAS	One normal and one sickle hemoglobin gene
HbC	Hemoglobin C
HbF	Fetal hemoglobin
HbS	Sickle hemoglobin
HbSβ^0-thalassemia	One sickle hemoglobin and one β^0-thalassemia gene
HbSβ$^+$-thalassemia	One sickle hemoglobin and one β$^+$-thalassemia gene
HbSC	One sickle hemoglobin and one hemoglobin C gene
HbSS	Homozygous sickle hemoglobin
Hgb	Hemoglobin
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem-cell transplantation
ISC	Irreversibly sickled cell
MCV	Mean corpuscular volume
NSAID	Nonsteroidal anti-inflammatory drug
PCA	Patient-controlled analgesia
PCV 13	13-Valent pneumococcal conjugate vaccine
PPV 23	23-Valent pneumococcal polysaccharide vaccine
SCA	Sickle cell anemia
SCD	Sickle cell disease
SCT	Sickle cell trait
STOP	Stroke Prevention Trial in Sickle Cell Anemia
VOC	Vasoocclusive crisis
WBC	White blood cell

REFERENCES

1. Stuart MJ, Nagel RL. Sickle-cell disease. Lancet. 2004; 364(9442): 1343–1360. Review.
2. Santosh LL, Molokie R, Nouraie M, et al. Differences in the clinical and genotypic presentation of sickle cell disease around the world. Paediatr Respir Rev. 2014;15(1):4–12.
3. Sickle Cell Disease. Centers for Disease Control and Prevention. Available from: www.cdc.gov/ncbddd/sicklecell/data.html. Accessed September 2, 2017.
4. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033–1058.
5. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010;376:2018–2031.
6. American Academy of Pediatrics Policy Statement. Recommended Childhood and Adolescent Immunization Schedule—United States, 2017. Pediatrics. 2017;139;e20164007.
7. Recommended Immunization Schedule for Adults Aged 19 Years of Older, United States 2017. Centers for Disease Control and Prevention Available from: https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf. Accessed September 2, 2017.
8. Nuorti JP, Whitney CG. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010;59:1–18.
9. Battersby AJ, Knox-Macaulay HHM, Carrol ED. Susceptibility to invasive bacterial infections in children with sickle cell disease. Pediatr Blood Cancer. 2010;55:401–406.
10. Hirst C, Owusu-Ofori S. Cochrane Review: prophylactic antibiotics for preventing pneumococcal infections in children with sickle cell disease. Evidence-Based Child Health. 2007;2:993–1009.
11. Kennedy TS, Fung EB, Kawchak DA, et al. Red blood cell folate and serum B12 status in children with sickle cell disease. J Pediatr Hematol Oncol. 2001;23:165–169.
12. Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health consensus development conference statement: hydroxyurea treatment for sickle cell disease. Ann Intern Med. 2008;148:932–938.
13. Steinberg MH, Bartin F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia. Risks and benefits up to 9 years of treatment. JAMA. 2003;289: 1645–1651.
14. Kinney TR, Helms RW, O'Branski EE, et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. Blood. 1999;94(5):1550–1554.
15. Strouse JJ, Lanzkron S, Beach MC, et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. Pediatrics. 2008;122:1332–1342.
16. Hankins JS, Ware RE, Rogers ZR, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. Blood. 2005;106:2269–2275.

17. Evidence-based management. of sickle cell disease: expert panel report, 2014. National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health; 2014. Available from: http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines. Accessed September 2, 2017.
18. Lexi-Comp. Hydroxyurea monograph. Lexi-Comp Online,™ Lexi-Drugs Online.™ Hudson, OH: Lexi-Comp, Inc; September 2, 2017.
19. Lexi-Comp. Deferoxamine monograph. Lexi-Comp Online,™ Lexi-Drugs Online.™ Hudson, OH: Lexi-Comp, Inc; September 2, 2017.
20. Lexi-Comp. Deferasirox monograph. Lexi-Comp Online,™ Lexi-Drugs Online.™ Hudson, OH: Lexi-Comp, Inc; September 2, 2017.
21. Lexi-Comp. Decitabine monograph. Lexi-Comp Online,™ Lexi-Drugs Online,™ Hudson, OH: Lexi-Comp, Inc, September 2, 2017.
22. Lexi-Comp. Deferiprone monograph. Lexi-Comp Online,™ Lexi-Drugs Online, Hudson, OH: Lexi-Comp, Inc; September 2, 2017.
23. Lexi-Comp. Folic acid monograph. Lexi-Comp Online,™ Lexi-Drugs Online,™ Hudson, OH: Lexi-Comp, Inc; September 2, 2017.
24. Aronoff GR, Bennett WM, Berns JS, et al., eds. Drug Prescribing in Renal Failure, 5th ed. Philadelphia, PA: American College of Physicians; 2007.
25. Hankins J, Aygun B. Pharmacotherapy in sickle-cell disease—state of the art and future prospects. Br J Haematol. 2009;145:296–308.
26. Endari [package insert]. Torrance, CA: Emmaus Medical, Inc; July 2017.
27. Oral L-glutamine powder for the treatment of sickle cell disease, NDA 208587. Oncologic Drugs Advisory Committee Briefing Document. 24 May 2017. Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM559736.pdf. Accessed September 2, 2017.
28. Brittenham GM. Iron-chelating therapy for transfusional iron overload. N Engl J Med. 2011;364:146–156.
29. Voskaridou E, Douskou M, Terpos E, et al. Deferiprone as an oral iron chelator in sickle cell disease. Ann Hematol. 2005;84:434–440.
30. Tanner MA, Galanello R, Dessi C, et al. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. Circulation. 2007;115:1876–1884.
31. Walters MC, De Castro LM, Sullivan KM, et al. Indications and results of HLA-identical sibling hematopoietic cell transplantation for sickle cell disease. Biol Blood Marrow Transplant. 2016;22:207–211.
32. Hsieh MM, Fitzhugh CD, Weitzel P, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle phenotype. JAMA. 2014;312(1):48–56.
33. Adams RJ, Brambilla DJ, Granger S, et al. Stroke and conversion to high risk in children screened with transcranial Doppler ultrasound during the STOP study. Blood. 2004;103:3689–3694.
34. Lee MT, Piomelli S, Granger S, et al. Stroke Prevention Trial in Sickle Cell Anemia (STOP): extended follow-up and final results. Blood. 2006;108:847–852.
35. Kwiatkowski JL, Granger S, Brambilla DJ, Brown RC, Miller ST, Adams RJ. Elevated blood flow velocity in the anterior cerebral artery and stroke risk in sickle cell disease; extended analysis from the STOP trial. Br J Haematol. 2006;134:333–339.
36. Caboot JB, Allen JL. Pulmonary complications of sickle cell disease in children. Curr Opin Pediatr. 2008;20:279–287.
37. Maples BL, Hagemann TM. Treatment of priapism in pediatric patients with sickle cell disease. Am J Health Syst Pharm. 2004;61:355–363.
38. Fuh BR, Perkin RM. Sickle cell disease emergencies in children. Ped Emer Med Report. 2009;14:145–155.
39. Saad STO, Lajolo C, Gilli S, et al. Follow-up of sickle cell disease patients with priapism treated by hydroxyurea. Am J Hematol. 2004;77:45–49.
40. Owusu-Ofori S, Riddington C. Splenectomy versus conservative management for acute sequestration crises in people with sickle cell disease. Cochrane Database Syst Rev. 2002;(4):CD003425.
41. Changes for acetaminophen-containing prescription products. Pharm Lett Prescribe Lett. 2011;27(2):270203.
42. Field JJ, Knight-Perry JE, Debaun MR. Acute pain in children and adults with sickle cell disease: management in the absence of evidence-based guidelines. Curr Opin Hematol. 2009;16:173–178.
43. Jerrell JM, Tripathi A, Stallworth JR. Pain management in children and adolescents with sickle cell disease. Am J Hematol. 2011;86:82–84.
44. Frei-Jones MJ, Baxter AL, Rogers ZR, Buchanan GR. Vaso-occlusive episodes in older children with sickle cell disease: emergency department management and pain assessment. J Pediatr. 2008;152:281–285.
45. Mousa SA, Al Momen A, Al Sayegh F, et al. Management of painful vaso-occlusive crisis of sickle-cell anemia: consensus opinion. Clin Appl Thromb Hemost. 2010;16:365–376.
46. Miller JM, Hagemann TM. Use of pure opioid antagonists for management of opioid-induced pruritus. Am J Health-Syst Pharm. 2011;68:1419–1425.

69 Antimicrobial Regimen Selection

Catherine M. Oliphant

LEARNING OBJECTIVES

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

1. Recognize that antimicrobial resistance is an inevitable consequence of antimicrobial therapy.
2. Describe how antimicrobials differ from other drug classes in terms of their effects on individual patients as well as on society as a whole.
3. Identify two guiding principles to consider when treating patients with antimicrobials, and apply these principles in patient care.
4. Differentiate between microbial colonization and infection based on patient history, physical examination, and laboratory and culture results.
5. Evaluate and apply at least six major drug-specific considerations when selecting antimicrobial therapy.
6. Evaluate and apply at least seven major patient-specific considerations when selecting antimicrobial therapy.
7. Select empirical antimicrobial therapy based on spectrum-of-activity considerations that provide a measured response proportional to the severity of illness. Provide a rationale for why a measured response in antimicrobial selection is appropriate.
8. Identify and apply five major principles of patient education and monitoring response to antimicrobial therapy.
9. Discuss two common causes of patients failing to improve while on antimicrobials, and recognize other less common but potential reasons for antimicrobial failure.
10. Define antimicrobial stewardship and describe the purpose of such a program.

INTRODUCTION

The CDC's Antibiotic Resistance Threats in the United States 2013 estimates more than 2 million patients per year are infected with resistant pathogens resulting in approximately 23,000 deaths.[1] For several decades, infectious disease–related mortality in the United States has increased, in part owing to increases in antimicrobial resistance. The discovery of virtually every new class of antimicrobials has occurred in response to the development of bacterial resistance and loss of clinical effectiveness of existing antimicrobials. KEY CONCEPT An inevitable consequence of exposing microbes to antimicrobials is that some organisms will develop resistance to the antimicrobial. Today, there are many antimicrobial classes and antimicrobials available for clinical use. However, in many cases, differences in mechanisms of action between antimicrobials are minor, and the microbiologic properties of the agents are similar. KEY CONCEPT Antimicrobials are different from other classes of pharmaceuticals because they exert their action on bacteria infecting the host as opposed to acting directly on the host. Because antimicrobial use in one patient affects not only that patient but also other patients if they become infected with resistant bacteria, correct selection, use, and monitoring of clinical response are paramount.

KEY CONCEPT There are two guiding principles to consider when treating patients with antimicrobials: (a) make the correct diagnosis and (b) do no harm! Patients with infections frequently present with signs and symptoms that are nonspecific and may be confused with other noninfectious diseases. Not only is it important to determine whether a disease process is of infectious origin, but it is also important to determine the specific causative pathogen of the infection. Antimicrobials vary in their spectrum of activity, the ability to inhibit or kill different species of bacteria. Antimicrobials that kill many different species of bacteria are called *broad-spectrum antimicrobials*, whereas antimicrobials that kill only a few species of bacteria are called *narrow-spectrum antimicrobials*. One might argue that treating everybody with broad-spectrum antimicrobials will increase the likelihood that a patient will get better even without knowing the bacteria causing infection. However, counter to this argument is the principle of "Do no harm!" Broad antimicrobial coverage does increase the likelihood of empirically killing a causative pathogen; unfortunately, the development of secondary infections can be caused by selection of antimicrobial-resistant nontargeted pathogens. In addition, adverse events are thought to complicate up to 10% of all antimicrobial therapy, and for select agents, the adverse-event rates are similar to high-risk medications such as warfarin, digoxin, or insulin.[2] Therefore, the overall goal of antimicrobial therapy should be to cure the patient's infection; limit harm by minimizing patient risk for adverse effects, including secondary infections; and limit societal risk from antimicrobial-resistant bacteria.

EPIDEMIOLOGY AND ETIOLOGY

Infectious disease–related illnesses, particularly respiratory tract infections, are among the most common reasons patients seek medical care.[3] Antimicrobial prescribing has been associated with inappropriate use of antimicrobial agents. Recent trends in prescribing suggest a modest reduction in antimicrobial use for these infections, suggesting an increased recognition of the negative consequences of antimicrobial use.[4,5] However, it is estimated that at least 30% of outpatient antibiotic prescriptions are unnecessary with the majority prescribed for acute respiratory tract infections.[6] Up to one-half of all patients receive at least one antimicrobial during hospitalization with a trend toward increased use of broad-spectrum antimicrobials.[7] In 2016, the CDC reported that there were reductions in central line–associated bloodstream infections, surgical site infections, and hospital-onset MRSA bloodstream infection.[8] Nosocomial infections tend to be associated with antimicrobial-resistant strains of bacteria. However, there has been a shift in the etiology of some community-acquired infections. Increasingly, infections caused by antimicrobial-resistant pathogens, traditionally nosocomial in origin, are being identified in ambulatory care settings. Reasons for this change include an aging population, improvement in the management of chronic comorbid conditions including immunosuppressive conditions, and increases in outpatient management of more debilitated patients. The majority of infections caused by antimicrobial-resistant pathogens in the ambulatory care setting occur in patients who have had recent exposure to the health care system. The converging bacterial etiologies and increasing resistance in all health care environments emphasize the need to "make the diagnosis."

PATHOPHYSIOLOGY

Microbiome and Endogenous Infection

Many areas of the human body are colonized with microbes—this is known as the microbiome. Infections often arise from one's own normal flora (called an *endogenous infection*). Endogenous infection may occur when there are alterations in the normal flora (eg, recent antimicrobial use may allow for overgrowth of other normal flora) or disruption of host defenses (eg, a break or entry in the skin). Knowing what organisms reside where can help guide empirical antimicrobial therapy (Figure 69–1 describes common human pathogens). In addition, it is beneficial to know what anatomic sites are normally sterile. These include the cerebrospinal fluid, blood, and urine.

Determining Colonization versus Infection

LO 4

Infection refers to the presence of bacteria that are causing disease (eg, organisms found in normally sterile anatomic sites or in nonsterile sites with signs/symptoms of infection). *Colonization* refers to the presence of bacteria that are not causing disease. KEY CONCEPT Only bacteria that cause disease should be targeted with antimicrobial therapy, and non–disease-producing colonizing flora should be left intact. It is important to differentiate infection from colonization because antimicrobial therapy targeting colonization is inappropriate and may lead to the emergence of resistant bacteria.

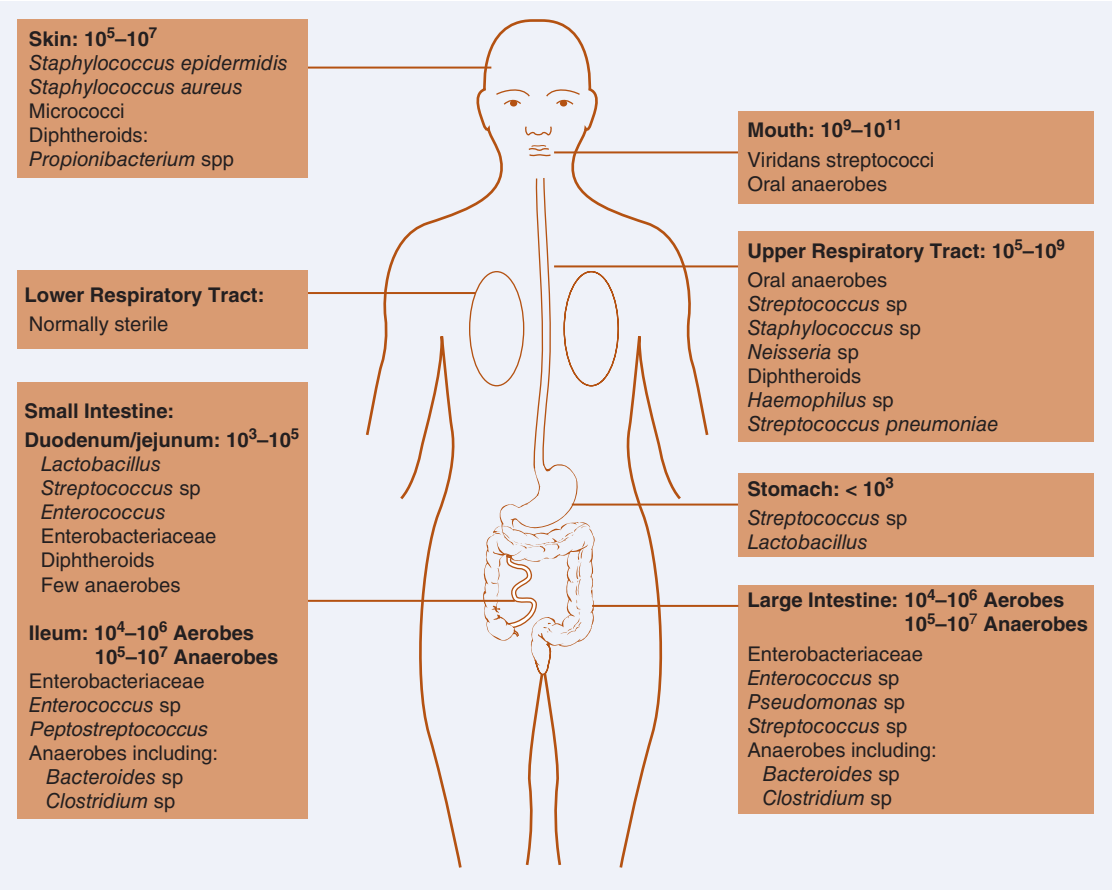

FIGURE 69–1. Normal flora and concentrations of bacteria (organisms per milliliter).

Exogenously Acquired Bacterial Infections

Infections acquired from an external source are referred to as *exogenous infections*. These infections may occur as a result of human-to-human transmission, contact with exogenous bacterial populations in the environment, and animal contact. Resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp (VRE) may colonize hospitalized patients or patients who access the health care system frequently. It is important to know which patients have acquired these organisms because patients generally become colonized prior to developing infection, and colonized patients should be placed in isolation to minimize transmission.

Contrasting Bacterial Virulence and Resistance

Virulence refers to the pathogenicity or disease severity produced by an organism. Bacteria may produce toxins or possess characteristics that contribute to their pathogenicity. Some virulence factors allow the organism to avoid the host immune response and cause significant disease. Virulence and resistance are different microbial characteristics. For example, *Streptococcus pyogenes*, a common cause of skin infections, produces toxins that can cause severe disease, yet it is very susceptible to penicillin. *Enterococcus faecium* is a highly resistant organism but is frequently a colonizing flora that causes disease primarily in the immunocompromised.

CLINICAL PRESENTATION AND DIAGNOSIS

Physical Examination

Findings on physical examination, along with the clinical presentation, can help identify the anatomic location of the infection. Once the anatomic site is identified, the most probable pathogens associated with disease can be determined based on likely endogenous or exogenous flora.

Fever often accompanies infection and is defined as a rise in body temperature above the normal 37°C (98.6°F). Oral and axillary temperatures may underestimate core temperature by at least 0.6°C (1°F), whereas rectal temperatures best approximate core temperatures. Fever is a host response to bacterial toxins. However, bacterial infections are not the sole cause of fever. Fever also may be caused by other infections (eg, fungal or viral), medications (eg, penicillins, cephalosporins, salicylates, and phenytoin), trauma, or other medical conditions (eg, autoimmune disease, malignancy, pulmonary embolism, and hyperthyroidism). Some patients with infections may present with hypothermia (eg, patients with overwhelming infection). Elderly patients may be afebrile, as may those with localized infections (eg, urinary tract infection [UTI]).[9] For others, fever may be the only indication of infection. Neutropenic patients may not have the ability to mount normal immune responses to infection (eg, infiltrate on chest x-ray, pyuria on urinalysis, or erythema or induration around catheter site), and the only finding may be fever.

Imaging Studies

Imaging studies also may help to identify anatomic localization of the infection. These studies usually are performed in conjunction with other tests to establish or rule out the presence of an infection. Radiographs are performed commonly to establish the diagnosis of pneumonia, as well as to determine the severity of disease. Computed tomography (CT) or magnetic resonance imaging (MRI) may also be obtained.

Clinical Presentation

- Review of symptoms consistent with an infectious etiology.
- Signs and symptoms may be nonspecific (eg, fever) or specific.
- Specific signs and symptoms are beyond the scope of this chapter (see disease state–specific chapters for these findings).

Patient History

- History of present illness (HPI)
- Comorbidities
- Current medications
- Allergies
- Previous antibiotic exposure (may provide clues regarding colonization or infection with new specific pathogens or pathogens that may be resistant to certain antimicrobials)
- Previous hospitalization or health care utilization (also a key determinant in selecting therapy because the patient may be at risk for specific pathogens and/or resistant pathogens)
- Travel history
- Social history
- Pet/animal exposure
- Occupational exposure
- Environmental exposure

Physical Findings

- Findings consistent with an infectious etiology
- Vital signs
- Body system abnormalities (eg, rales, altered mental status, localized inflammation, erythema, warmth, edema, pain, and pus)

Diagnostic Imaging

- Radiographs (x-rays)
- CT scans
- MRI
- Labeled leukocyte scans

Nonmicrobiologic Laboratory Studies

- White blood cell count (WBC) with differential
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein
- Procalcitonin

Microbiologic Studies

- Gram stain
- Culture and susceptibility testing

Nonmicrobiologic Laboratory Studies

Nonmicrobiological laboratory tests include the white blood cell count (WBC) and differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin levels. In most cases, the WBC count is elevated in response to infection, but it may be decreased owing to overwhelming or long-standing infection. The differential is the percentage of each type of WBC (Table 69–1). In response to physiologic stress, neutrophils leave the bloodstream and enter the tissue to "fight" against the offending pathogens (ie, leukocytosis). It is important to recognize that leukocytosis is nonspecific for infection and may temporarily occur in response to noninfectious conditions such as acute myocardial infarction. During an infection, immature neutrophils (eg, bands) are released at an increased rate to help fight infection, leading to what is known as a "bandemia" or "left shift". Therefore, a WBC count differential is key to determining whether an infection is present. Some patients may present with a normal total WBC with a left shift (eg, the elderly). ESR and CRP are nonspecific markers of inflammation that increase as a result of the acute-phase reactant response, which is a response to inflammatory stimuli such as infection or tissue injury. These tests may be used as markers of infectious disease response because they are elevated when the disease is acutely active and usually fall in response to successful treatment. Clinicians may use these tests to monitor a patient's response to therapy in osteomyelitis and infective endocarditis. These tests should not be used to diagnose infection because they may be elevated in noninfectious inflammatory conditions. In contrast, procalcitonin, a prohormone of calcitonin, is rapidly produced in response to bacterial infection. Procalcitonin serum levels in conjunction with clinical findings are increasingly being utilized to assess both the need to initiate antibiotic therapy as well as determine when antibiotic therapy may be safely discontinued.[10,11]

Table 69–1

WBC and Differential

Type of Cell	Normal Value % (or Fraction)	Function	Abnormalities
Neutrophil	Segs 40–60 (0.40–0.60) Bands 3–5 (0.03–0.05)	Phagocytic	Leukocytosis • Bacterial infections • Fungal infections • Physiologic stress • Tissue injury (eg, myocardial Infarction) • Medications (eg, corticosteroids) Leukopenia • Long-standing infection • Cancer • Medications (eg, chemotherapy)
Lymphocyte	20–40 (0.20–0.40)	T cells (cell-mediated immunity) B cells (humoral antibody response)	Lymphocytosis • Viral infections (eg, mononucleosis) • Tuberculosis • Fungal infections Lymphopenia • HIV
Monocyte	2–8 (0.02–0.08)	Phagocytic precursor to macrophage	Monocytosis • Tuberculosis • Protozoal infections • Leukemia
Eosinophil	1–4 (0.01–0.04)	Antigen-antibody reactions	Eosinophilia • Hypersensitivity reactions, including medications • Parasitic infections
Basophil	< 1 (0.01)		Hypersensitivity reactions

Patient Encounter 1

HPI: SC is a 76-year-old man who has been in the intensive care unit (ICU) for 6 days s/p myocardial infarction. He has been unresponsive since his MI and has required mechanical ventilation for 6 days. On day 6, SC becomes hypotensive, tachycardic, tachypneic, and febrile. His oxygen requirements have increased significantly overnight. SC also has increased secretions coming from his endotracheal tube.

Allergies: Sulfa

Meds:

Metoprolol 2.5 mg IV Q6hours

Insulin glargine 20 u QPM

Insulin lispro as needed

Aspirin 81 mg daily

Enoxaparin 40 mg SQ daily

Pantoprazole 40 mg IV daily

Enalaprilat 2.5 mg IV Q6hours

Ipratropium Q6hours

Albuterol Q6hours and prn

What information in the history supports an infectious etiology?

Is this patient at risk for resistant pathogens? Why?

Microbiologic Studies

Microbiologic studies that allow for direct examination of a specimen (eg, sputum, blood, or urine) may aid in a presumptive diagnosis and give an indication of the characteristics of the infecting organism. Generally, microbial cultures are obtained with a Gram stain of the cultured material.

A Gram stain of collected specimens can give rapid information that can be applied immediately to patient care. A Gram stain may identify whether bacteria are present and determine bacterial morphologic characteristics (eg, gram-positive or gram-negative and shape—cocci, bacilli). Certain specimens do not stain well or at all and must be identified by alternative staining techniques (*Mycoplasma* spp., *Legionella* spp., *Mycobacterium* spp.). Figure 69–2 identifies bacterial pathogens classified by Gram stain and morphologic characteristics. The presence of WBCs on a Gram stain

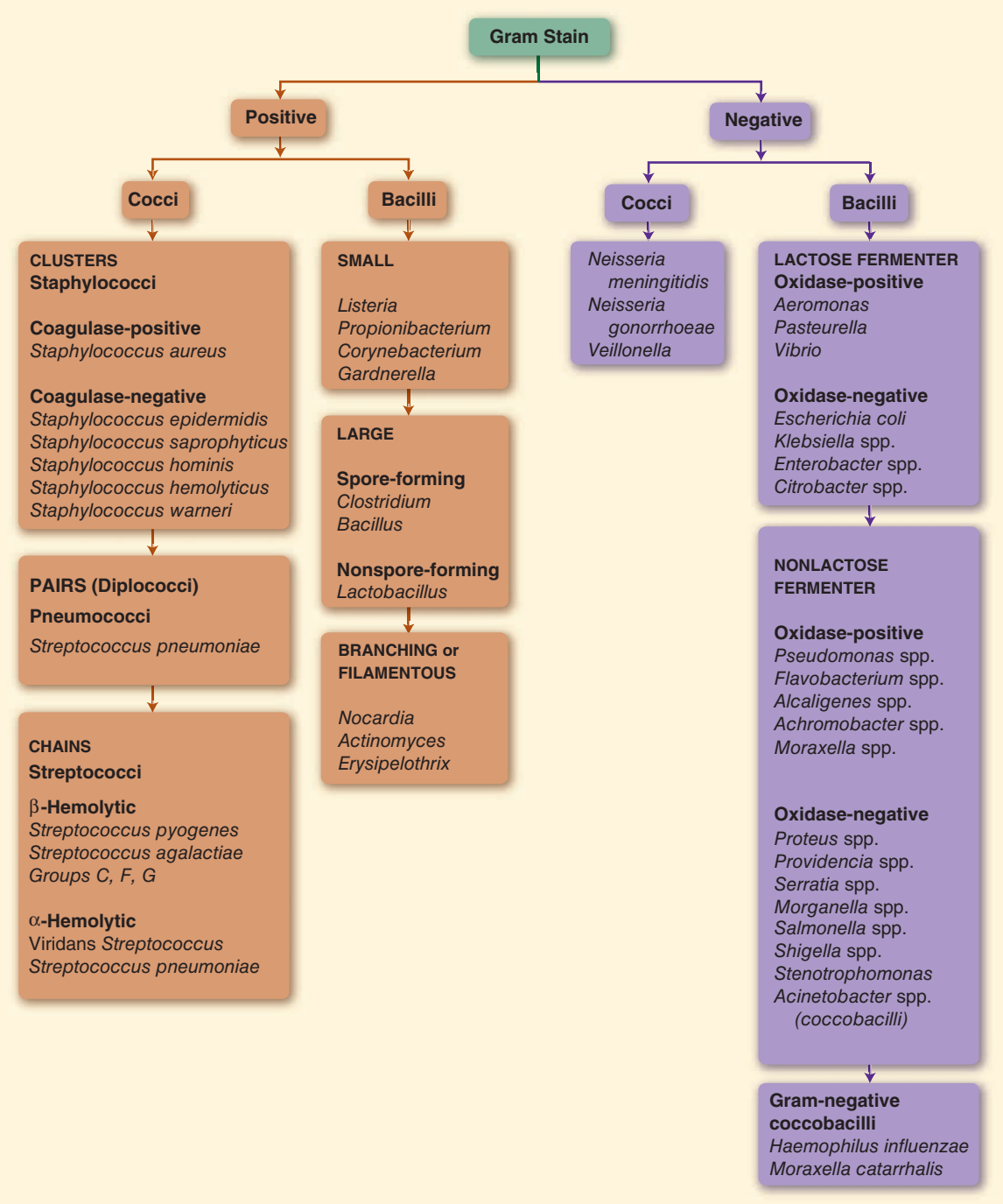

FIGURE 69–2. Important bacterial pathogens classified according to Gram stain and morphologic characteristics. (From Rybak MJ, Aeschlimann JR. Laboratory tests to direct antimicrobial pharmacotherapy. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014.)

indicates inflammation and suggests that the identified bacteria are pathogenic. The Gram stain may be useful in evaluating a sputum specimen's adequacy (eg, the presence of epithelial cells on sputum Gram stain suggests that the specimen is either poorly collected or contaminated). A poor specimen can give misleading information regarding the underlying pathogen and may result in inappropriate antimicrobial use.

Culture and susceptibility testing provides additional information to the clinician to select appropriate therapy. Specimens are placed in or on culture media that provide proper growth conditions. Once the bacteria grow on culture media, they can be identified through biochemical tests. When a pathogen is identified, susceptibility tests can be performed to various antimicrobial agents. The minimum inhibitory concentration (MIC) is a standard susceptibility test. The MIC is the lowest concentration of antimicrobial that inhibits visible bacterial growth after approximately 24 hours (Figure 69–3). **Breakpoint** and MIC values determine whether the organism is susceptible (S), intermediate (I), or resistant (R) to an antimicrobial. If the MIC is below the breakpoint, the organism is considered to be

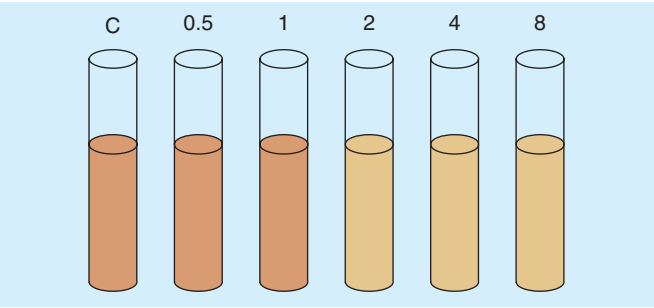

FIGURE 69–3. Macrotube minimal inhibitory concentration (MIC) determination. The growth control (C), 0.5 mg/L, and 1 mg/L tubes are visibly turgid, indicating bacterial growth. The MIC is read as the first clear test tube (2 mg/L). (From Rybak MJ, Aeschlimann JR. Laboratory tests to direct antimicrobial pharmacotherapy. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014.)

susceptible to that agent. If the MIC is above the breakpoint, the organism is said to be resistant. Reported culture and susceptibility results may not provide MIC values but generally report the S, I, and R results.

KEY CONCEPT In general, bacterial cultures should be obtained prior to initiating antimicrobial therapy in patients with a systemic inflammatory response, risk factors for antimicrobial resistance, or infections where diagnosis or antimicrobial susceptibility is uncertain. The decision to collect a specimen for culture depends on the physical and diagnostic findings, and whether or not the pathogens are readily predictable. Culture and susceptibility testing usually is not warranted in a young, otherwise healthy woman who presents with signs and symptoms consistent with a UTI because the primary pathogen, *Escherichia coli*, is readily predictable. Cultures and susceptibility testing are routine for sterile-site specimens (eg, blood and spinal fluid), as well as for material presumed to be infected (eg, material obtained from joints and abscesses). Cultures need to be interpreted with caution. Poor specimen collection technique and processing speed can result in misleading information and inappropriate use of antimicrobials.

TREATMENT

General Approach to Treatment, Including Nonantimicrobial Treatment

While antimicrobial therapy selection may be a major consideration in treating infectious diseases, it may not be the only therapeutic intervention. Other important therapies may include hydration, ventilatory support, and supportive medications. In addition, antimicrobials are unlikely to be effective if the source that leads to the infection is not controlled. **Source control** refers to this process and may involve removal of prosthetic materials such as catheters and infected tissue or drainage of an abscess. Source control considerations should be a fundamental component of any infectious diseases treatment. It is also important to recognize that there may be many different antimicrobial regimens that may cure the patient. While the following therapy sections provide factors to consider when selecting antimicrobial regimens, excellent and more in-depth resources for selecting antimicrobial regimens for a variety of infectious diseases are the Infectious Diseases Society of America Guidelines.[12]

Antimicrobial Considerations in Selecting Therapy

LOS KEY CONCEPT Drug-specific considerations in antimicrobial selection include spectrum of activity, effects on nontargeted microbial flora, appropriate dose, pharmacokinetic and pharmacodynamic properties, adverse-effect and drug-interaction profile, and cost (Table 69–2).

▶ *Spectrum of Activity and Effects on Nontargeted Flora*

Most initial antimicrobial therapy is empirical because cultures have not had sufficient time for identification of a pathogen. KEY CONCEPT Empirical therapy should be based on patient- and antimicrobial-specific factors such as the anatomic location of the infection, the likely pathogens associated with the presentation, the potential for adverse effects in a given patient, and the antimicrobial spectrum of activity. Prompt initiation of appropriate therapy is paramount in hospitalized patients who are critically ill. Patients who receive appropriate initial antimicrobial therapy survive at twice the rate of patients who receive inadequate therapy.[13] Empirical selection of antimicrobial spectrum of activity should be based on the pathogens most likely causing the infection as well as the severity of the illness. Generally, acutely ill patients require broader-spectrum antimicrobial coverage, whereas less ill patients may

Patient Encounter 2: Review of Symptoms, Physical Examination, and Laboratory Data

ROS: Elderly gentleman who is intubated and unable to answer questions.

PE:

- VS: BP 90/50 mm Hg, P 120 beats/min, RR 30 breaths/min, T 38.9°C, FiO_2 0.7 (increased from 0.4), PEEP 10 cm H_2O, Ht 5′10″ (178 cm), Wt 78 kg
- Chest: Rhonchi with decreased breath sounds
- CV: Tachycardic with regular rate and rhythm

Labs:

- WBC 18.5 × 10^3/mm^3 (16.5 × 10^9/L), segs 76% (0.76), bands 17% (0.17), lymphs 7% (0.07)
- SCr 1.8 mg/dL (159 µmol/L)
- Glucose 242 mg/dL (13.4 mmol/L)
- Procalcitonin 1.0 µg/L
- Sputum gram-stain: < 10 epis/lpf, > 25 WBCs/lpf, gram-negative bacilli
- Sputum Culture: Pending
- Blood Cultures: Pending

Chest radiography: bilateral lower lobe infiltrates.

What findings on physical examination are suggestive of an infectious process?

What laboratory findings and/or diagnostic studies have been performed to help establish the presence of an infection?

Are the findings of these laboratory and diagnostic studies suggestive of an infection?

What is your working diagnosis based on this patient encounter?

Table 69–2

Considerations for Selecting Antimicrobial Regimens

Drug Specific	Patient Specific
Spectrum of activity and effects on nontargeted flora	Anatomic location of infection
Dosing	Antimicrobial history
Pharmacokinetic properties	Drug allergy history
Pharmacodynamic properties	Renal and hepatic function
Adverse-effect potential	Concomitant medications
Drug-interaction potential	Pregnancy or lactation
Cost	Compliance potential

be managed initially with narrow-spectrum therapy. Either approach should ensure that the selected antimicrobial therapy covers the most likely pathogens causing the infection. While a detailed description of antimicrobial pathogen-specific spectrum of activity is beyond the scope of this chapter, this information can be obtained readily from a number of sources.[14,15]

Collateral damage is defined as the development of resistance occurring in a patient's nontargeted flora that can cause secondary infections. *Clostridium difficile* infection (CDI) is an example of a disease that occurs secondary to collateral damage. Antibiotics, especially high-risk agents such as fluoroquinolones, can increase the risk of CDI by suppressing normal intestinal flora, resulting in overgrowth of the nonsusceptible *C. difficile* bacteria.[16] If several different antimicrobials possess activity against a targeted pathogen, the antimicrobial that is least likely to be associated with collateral damage may be preferred.

▶ *Single versus Combination Therapy*

A common debate involves the need for empiric coverage with two antimicrobials for serious infections. Proponents state that double coverage may be synergistic, prevent the emergence of resistance, and improve outcome by ensuring activity against the infecting pathogen. However, there are few clinical examples in the literature to support these assertions. Examples where double coverage is considered superior are limited to infections associated with large bacterial loads and in species that are known to readily develop resistance such as active tuberculosis or enterococcal endocarditis.[17,18] Double antimicrobial coverage with two agents of similar spectra of activity may be beneficial for selected infections associated with high bacterial loads or for initial empirical coverage of critically ill patients in whom antimicrobial-resistant organisms are suspected. In these cases, monotherapy usually is satisfactory once antimicrobial susceptibilities are established.[19]

▶ *Antimicrobial Dose*

Clinicians should be aware that antimicrobial dosage regimens may be different depending on the infectious process. For example, ciprofloxacin, a fluoroquinolone, has various dosage regimens based on site of infection. The dosing for uncomplicated UTIs is 250 mg twice daily for 3 days. For pyelonephritis, the dose is 500 mg twice daily for 7 to 14 days. Severe complicated pneumonia may require a dosage regimen of 750 mg twice daily for 7 to 14 days. Clinicians are encouraged to use dosing regimens designed for treatment of the diagnosed infection because they have demonstrated proven efficacy and are most likely to minimize harm.

▶ *Pharmacokinetic Properties*

Pharmacokinetic properties of an antimicrobial may be important in antimicrobial regimens. Pharmacokinetics refers to a mathematical method of describing a patient's drug exposure in vivo in terms of absorption, distribution, metabolism, and elimination. Bioavailability refers to the amount of antimicrobial that is absorbed orally relative to an equivalent IV dose administered. Drug-related factors that may affect oral bioavailability include the formulation of the antimicrobial, dosage form, and stability of the drug in the gastrointestinal (GI) tract. Patients with systemic signs of infection such as hypotension should receive intravenous antimicrobials to ensure drug delivery as absorption is affected by GI blood flow. In cases where patients have a functioning GI tract and are not hypotensive, antimicrobials with almost complete bioavailability (> 80%) such as the fluoroquinolones, fluconazole, and linezolid may be given orally. With antimicrobials with modest bioavailability (eg, many β-lactams), the decision to choose an oral product will depend more on the severity of the illness and the anatomic location of the infection. In sequestered infections, where higher systemic concentrations of antimicrobial may be necessary to reach the infected source (eg, meningitis) or for antimicrobials with poor bioavailability, IV formulations should be used.

Some antimicrobials may be bound to proteins in serum. Only unbound drug is biologically active and distributes freely between tissues. Protein binding is clinically relevant in highly protein-bound antimicrobials (> 50%) as the agents may not be able to penetrate sequestered compartments, such as cerebral spinal fluid, resulting in insufficient concentrations to inhibit bacteria. In addition, some drugs may not achieve sufficient concentrations in specific compartments based on distribution characteristics. For example, *Legionella pneumophila*, an organism that causes severe pneumonia, is known to survive and reside inside pulmonary macrophages. Treatment with an antibiotic that inhibits bacterial cell wall synthesis, such as a cephalosporin, will be ineffective because it only distributes into extracellular host tissues. However, macrolide, tetracycline, or fluoroquinolone antimicrobials, which concentrate in human pulmonary macrophages, are highly effective against this organism.

Many antimicrobials undergo some degree of metabolism once ingested. Metabolism may occur via hepatic, renal, or non-organ-specific enzymatic processes. The route of elimination of the metabolic pathway may be exploited for infections associated with tissues related to the metabolic pathways. For example, many fluoroquinolone antimicrobials have renal elimination. Urinary concentrations of active drug are many times those achieved in the systemic circulation, making these agents good choices for complicated UTIs.

▶ *Pharmacodynamic Properties*

Pharmacodynamics describes the relationship between drug exposure and pharmacologic effect of antibacterial activity or human toxicology. Antimicrobials are categorized based on their concentration-related effects on bacteria. Concentration-dependent activity occurs where higher drug concentrations are associated with greater rates and extents of bacterial killing. Concentration-dependent antimicrobial activity is maximized when peak antimicrobial concentrations are high. In contrast, concentration-independent (or time-dependent) activity refers to a minimal increase in the rate or extent of bacterial killing with an increase in antimicrobial dose. Concentration-independent antimicrobial activity is maximized when these antimicrobials are dosed to maintain blood and/or tissue

concentrations above the MIC in a time-dependent manner. Fluoroquinolones, aminoglycosides, and metronidazole are examples of antimicrobials that exhibit concentration-dependent activity, whereas β-lactam and glycopeptide antimicrobials exhibit concentration-independent activity. Pharmacodynamic properties have been optimized to develop new dosing strategies for older antimicrobials. Examples include single-daily-dose aminoglycoside or β-lactam therapy administered by continuous or extended infusion.

Antimicrobials also can be classified as possessing bactericidal or bacteriostatic activity in vitro. Bactericidal antibiotics reduce the bacterial population by greater than or equal to a 3 log reduction, whereas bacteriostatic antibiotics possess antimicrobial activity but reduce bacterial load by less than 3 logs. Clinically, bactericidal antibiotics may be necessary to achieve success in infections such as endocarditis or meningitis. A full discussion of the application of antimicrobial pharmacodynamics is beyond the scope of this chapter, but excellent sources of information are available.[20]

▶ *Adverse-Effect and Drug-Interaction Properties*

A major concern when selecting antimicrobial regimens should be the propensity for the regimen to cause adverse effects and the potential for drug interactions. In general, if several different antimicrobial options are available, antimicrobials with a low propensity to cause adverse events should be selected, particularly for patients with risk factors for a particular complication. Risk factors for adverse events may include the coadministration of other drugs that are associated with a similar type of adverse event. For example, coadministration of the known nephrotoxin gentamicin with vancomycin increases the risk for nephrotoxicity compared with administration of either drug alone.[21] Other drug interactions may predispose the patient to dose-related toxicity through inhibition of drug metabolism. For example, macrolides have the potential to prolong cardiac QT intervals in a dose-dependent manner, potentially increasing the risk for sudden cardiac death.[22]

▶ *Antimicrobial Cost*

A final consideration in selecting antimicrobial therapy relates to cost. The least expensive antimicrobial is not necessarily the most cost-effective antimicrobial. Antimicrobial costs constitute a relatively small portion of the overall cost of care. Careful consideration of antimicrobial microbiologic, pharmacologic, and patient-related factors such as adherence and a variety of clinical outcomes is necessary to establish the cost versus benefit of an antimicrobial in a given patient. If there is no difference or a small difference in these factors, the least costly antimicrobial may be the best choice.

Patient Considerations in Antimicrobial Selection

LO 6

KEY CONCEPT Key patient-specific considerations in antimicrobial selection include recent antimicrobial exposures, identification of the anatomic location of infection through physical examination and diagnostic imaging, history of drug allergies, pregnancy or breast-feeding status, organ dysfunction that may affect drug clearance, immunosuppression, compliance, and the severity of illness (see Table 69–2).

▶ *Host Factors*

Host factors can help to ensure selection of the most appropriate antimicrobial agent. Age is an important factor in antimicrobial selection. Populations with diminished renal function include neonates and the elderly. Hepatic function in the neonate is not fully developed, and drugs that are metabolized or eliminated by this route may produce adverse effects. For example, sulfonamides and ceftriaxone may compete with bilirubin for binding sites and may result in hyperbilirubinemia and kernicterus. Gastric acidity also depends on age; the elderly and children younger than 3 years tend to be achlorhydric. Drugs that need an acidic environment (eg, ketoconazole) are not well absorbed, and those whose absorption is enhanced in an alkaline environment will have increased concentrations (eg, penicillin).

Disruption of host defenses due to IV or indwelling Foley catheters, burns, trauma, surgery, and increased gastric pH may place patients at higher risk for infection. Breaks in skin integrity provide a route for infection because the natural barrier of the skin is disrupted. Increased gastric pH can allow for bacterial overgrowth and has been associated with an increased risk of pneumonia.[23]

Recognizing the presumed site of infection and most common pathogens associated with the infectious source should guide antimicrobial choice, dose, and route of administration. For example, community-acquired pneumonia is caused most commonly by *Streptococcus pneumoniae*, *E. coli* is the primary cause of uncomplicated UTIs, and staphylococci and streptococci are implicated most frequently in skin and skin-structure infections (eg, cellulitis).

Patients with a history of recent antimicrobial use may have an altered microbiome or harbor resistant organisms. These patients should receive a different antimicrobial agent than was recently used. If a patient develops a new infection while on therapy or fails therapy, it is reasonable to prescribe either a different class of antimicrobial or alternative agent directed at the most likely pathogens. Failure may not be related to the antimicrobial agent but to poor source control. Previous hospitalization or health care utilization (eg, residing in a nursing home, hemodialysis, and outpatient antimicrobial therapy) are risk factors for the acquisition of nosocomial pathogens, which are often resistant organisms.

Antimicrobial allergies are some of the most common drug-related allergies reported and have significant potential to cause adverse events. In particular, reported penicillin-related allergy is common and can be problematic as this contributes to the unnecessary or inappropriate use of other antimicrobial agents.

Patient Encounter 3: Empirical Selection of Antibiotics

Based on the information presented, select an empirical antimicrobial regimen for this patient. Your plan should include:

(a) A tentative infectious diagnosis or source, including likely pathogens or resistant organisms;

(b) A specific antimicrobial regimen, including drug(s), dose, and route of administration;

(c) Description of any ancillary treatments;

(d) A rationale for your empirical antimicrobial selection based on drug- and patient-specific considerations.

A patient's medical history should be reviewed to determine the offending β-lactam and nature of the allergic reaction. Patients with mild or certain nonimmunologic reactions to penicillins may receive a β-lactam antimicrobial. Non-IgE- mediated findings such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or interstitial nephritis, should not be rechallenged with the offending agent, desensitized to penicillin, or undergo penicillin allergy skin testing. Previously it was thought that patients with a history of findings consistent with IgE-mediated reactions (type I) such as anaphylaxis, urticaria, or bronchospasm should not be administered any type of β-lactam antimicrobial. However, newer data suggests that β-lactam antimicrobials may be safely administered. Data demonstrate that the actual cross-reactivity between penicillins and cephalosporins is likely less than 1% and slightly lower with carbapenems. Penicillins, cephalosporins, and carbapenems have the β-lactam ring in common; however, it is more likely that the allergy cross-reactivity between penicillins and cephalosporins is secondary to side chain groups (R_1 and R_2). Therefore, in the majority of patients with a penicillin allergy, cephalosporins with dissimilar side chains, carbapenems, and monobactams may be safely administered.[24,25] Structural side chain similarities among β-lactam agents may be found in the literature (reference 24 contains a chart).

Renal and/or hepatic function should be considered prior to initiation of antimicrobial therapy. Most antimicrobials undergo renal elimination and dosing adjustments are frequently necessary and recommendations for adjustment are available in the literature.[26] In contrast, dosing adjustments for antimicrobials that undergo nonrenal elimination are less well documented. Failure to adjust the antimicrobial dose or interval may result in drug accumulation and adverse effects.

Concomitant administration of other medications may influence the selection of the antimicrobial, dose, and monitoring. Medications that commonly interact with antibiotics include, but are not limited to, warfarin, rifampin, phenytoin, digoxin, theophylline, multivalent cations (eg, calcium, magnesium, and zinc), and sucralfate. Drug interactions between antimicrobials and other medications may occur via the cytochrome P-450 system, protein-binding displacement, and alteration of vitamin K–producing bacteria. Interactions may result in increased concentrations of one or both agents, increasing the risk of adverse effects or additive toxicity. A key consideration in selecting antimicrobial regimens starts with obtaining a good patient medical and drug history, recognizing drug-specific adverse-event characteristics, and anticipating potential problems proactively. If it is necessary to use an antimicrobial with a relatively high frequency of adverse effects, informing patients of the risks and benefits of therapy, as well as what to do if an adverse effect occurs, may improve patient compliance and safety.

Antimicrobial agents must be used with caution in pregnant and nursing women. Some agents pose potential threats to the fetus or infant (eg, quinolones, tetracyclines, and sulfonamides). For some agents, avoidance during a specific trimester of pregnancy is warranted (eg, the first trimester with trimethoprim/sulfamethoxazole). Pharmacokinetic variables also are altered during pregnancy. Both the clearance and volume of distribution are increased during pregnancy. As a result, increased dosages and/or more frequent administration of certain drugs may be required to achieve adequate concentrations. This information can be obtained from a number of sources.[27]

Adherence is essential to ensure efficacy. Patients may stop taking their antibiotics once the symptoms subside and save them for a "future" infection. Self-medication with saved antibiotics may be harmful, leading to overtreatment, which may further contribute to antibiotic resistance. Poor adherence may be due to adverse effects, tolerability, cost, and lack of patient education.

OUTCOME EVALUATION

LO 7 Figure 69–4 provides an overview of patient- and antimicrobial agent-specific factors to consider when selecting an antimicrobial regimen. It further delineates monitoring of therapy and actions to take depending on the response to therapy. Duration of therapy depends on patient response and type of infection being treated.

After selection and initiation of an antimicrobial regimen, there are additional patient care and monitoring considerations that should be addressed to improve the likelihood of a successful outcome. LO 8 KEY CONCEPT Patient education, de-escalation of antimicrobial therapy based on culture results, monitoring for clinical response and adverse effects, and appropriate duration of therapy are important.

Modifying Empirical Therapy Based on Cultures and Clinical Response

If a successful clinical response occurs and culture results are available, therapy should be de-escalated. Antibiotic de-escalation generally refers to the discontinuation of antibiotics that are providing a spectrum of activity greater than necessary to treat the infection, discontinuation of duplicative spectrum antibiotics, or switching to a narrower spectrum antibiotic once a patient is clinically stable. De-escalation of empirical therapy may also include discontinuing antibiotics based on clinical criteria and negative culture results, such as the absence of antibiotic-resistant pathogens.[28] The purpose of de-escalation therapy is to prevent problematic effects such as adverse events and to minimize the risk of *C. difficile* infections and development of resistance. In cases in which a specific organism is recovered that has a known preferred antimicrobial treatment of choice, therapy might be changed to that specific agent. For example, antistaphylococcal penicillins and first-generation cephalosporins (ie, cefazolin) are considered to be the agents of choice for methicillin-susceptible *S. aureus* owing to their bactericidal activity and narrow-spectrum activity and may be preferable to other antibiotic regimens. In other cases, empirical coverage might be discontinued if a specific suspected pathogen is excluded by culture or an alternative, noninfectious diagnosis is established. In addition, IV antimicrobials frequently are more expensive than oral therapy. Therefore, it is usually desirable to convert to oral antimicrobials with a comparable antimicrobial spectrum or specific pathogen sensitivity as soon as the patient improves clinically.[29]

Failure of Antimicrobial Therapy

While many infections respond readily to antimicrobials, some infections do not. A common question when a patient fails to improve relates to whether the antimicrobial therapy has failed. Changing antimicrobials generally is one of the easiest interventions relative to other options. However, it is important to remember that antimicrobial therapy comprises only a portion of the overall disease treatment, and there may be many factors that contribute to a lack of improvement. LO 9 KEY CONCEPT In general,

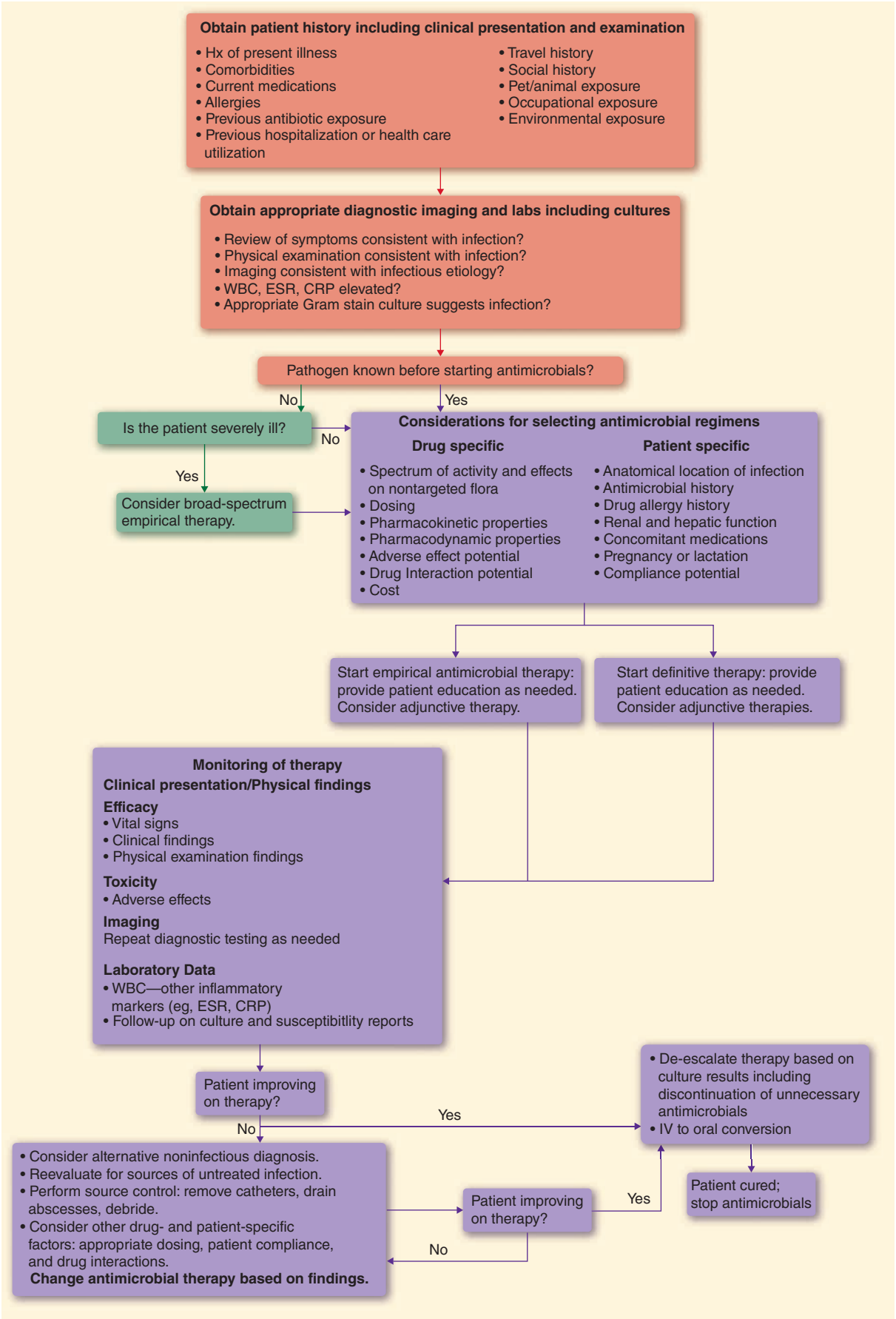

FIGURE 69–4. Approach to selection of antimicrobial therapy.

inadequate diagnosis resulting in poor initial antimicrobial or other nonantibiotic drug selection, poor source control, or the development of a new infection with a resistant organism are relatively common causes of antimicrobial failure. An infection-related diagnosis may be difficult to establish and generally has two components: (a) differentiating infection from noninfectious disease and (b) providing adequate empirical spectrum of activity if the cause is infectious. Failure of improvement in a patient's condition should warrant broadening the differential diagnosis to include noninfectious causes, as well as considering other potential infectious sources and/or pathogenic organisms. Another common cause of failure is poor source control. A diagnostic search for unknown sources of infection and removal of indwelling devices in the infected environment or surgical drainage of abscesses should be undertaken if the patient's condition is not improving. Less common causes of therapeutic failure include the development of secondary infections. In this case, the patient generally improves, but then develops a new infection caused by an antimicrobial-resistant pathogen and relapses. The emergence of resistance to a targeted pathogen while on antimicrobial therapy can be associated with clinical failure but usually is limited to tuberculosis, pseudomonads, or other gram-negative enterics. Drug- and patient-specific factors such as appropriate dosing, patient compliance, and drug interactions can be associated with therapeutic failure and also should be considered. A common assumption is that the correct diagnosis was made, but the patient was not treated long enough with antimicrobials. There are certain types of infections (eg, endocarditis or osteomyelitis) where the standard of care is to treat for prolonged periods of time (ie, weeks or months). However, the optimal duration of therapy for many infectious diseases is somewhat subjective. Studies of several infectious processes have suggested that shorter durations of therapy can result in similar clinical outcomes as longer durations of therapy, frequently with fewer complications or secondary infections.[30,31] In this period of extensive antimicrobial resistance, clinicians should keep abreast of changing recommendations emphasizing shorter durations of therapy.

Table 69–3

CDC Core Elements of Antibiotic Stewardship Programs

Leadership commitment
Accountability
Drug expertise
Key support groups
Action (implement policies/interventions to improve patient care)
Tracking/reporting antimicrobial use and outcomes
Education

ANTIBIOTIC STEWARDSHIP

LO 10

KEY CONCEPT Antibiotic stewardship promotes the optimal use of antimicrobial agents to reduce the emergence of resistant pathogens, improve the quality of patient care and safety, and reduce costs. Optimal use of antimicrobial agents includes appropriate selection, dose, route, and duration of therapy. Antibiotic stewardship programs have been implemented in many acute care institutions. As of January 1, 2017, the Joint Commission's Antimicrobial Stewardship Standard became effective for hospitals, critical access hospitals and nursing care centers. See Table 69–3.

Program leaders are often a physician trained in infectious diseases and a pharmacist. Other key personnel/support include clinicians, infection prevention, quality improvement, microbiology laboratory, information technology, and nursing. The goal is to support optimal antimicrobial use through various interventions and measures. Readers are encouraged to view the IDSA guidelines on implementing an antibiotic stewardship program and the CDC's Get Smart Campaign for further information.[4,28]

Patient Encounter 4: Patient Care and Monitoring

Update: Vancomycin, piperacillin/tazobactam, and levofloxacin were initiated.

After 48 hours of therapy, the following parameters are obtained:

PE:

- VS: BP 130/70 mm Hg, P 70 beats/min, RR 22 breaths/min, T 37.2°C (98.9°F), FiO_2 0.3, PEEP 5 cm H_2O

Labs:

- WBC 9.2 × 10^3/mm^3 (9.2 × 10^9/L)/differential 85% segs, 10% lymphs, 5% monos
- SCr 1.1 mg/dL (97.2 µmol/L)
- Glucose 126 mg/dL (6.9 mmol/L)
- Blood cultures × 2: No growth
- Sputum culture: *Pseudomonas aeruginosa*

Susceptibility Report:

Cefepime susceptible (MIC > 16 mg/L)

Ceftazidime susceptible (MIC < 16 mg/L)

Piperacillin/tazobactam susceptible (MIC ≤ 16 mg/L)

Meropenem susceptible (MIC ≤ 1 mg/L)

Gentamicin susceptible (MIC ≤ 4 mg/L)

Tobramycin susceptible (MIC < 4 mg/L)

Ciprofloxacin resistant (MIC > 4 mg/L)

Levofloxacin resistant (MIC > 4 mg/L)

What information suggests improvement in the patient's condition?

Do any of the antimicrobial doses need to be adjusted for changes in organ function?

Should antimicrobial therapy be modified based on the culture results?

Can the antimicrobial therapy be converted from IV to oral therapy?

Patient Care Process

Collect Information:

- Review pertinent patient medical history including significant comorbid conditions
- Determine patient allergy histories (including reactions and timing)
- Determine and document recent antibiotic exposure

Assess the Information:

- Review patient labs, including labs obtained for specific infectious syndromes and vital signs
- Determine if patient may have any potential sources for infection (eg, central venous catheter, urinary catheter)
- Assess the severity of illness
- Assess patient-specific risk factors based on infection type to aid in determining appropriate empirical therapy
- Review local antibiotic susceptibility patterns including hospital antibiograms

Develop a Care Plan:

- Based on proposed infectious diagnosis combined with above data assessed, select empirical antibiotic regimen
- Consider additional diagnostics and culture and susceptibility reports

Implement the Care Plan:

- Timely antibiotics are required, especially in critically ill patients, including those with sepsis

Follow-up: Monitor and Evaluate:

- Follow-up on culture and susceptibility reports to determine opportunities to streamline antibiotic therapy
- Some antibiotics may require therapeutic drug monitoring (eg, vancomycin) to evaluate for safety and effectiveness
- Duration of therapy should be determined based on several factors including but not limited to infection type, culture results, host immune status, and source control (eg, removal of a central venous catheter)

Abbreviations Introduced in This Chapter

CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
HPI	History of present illness
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
PMH	Past medical history
UTI	Urinary tract infection
VRE	Vancomycin-resistant *Enterococcus*
WBC	White blood cell count

REFERENCES

1. Antibiotic resistance threats in the United States, 2013. Centers for Disease Control. Available from: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed August 20, 2017.
2. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis. 2008;47:735–743.
3. Chow AC, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–e112.
4. Get Smart Campaign. Centers for Disease Control and Prevention. Available from: www.cdc.gov/getsmart. Accessed August 20, 2017.
5. Suda KJ, Hicks LA, Roberts RM, Hunkler RJ, Taylor TH. Trends and seasonal variation in outpatient prescription rates in the US, 2006-2010. Antimicro Agent Chemo. 2014;58(5):2763–2766.
6. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA. 2016;315(17):1864–1873.
7. Braggs J, Fridkin SK, Pollack LA, Srinavasan A, Jernigan JA. Estimating national trends in inpatient antibiotic use among US hospitals from 2006-2012. JAMA Intern Med. 2016;176(11):1639–1648.
8. National and State Healthcare Associated Infections: progress report. Centers for Disease Control. Available from: http://www.cdc.gov/HAI/pdfs/progress-report/hai-progress-report.pdf. Accessed August 8, 2017.
9. Sajadi MM, Mackowiak PA. Temperature regulation and the pathogenesis of fever. In: Bennett JE, Dolin R, Blaser M, eds. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases, 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:Chap 55.
10. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum calcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004;39:206–217.
11. Agarwal R, Schwartz DN. Procalcitonin to guide duration of antimicrobial therapy in intensive care units: a systematic review. Clin Infect Dis. 2011;53(4):379–387.
12. Practice Guidelines from the Infectious Diseases Society of America (IDSA). Infectious Diseases Society of America. Available from: http://www.idsociety.org/PracticeGuidelines/. Accessed August 8, 2017.
13. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000;118(1):146–55.
14. Antimicrobial spectra. In: Gilbert DN, Chambers HF, Eliopoulos GM, Saag MS, eds. The Sanford Guide to Antimicrobial Therapy 2017, 47th ed. Sperryville, VA: Antimicrobial Therapy Inc; 2017.
15. Bartlett JB, ed. The John Hopkins Antibiotic Guide. Available from: http://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/Antibiotics. Accessed August 8, 2017.
16. Cohen SH, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431–455.
17. Namdar R, Lauzardo M, Peloquin CA. Tuberculosis. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiological Approach, 10th ed. New York, NY: McGraw-Hill; 2016:Chap 112.
18. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals

from the American Heart Association: Endorsed by the Infectious Diseases Society of America. Circulation. 2015;132:1435–1486.
19. Peña C, Suarez C, Ocampo-Sosa A, et al. Effect of adequate single-drug vs. combination antimicrobial therapy on mortality in pseudomonas aeruginosa bloodstream infections: a post hoc analysis of a prospective cohort. Clin Infect Dis. 2013;57(2):208–216.
20. Craig WA. Pharmacodynamics of antimicrobials: general concepts and applications. In: Nightingale CH, Ambrose PG, Drusano GL, eds. Antimicrobial Pharmacodynamics in Theory and Clinical Practice, 2nd ed. New York: Informa Healthcare; 2007:1–19.
21. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health-Syst Pharm. 2009;66:82–98.
22. Albert RK, Schuller JL, COPD Clinical Research Network. Macrolide antibiotics and the risk of cardiac arrhythmias. Am J Respir Crit Care Med. 2014;189(10):1173–1180.
23. Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. Expert Rev Clin Pharmacol. 2012;5(3):337–344.
24. Zagursky RJ, Pichichero ME. Cross-reactivity in β-lactam allergy. J Allergy Clin Immunol Pract. 2018;6:72–81.
25. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. Curr Allergy Asthma Rep. 2014;14(11):476.
26. Battistella M, Matzke GR. Drug therapy individualization for patients with chronic kidney disease. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiological Approach, 10th ed. New York, NY: McGraw-Hill; 2016:Chap 48.
27. Briggs GG, Freeman RK, Towers CV et al. Drugs in Pregnancy and Lactation, 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017.
28. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51–e77.
29. Athanassa Z, Makris G, Dimopoulos G, Falagas ME. Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis. Drugs. 2008;68:2469–2481.
30. Mandell LA, Wunderink RG, Anzueo A, et al. Infectious Diseases Society of American/American Thoracic Society consensus guideline on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(suppl 2):S27–S72.
31. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–e111. https://doi.org/10.1093/cid/ciw353

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70 Central Nervous System Infections

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LEARNING OBJECTIVES

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

1. Discuss the pathophysiology of central nervous system (CNS) infections and the impact on antimicrobial treatment regimens (including antimicrobial dosing and CNS penetration).
2. Describe the signs, symptoms, and clinical presentation of CNS infections.
3. List the most common pathogens causing CNS infections and identify risk factors for infection with each pathogen.
4. State the goals of therapy for CNS infections.
5. Outline the initial management strategies for CNS infections.
6. Design appropriate empirical antimicrobial regimens for patients suspected of having CNS infections (taking age, vaccine history, and other patient-specific information into account) caused by each of the following pathogens, and analyze the impact of antimicrobial resistance on both empirical and definitive therapy: *Neisseria meningitidis* meningitis, *Haemophilus influenzae* meningitis, *Listeria monocytogenes* meningitis, group B *Streptococcus* meningitis, gram-negative bacillary meningitis, postneurosurgical infection, CNS shunt infection, herpes simplex encephalitis.
7. Modify empirical antimicrobial regimens based on laboratory data and other diagnostic criteria.
8. Discuss the management of close contacts of patients diagnosed with CNS infections.
9. Identify candidates for vaccines and other prophylactic therapies to prevent CNS infections.
10. Describe the role of adjunctive agents (eg, dexamethasone) in the management of CNS infections.

INTRODUCTION

The term *central nervous system (CNS) infections* describes a variety of infections involving the brain and spinal cord and associated tissues, fluids, and membranes, including meningitis, encephalitis, brain abscess, cerebrospinal fluid (CSF) shunt infections, and postoperative infections. KEY CONCEPT CNS infections, such as meningitis, are considered neurologic emergencies that require prompt recognition, diagnosis, and management to prevent death and residual neurologic deficits. Improperly treated, CNS infections are associated with high rates of morbidity and mortality. Despite advances in care, the overall mortality of bacterial meningitis in the United States remains at approximately 15%, and at least 10% to 30% of survivors are afflicted with neurologic impairment, including hearing loss, hemiparesis, and learning disabilities.[1,2] Antimicrobial therapy and preventive vaccines have revolutionized management and improved outcomes of bacterial meningitis and other CNS infections dramatically.

EPIDEMIOLOGY AND ETIOLOGY

CNS infections are uncommon and declining in incidence, with a rate of 0.8 per 100,000 persons between 1997 and 2010.[3] However, the severity of these infections demands prompt medical intervention and treatment. CNS infections can be caused by bacteria, fungi, mycobacteria, viruses, parasites, and spirochetes.

Bacterial meningitis is the most common cause of CNS infections. While vaccination has reduced the incidence of disease by many common pathogens, *Streptococcus pneumoniae* (pneumococcus) was the most common pathogen for bacterial meningitis (0.306 cases per 100,000), followed by *Neisseria meningitidis* (meningococcus, 0.123 cases per 100,000).[3] Staphylococcal species and gram-negative bacteria account for 0.114 and 0.127 cases per 100,000 persons, respectively in the United States.[3] Group B *Streptococcus* (GBS) and *Listeria monocytogenes* remain important causes, but current data on their incidence are lacking.[2] Vaccines directed against bacteria causing meningitis and related infections (eg, pneumonia and ear infections) have reduced the risk of infections due to *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type B (Hib) dramatically.[2,3] Prior to the availability of Hib conjugate vaccines, Hib meningitis or other invasive disease was documented in one in 200 children by the age of 5 years and due to widespread use, its incidence has decreased such that it is no longer a leading pathogen.[3] Historically, a 7-valent conjugate pneumococcal vaccine (PCV7) was administered, but despite use of the PCV7, *S. pneumoniae* remained the most common pathogen for pediatric bacterial meningitis. In 2010, a 13-valent conjugate pneumococcal vaccine was licensed for use in the

United States; however, its impact on the epidemiology of disease in the United States is still unknown. In France, the 13-valent vaccine reduced the incidence of pneumococcal meningitis by 27.4% and similar reductions were seen in Canada with strains found in the vaccine.[4,5]

Encephalitis may result from viral, bacterial, parasitic, or other noninfectious causes. Herpes simplex virus (HSV) is the most common cause of encephalitis in the United States, accounting for 10% of all cases.[6] The annual incidence of viral encephalitis is 3.5 to 7.4 infections per 100,000 persons.[6] Other pathogens including common bacterial meningitis causes, *Rickettsia* species, enteroviruses, arboviruses, varicella-zoster virus, rotavirus, coronavirus, influenza viruses A and B, West Nile virus, and Epstein-Barr virus may be associated with a meningoencephalopathic presentation.[7] Approximately 20,000 hospitalizations each year are secondary to encephalitis, accounting for $650 million in health care costs.[8] Over the past 10 to 20 years, mortality secondary to encephalitis has remained constant, correlating with the increased number of people living with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS).

Neurosurgical procedures may place patients at risk for meningitis due to bacteria acquired at the time of surgery or in the postoperative period, including *Staphylococcus aureus*, coagulase-negative staphylococci, and gram-negative bacilli. In addition to bacteria, other pathogens may cause meningitis in at-risk patients. Immunocompromised patients, such as solid-organ transplant patients and patients living with HIV infection, are at risk for fungal meningitis with *Cryptococcus neoformans* and encephalitis secondary to *Toxoplasma gondii* and JC virus. Tuberculosis can spread from pulmonary sites to cause clinical disease in the CNS. Life-threatening viral encephalitis and meningitis can occur in otherwise healthy, young individuals, as well as in patients immunocompromised by age or other factors.

Risk factors for CNS infections can be classified as follows:

- *Environmental:* Recent exposures (eg, close contact with meningitis or respiratory tract infection, contaminated foods), active or passive exposure to cigarette smoke, close living conditions
- *Recent infection in the patient:* Respiratory infection, otitis media, sinusitis, mastoiditis
- *Immunosuppression:* Anatomic or functional asplenia, sickle cell disease, alcoholism, cirrhosis, immunoglobulin or complement deficiency, cancer, HIV/AIDS, uncontrolled diabetes mellitus, debilitated state of health
- *Surgery, trauma:* Neurosurgery, head trauma, CSF shunt, cochlear implant
- Noninfectious causes of meningitis include malignancy, medications (eg, sulfonamides, nonsteroidal anti-inflammatory drugs [NSAIDs], IV immunoglobulin), autoimmune disease (eg, lupus), and trauma.[6,7]
- The most common pathogens causing bacterial meningitis, by age group and other risk factors, are found in Table 70–1.

Table 70–1

Most Likely Pathogens and Recommended Empirical Therapy, by Risk Factor, for Bacterial Meningitis[2,24,25]

Predisposing Factor	Most Likely Pathogens	Recommended Empirical Antibiotic Therapy
Age		
Less than 3 months	Group B *Streptococcus* *Escherichia coli* *Klebsiella pneumoniae* *Listeria monocytogenes*	Ampicillin *plus* cefotaxime *or* aminoglycoside
3 months to less than 18 years	*Streptococcus pneumoniae* *Neisseria meningitidis*	Cefotaxime *or* ceftriaxone *plus* vancomycin
18 years to less than 60 years	*S. pneumoniae* *N. meningitidis*	Cefotaxime *or* ceftriaxone *plus* vancomycin
60 years *or* older	*S. pneumoniae* Gram-negative bacilli *L. monocytogenes*	Cefotaxime *or* ceftriaxone *plus* vancomycin *plus* ampicillin
Immunocompromised	*S. pneumoniae* *N. meningitidis* *L. monocytogenes* Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Cefotaxime *or* ceftriaxone *plus* vancomycin *plus* ampicillin (consider double antibiotic coverage against *Pseudomonas* spp. if suspected)
Surgery, Trauma		
Postneurosurgical infection	*S. aureus* (including MRSA) Coagulase-negative *Staphylococcus* (including MRSE) Gram-negative bacilli (including *P. aeruginosa*)	Vancomycin *or* linezolid *plus* cefepime or ceftazidime *or* meropenem (consider empiric use of two active antibiotics against *Pseudomonas* spp. if suspected)
Penetrating head trauma	*S. aureus* (including MRSA) coagulase-negative *Staphylococcus* Gram-negative bacilli (including *P. aeruginosa*)	Vancomycin *or* linezolid *plus* cefepime or ceftazidime *or* meropenem (consider empiric use of two active antibiotics against *Pseudomonas* spp. if suspected)
CSF shunt	Coagulase-negative *Staphylococcus* (including MRSE) *S. aureus* (including MRSA) Gram-negative bacilli (including *P. aeruginosa*)	Vancomycin *or* linezolid *plus* cefepime or ceftazidime or meropenem (consider empiric use of two active antibiotics against *Pseudomonas* spp. if suspected)

MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

Patient Encounter 1, Part 1

NB is a 10-year-old, 35 kg boy without a significant past medical history. He is active in sports and recently returned from a baseball tournament where he lived in shared housing with his teammates. He now presents to the emergency department with a 2-day history of headache, fever, and confusion. Physical findings and laboratory values include temperature of 38.9°C (102°F) and WBC of 18.7 × 10^3/mm^3 (18.7 × 10^9/L), with 73% (0.73) polymorphonuclear cells (PMNs). Examination reveals nuchal rigidity and altered mental status. He is up to date on his vaccinations.

What signs and symptoms consistent with meningitis are present in NB?

What causative pathogens should be suspected in NB?

What empiric antimicrobials should be started?

PATHOPHYSIOLOGY

Meningitis is an inflammation of the membranes of the brain and spinal cord (**meninges**) and the CSF in contact with these membranes, whereas encephalitis is an inflammation of the brain tissue. CSF produced in the brain ventricles flows through the subarachnoid space and downward through the spinal cord, insulating and protecting delicate CNS tissue.

To initiate a CNS infection, pathogens must gain entry into the CNS by **contiguous** spread, **hematogenous** seeding, direct inoculation, or reactivation of latent infection. Contiguous spread occurs when infections in adjacent structures (eg, sinus cavities or the middle ear) invade directly through the blood–brain barrier. Hematogenous seeding occurs when a remote infection causes bacteremia that seeds the CSF, such as pneumococcal pneumonia. Reactivation of latent infection results from dormant viral, fungal, or mycobacterial pathogens in the spine, brain, or nerve tracts. Direct inoculation of bacteria into the CNS is the result of trauma, congenital malformations, or complications of neurosurgery.

Once through the blood–brain barrier, pathogens replicate due to limited host defenses in the CNS. **Figure 70–1** depicts the pathophysiologic changes associated with meningitis. Neurologic tissue damage is the result of the host's immune reaction to bacterial cellular components, which trigger cytokine production, particularly tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1), and other inflammatory mediators.[9] Bacteriolysis resulting from antibiotic therapy further contributes to the inflammatory process. Cytokines increase permeability of the blood–brain barrier, allowing influx of neutrophils and other host defense cells that contribute to the development of cerebral edema and increased intracranial pressure characteristic of meningitis.[10] The increase in intracranial pressure is responsible for the hallmark clinical signs and symptoms of meningitis: headache, neck stiffness, altered mental status, photophobia, and seizures. Untreated, these pathophysiologic changes may result in cerebral ischemia and death.

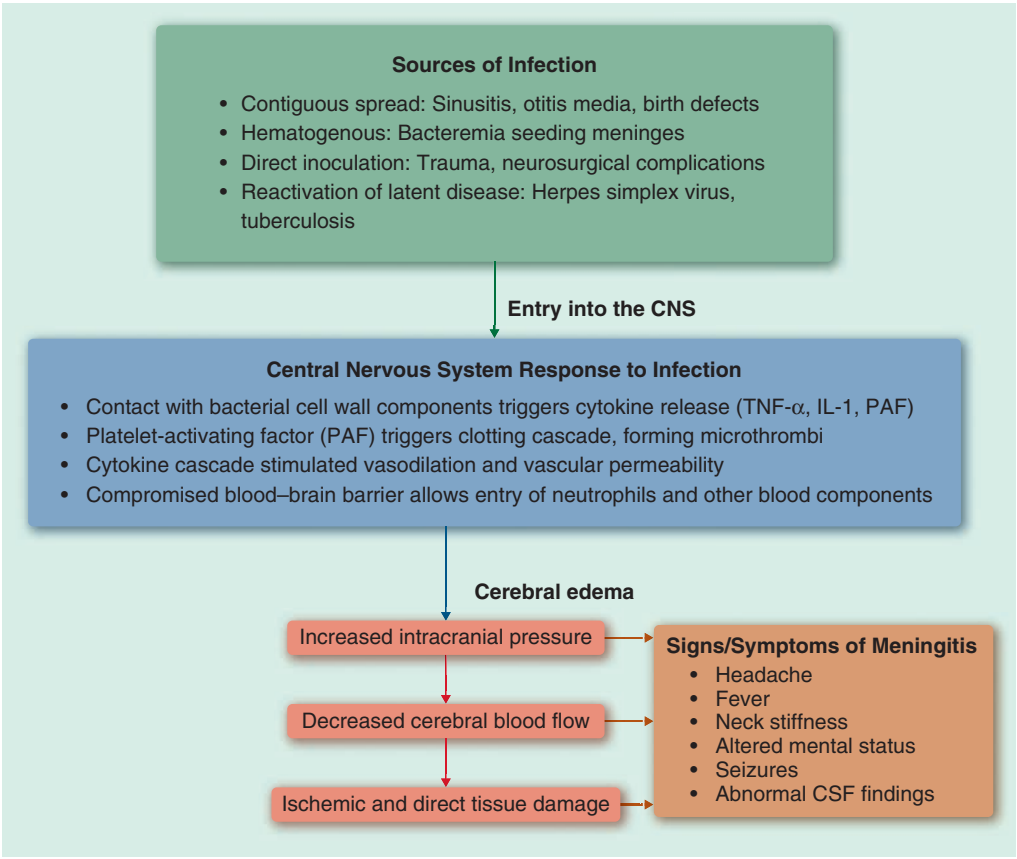

FIGURE 70–1. Pathophysiology of bacterial meningitis.

Table 70–2

CNS Response to Infection (CSF Findings)

	Normal CSF	Bacterial Infection	Viral Infection	Fungal Infection	Tuberculosis
WBC ($\times 10^3$/mm^3 *or* $\times 10^9$/L)	< 0.005	1.0–greater than 5.0	0.1–1	0.1–0.4	50–500
WBC differential (% or fraction in brackets, predominant cell type)	> 85% (0.85) monocytes	At least 80% (0.80) PMNs	50% (0.50) lymphocytes (PMN early)	> 50% (0.50) lymphocytes	> 80% (0.80) lymphocytes (PMNs early)
Protein (mg/dL, mg/L)	20–45 (200–450)	> 100 (> 1000)	50–100 (500–1000)	100–200 (1000–2000)	40–150 (400–1500)
Glucose (mg/dL, mmol/L)	45–80 (2.5–4.4)	5–40 (0.3–2.2)	30–70 (1. 7–3. 9)	< 30–70 (< 1. 7–3. 9)	< 30–70 (< 1. 7–3. 9)
CSF: serum glucose ratio	At least 0.6 serum glucose	< 0.4 serum glucose	At least 0.6 serum glucose	< 0.4 serum glucose	< 0.4 serum glucose
CSF stain	Negative	Positive Gram stain (60%–90%)	Negative	Positive India ink stain (Cryptococcus)	Positive acid-fast bacilli stain
Opening pressure	< 20 mm Hg	> 20 mm Hg	< 20 mm Hg	> 20 mm Hg	> 20 mm Hg

CSF, cerebrospinal fluid; PMNs, polymorphonuclear neutrophils.

From Refs. 5 and 11.

LO 5

The CNS response to infection is cellular and chemical changes in the CSF. KEY CONCEPT Ideally, lumbar puncture (LP) to obtain CSF for direct examination and laboratory analysis, as well as blood cultures and other relevant cultures, should be obtained before initiation of antimicrobial therapy. However, initiation of antimicrobial therapy should not be delayed if a pretreatment LP cannot be performed.

Normal CSF has a characteristic composition in terms of protein and glucose content, as well as cell count. Table 70–2 lists CSF findings normally observed and in the setting of meningitis.

CLINICAL PRESENTATION AND DIAGNOSIS

A high index of suspicion should be maintained for patients at risk for CNS infections. Prompt recognition and diagnosis are essential so that antimicrobial therapy can be initiated as quickly as possible. A medical history (including risk factors for infection and history of possible recent exposures) and physical examination yield important information to help guide the diagnosis and treatment of meningitis. Common signs and symptoms include fever, headache, **nuchal rigidity**, and photophobia. Infants present with nonspecific signs and symptoms, including excessive irritability or crying, vomiting or diarrhea, tachypnea, altered sleep pattern, and poor eating. Depending on involved pathogens and disease severity, patients may also present with altered mental status, stupor, and seizures.

TREATMENT

Goals of Therapy

Prior to antibiotic therapy and vaccination bacterial meningitis was almost universally fatal, with survivors suffering from debilitating residual neurologic deficits, such as permanent hearing loss.[1,2] Although significant improvements have been made, the fatality rate of meningitis remains above 15% in adults, likely due to its occurrence in debilitated patient populations.[2]

KEY CONCEPT The treatment goals for CNS infections are to prevent death and residual neurologic deficits, eradicate or control causative micro-organisms, ameliorate clinical signs and symptoms, and implement vaccination and suppressive measures to prevent future infections. Surgical debridement should be employed, if appropriate (as in postneurosurgical infections and brain abscess). Supportive care, consisting of hydration, electrolyte replacement, antipyretics, antiemetics, analgesics, antiepileptic drugs, and wound care (for surgical wounds), is an important adjunct to antimicrobial therapy, particularly early in the treatment course.

LO 4

Treatment Principles

KEY CONCEPT Prompt initiation of IV high-dose bactericidal antimicrobial therapy directed at the most likely pathogen(s) is essential due to the high morbidity and mortality associated with CNS infections. Although there are no prospective studies that relate timing of antibiotic administration to clinical outcome in bacterial meningitis, a longer duration of symptoms and more advanced disease before treatment initiation increase the risk of a poor outcome.[2,11] Initiation of antibiotic therapy as soon as possible after bacterial meningitis is suspected or proven (even before hospitalization) reduces mortality and neurologic sequelae.[11-13]

LO 5

High-dose parenteral bactericidal antibiotic therapy is required to achieve CSF antibiotic concentrations adequate to rapidly sterilize the CSF and reduce the risk of complications. Data from animal studies and patients demonstrate better outcomes when bactericidal antibiotic therapy (vs bacteriostatic therapy) is used to sterilize the CSF.[14] However, successful treatment of meningitis has been reported with bacteriostatic agents. The presence of infection in the CSF reduces the activity of some classes of antibiotics. For example, the decreased pH of CSF associated with meningitis significantly reduces the activity of aminoglycoside antibiotics.[15]

Antimicrobial pharmacokinetics and pharmacodynamics must be considered when designing treatment regimens for CNS infections. The key of treatment success is the ability of antibiotics to reach and achieve effective concentrations at the infection site. In experimental models of meningitis, maximum bactericidal activity is achieved when CSF concentrations exceed the minimum bactericidal concentration (MBC) of the infecting pathogen by 10- to 30-fold.[16] In general, low-molecular-weight

Clinical Presentation and Diagnosis of CNS Infections

General

- Evaluate patient risk factors and recent exposures
- Evaluate other possible causes: space-occupying lesion (which may *or* may not be malignant), drug-induced CNS pathology autoimmune disease, and trauma[12,13]

Signs and Symptoms[2]

- 95% of patients with bacterial meningitis have two of the following: headache, fever, neck stiffness, and altered mental status
- Headache (87%)
- Nuchal rigidity (stiff neck) (83%)
- Fever (77%)
- Nausea (74%)
- Altered mental status (ie, confusion, lethargy, and obtundation) (69%)
- Focal neurologic defects (including positive Brudzinski sign and Kernig sign) (33%)
- Seizures
- Malaise, restlessness
- Photophobia
- Skin lesions (diffuse petechial rash observed in 50% of patients with meningococcal meningitis)
- Signs and symptoms in neonates, infants, and young children: nonspecific findings, such as altered feeding and sleep patterns, vomiting, irritability, lethargy, bulging fontanel, seizures, respiratory distress, and petechial/purpuric rash[17]
- Predictors of an unfavorable outcome: seizures, focal neurologic findings, altered mental status, papilledema, hypotension, septic shock, and pneumococcal meningitis[4]

Laboratory Tests[5,18,44]

- CSF examination via lumbar puncture (LP, spinal tap); contraindicated in patients with cardiorespiratory compromise, increased intracranial pressure and papilledema, focal neurologic signs, seizures, bleeding disorders, abnormal level of consciousness, and possible brain herniation (a CT scan should be performed before LP if there is a question of a CNS mass to avoid potential for brain herniation) (see Table 70–2 for specific CSF findings)
- Elevated opening pressure (may be decreased in neonates, infants, and children)
- Cloudy CSF
- Decreased glucose
- Elevated protein
- Elevated WBC (differential provides clues to offending pathogen)
- Gram stain (adequate for diagnosis in 60%–90% of patients with bacterial meningitis)
- Culture and sensitivity (positive in 70%–85% without prior antibiotic therapy, likelihood of positivity reduced by 20% in those who have had prior therapy)
- If CSF Gram stain and/or culture is negative, rapid diagnostic tests (such as latex agglutination) may be useful; these tests are positive even if bacteria are dead
- Polymerase chain reaction (PCR; DNA amplification of the most common bacterial meningitis pathogens) may be useful to help exclude bacterial meningitis
- Elevated CSF lactate and C-reactive protein
- Blood cultures (at least two cultures, one set; positive in 66%)
- Scraping of skin lesions (eg, rash) for direct microscopic examination and culture
- Other cultures should be obtained as clinically indicated (eg, sputum)
- WBC with differential
- Fungal meningitis: CSF culture, CSF and serum cryptococcal antigen titers, microscopic examination of CSF specimens
- Tuberculous meningitis: CSF culture, PCR evaluation (preferred), and acid-fast stain

Patient Encounter 1, Part 2

NB, the 10-year-old patient with signs and symptoms of meningitis underwent lumbar puncture. Initial results from CSF studies are WBC 2×10^3/mm^3 (2×10^9/L) with 85% (0.85) PMNs and 39% (0.39) monocytes, protein 182 mg/dL (1820 mg/L), glucose 18 mg/dL (1.0 mmol/L). Gram stain shows gram-positive cocci. Vital signs remain stable in the ED. First doses of antimicrobial therapy are initiated in the ED, and NB is admitted to a pediatric medicine ward for continued treatment and confirmation of final diagnosis. Culture results confirm *Streptococcus pneumoniae* with a penicillin MIC of 1 mg/L and ceftriaxone/cefotaxime susceptibility. Antimicrobials are streamlined and continued for the full duration.

What clues in the CSF results are suggestive of bacterial meningitis?

Would adjunctive steroids offer additional benefit in this patient?

How can his antibiotic regimen be streamlined at this time?

Patient Encounter 1, Part 3

NB has clinically improved on hospital day 3 and would like to be discharged home to continue therapy, but would prefer oral therapy if available. As his teammate's parents learn of his illness, they are concerned about the possibility of their children getting sick and begin to follow-up with their own primary care providers. They wonder about medications and vaccinations to prevent the disease.

How long should therapy be continued in NB?

What oral options are viable options for continuation as an outpatient in this case?

Who should receive antimicrobial prophylaxis for Streptococcus pneumoniae?

lipophilic antibiotics that are nonionized at physiologic pH and not highly protein bound penetrate best into CSF and other body tissues and fluids.[15,17] In addition to drug characteristics, integrity of the blood–brain barrier determines antibiotic penetration into CSF. The CSF penetration of most, but not all, antibiotics is enhanced by the presence of infection and inflammation. Sulfonamides, trimethoprim, chloramphenicol, rifampin, and most antitubercular drugs achieve therapeutic CSF levels even without meningeal inflammation.[7] Most β-lactams and related antibiotics (ie, carbapenems and monobactams), vancomycin, quinolones, acyclovir, linezolid, daptomycin, and colistin achieve therapeutic CSF levels in the presence of meningeal inflammation.[7] Aminoglycosides, first-generation cephalosporins, second-generation cephalosporins (except cefuroxime), clindamycin, and amphotericin do not achieve therapeutic CSF levels, even with inflammation, but clindamycin does achieve therapeutic brain tissue levels.[7]

An adequate duration of therapy is required to treat meningitis successfully (Table 70–3). KEY CONCEPT Parenteral (IV) therapy is administered for the full course of therapy for CNS infections to ensure adequate CSF penetration throughout the course of treatment. Antibiotic treatment (and dexamethasone, if used as a treatment adjunct) reduces the inflammation associated with meningitis, which, in turn, reduces the penetration of some antibiotics into the CSF, and parenteral therapy must be used throughout the entire treatment course to ensure adequate concentrations. Carefully selected patients who have close medical monitoring and follow-up may be able to receive a portion of their parenteral meningitis treatment on an outpatient basis.[11,18] A management algorithm for adults with suspected bacterial meningitis, as recommended by the Infectious Diseases Society of America (IDSA), is summarized in Figure 70–2.

Empirical Antimicrobial Therapy

After diagnosis, prompt and aggressive antimicrobial therapy with an appropriate empirical treatment is of the utmost importance in patients with suspected CNS infections. In most patients, a diagnostic LP will be performed before beginning antibiotics, but this should never delay initiation of antimicrobials. Antibiotic pretreatment may alter the CSF profile and complicate interpretation. KEY CONCEPT Empirical therapy should be directed at the most likely pathogen(s) for a specific patient, taking into account age, risk factors for infection (including underlying disease and immune dysfunction, vaccine history, and recent exposures), CSF Gram stain results, CSF antibiotic penetration, and local antimicrobial resistance patterns. Results of the CSF Gram stain may be used to help narrow empirical therapy for bacterial meningitis. In the absence of a positive Gram stain, empirical therapy should be continued for at least 48 to 72 hours, when meningitis may, in most cases, be ruled out by CSF findings inconsistent with bacterial meningitis, negative CSF culture, and negative polymerase chain reaction (PCR) evaluations. A repeat LP may be useful in the absence of other findings. Table 70–1 outlines recommendations for empirical antibiotic therapy for bacterial meningitis by most likely pathogen(s) and patient risk factors.

Impact of Antimicrobial Resistance on Treatment Regimens for Meningitis

Development of resistance to β-lactam antibiotics, including penicillins and cephalosporins, has significantly impacted the management of bacterial meningitis with one-fifth of CSF isolates resistant to penicillin and 3.5% of isolates resistant to cephalosporins.[19] The Clinical and Laboratory Standards Institute (CLSI) has set a lower ceftriaxone susceptibility breakpoint for pneumococcal CSF isolates (1 mg/L) than for isolates from non-CNS sites (2 mg/L). Empirical treatment regimens now include the combination of a third-generation cephalosporin plus vancomycin. Recognition of relative and high-level resistance to *N. meningitidis* in the laboratory, as well as in clinical treatment failures, has led to greater use of third-generation cephalosporins for empirical therapy of meningococcal meningitis.[3,11] Treatment of suspected or proven β-lactamase-mediated Hib meningitis also requires a third-generation cephalosporin. Increasing rates of methicillin-resistant *S. aureus* (about one-third of staphylococcal CSF isolates) and coagulase-negative staphylococci require the use of vancomycin for empirical therapy when these staphylococcal pathogens are suspected.[11,18]

The emergence and continued rise of multidrug-resistant strains of gram-negative organisms such as *Pseudomonas aeruginosa*, *Acinetobacter* species, AmpC, and extended-spectrum β-lactamase (ESBL) producing strains of Enterobacteriaceae have become a recognized threat nationally, and broad-spectrum therapy taking into account local resistance patterns should be used.

Pathogen-Directed Antimicrobial Therapy

KEY CONCEPT Empirical antimicrobial therapy should be modified on the basis of laboratory data and clinical response. If cultures, CSF Gram stain, or antigen/antibody testing indicate a specific pathogen, therapy should be adjusted quickly as needed to ensure adequate coverage for the offending pathogen(s). Table 70–3 outlines recommended definitive pathogen-directed treatment regimens, recommended treatment duration, and key adverse effects that should be monitored during antibiotic therapy for meningitis. Table 70–4 provides pediatric doses of selected agents used in bacterial meningitis treatment.

▶ *Neisseria meningitidis* Meningitis

N. meningitidis CNS infections most commonly occur in children and young adults. From 11% to 19% of survivors of meningococcal meningitis experience long-term sequelae, including hearing loss, limb loss, and neurologic deficits.[20] Nearly all meningococcal disease is caused by five serogroups: A, B, C, Y, and W-135. In the United States, serotypes B, C, and Y each are responsible for approximately 30% of cases.[3,4]

Meningococcal meningitis is observed most commonly in individuals living in close quarters (eg, college students, military personnel). Infants younger than 1 year are at highest risk, possibly because pneumococcal vaccination reduces bactericidal antibodies.[21] However, nearly 60% of cases occur in patients over 11 years of age.[20,22] *N. meningitidis* colonizes the nasopharynx and usually is transmitted via inhaled respiratory droplets from patients or asymptomatic carriers. A subclinical bacteremia typically ensues, seeding the meninges. Meningococcal disease is often (approximately 50%) associated with a diffuse petechial rash, and patients may experience behavioral changes. Patients may develop fulminant meningococcal sepsis, characterized by shock, disseminated intravascular coagulation (DIC), and multiorgan failure.[23] Meningococcal sepsis has a poor prognosis and carries a mortality rate of up to 80%, whereas the mortality rate with meningococcal meningitis alone is 13%.[23,24] Patients with suspected meningococcal infection should be kept on respiratory isolation for the first 24 hours of treatment.[20]

Increasing penicillin resistance requires that third-generation cephalosporins now be used for empirical treatment until *in vitro* susceptibilities are known.[11,15] Patients with a history of type I penicillin allergy or cephalosporin allergy may be treated with

Table 70–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24]

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
Neisseria meningitidis[a]	*Standard Therapy*			
Penicillin MIC < 0.1 mg/L	Penicillin G 4 million units IV every 4 hours *or*	Hypersensitivity (rash, anaphylaxis), diarrhea	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 3 million units IV every 4 hours; CrCl < 10 mL/min (0.17 mL/s): 2 million units IV every 4 hours *Hepatic*: No dose adjustment	7
	Ampicillin 2 g IV every 4 hours	Hypersensitivity (rash, anaphylaxis), diarrhea	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 8 hours; CrCl < 30 mL/min (0.50 mL/s): 2 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 2 g IV every 24 hours *Hepatic*: No dose adjustment	
	Alternative Therapies			
	Ceftriaxone 2 g IV every 12 hours *or*	LFT elevation, cholecystitis	*Renal*: No dose adjustment *Hepatic:* Caution in severe hepatic impairment	
	Cefotaxime 2 g IV every 4 hours	Pseudocholelithiasis	*Renal*: CrCl < 80 mL/min (1.34 mL/s): 2 g IV every 6–8 hours; CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 8–12 hours; CrCl < 30 mL/min (0.50 mL/s): 2 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 2 g IV every 24 hours *Hepatic:* No dose adjustment	
Penicillin MIC 0.1–1 mg/L	*Standard Therapy*			
	Ceftriaxone *or* cefotaxime			
	Alternative Therapies			
	Moxifloxacin 400 mg IV every 24 hours *or*	Nausea/vomiting/diarrhea, dizziness, headache, QT prolongation	*Renal*: No dose adjustment *Hepatic*: Caution in severe hepatic impairment	
	Meropenem 2 g IV every 8 hours *or*	Rash, hypersensitivity, diarrhea, decreased seizure threshold	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 12 hours; CrCl < 30 mL/min (0.50 mL/s): 500 mg to 1 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 500 mg to 1 g IV every 24 hours *Hepatic*: No dose adjustment	
	Chloramphenicol 1–1.5 g IV every 6 hours	Rash, diarrhea, seizures, anemia, gray baby syndrome, hypersensitivity, neurotoxicity (last choice due to toxicities)	*Renal*: No dose adjustment *Hepatic*: Reduce dose in moderate to severe impairment; consider serum drug monitoring	
Streptococcus pneumoniae				
Penicillin MIC < 0.1 mg/L	*Standard Therapy*			10–14
	Penicillin G *or* ampicillin			
	Alternative Therapies			
	Ceftriaxone *or* cefotaxime *or* chloramphenicol			
Penicillin MIC 0.1–1 mg/L (ceftriaxone/cefotaxime-sensitive strains)	*Standard Therapy* Ceftriaxone *or* cefotaxime			

(*Continued*)

Table 70–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24] (*Continued*)

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
	Alternative Therapies Cefepime 2 g IV every 8 hours *or* meropenem	Hypersensitivity (rash, anaphylaxis), decreased seizure threshold	*Renal:* CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 12–24 hours; CrCl < 30 mL/min (0.50 mL/s): 1–2 g IV every 24 hours *Hepatic*: No dose adjustment	
Penicillin MIC 2 mg/L *or* greater	*Standard Therapy* Vancomycin 15 mg/kg IV every 8–12 hours (with dosing based on serum levels) plus ceftriaxone *or* cefotaxime	Vancomycin: rash, red man syndrome (if infused too quickly) nephrotoxicity, thrombocytopenia	*Renal:* CrCl < 50 mL/min (0.83 mL/s): dosing every 24 hours; CrCl < 20 mL/min (0.33 mL/s): dosing based on serum concentrations; all dose adjustments should be made based on serum concentrations *Hepatic:* No dose adjustment	
	Alternative Therapies Moxifloxacin			
Cefotaxime/ceftriaxone MIC at least 1 mg/L	*Standard Therapy* Vancomycin *plus* ceftriaxone *or* cefotaxime			
	Alternative Therapies Moxifloxacin			
H. influenzae β-Lactamase-negative	*Standard Therapy* Ampicillin			7
	Alternative Therapies Ceftriaxone *or* cefotaxime *or* cefepime *or* moxifloxacin *or* chloramphenicol			
β-Lactamase-positive	*Standard Therapy* Ceftriaxone *or* cefotaxime			
	Alternative Therapies Cefepime *or* moxifloxacin *or* chloramphenicol			
Listeria monocytogenes	*Standard Therapy*			
	Ampicillin *or* penicillin G *plus* gentamicin (5 mg/kg/day, dosing based on serum concentrations)	Gentamicin: nephrotoxicity, ototoxicity	*Renal:* CrCl < 60 mL/min (1.00 mL/s): Use of traditional pharmacokinetic dosing; dose adjustments per serum concentrations *Hepatic:* No dose adjustment	21
	Alternative Therapies Trimethoprim-sulfamethoxazole (10–20 mg/kg trimethoprim) IV per day in divided doses every 6–8 hours *or* meropenem	Trimethoprim-sulfamethoxazole: rash, SJS, bone marrow suppression, hepatotoxicity, elevated serum creatinine, hyperkalemia	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 10–15 mg/kg trimethoprim IV per day divided every 8 hours; CrCl < 10 mL/min (0.17 mL/s): 7–10 mg/kg trimethoprim IV per day divided every 8–12 hours *Hepatic:* No dose adjustment	
Streptococcus agalactiae (group B. *Streptococcus*)	*Standard Therapy* Ampicillin *or* penicillin G *Alternative Therapies* Ceftriaxone *or* cefotaxime			14–21
Enterobacteriaceae	*Standard Therapy* Ceftriaxone *or* cefotaxime			

(*Continued*)

Table 70–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24] (*Continued*)

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
	Alternative Therapies Aztreonam 2 g IV every 6–8 hours	Phlebitis, fever, rash, headache, confusion, seizures	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 2 g IV every 8 hours; CrCl < 30 mL/min (0.50 mL/s): 2 g IV every 12 hours; CrCl < 10 mL/min (0.17 mL/s): 1 g IV every 12 hours *Hepatic:* No dose adjustment	
	Moxifloxacin *or* meropenem *or* trimethoprim-sulfamethoxazole *or* ampicillin			
Pseudomonas aeruginosa	*Standard Therapy* cefepime *or* ceftazidime 2 g IV every 8 hours *or* meropenem (addition of aminoglycoside should be considered)	Hypersensitivity, rash, anemia, neutropenia, eosinophilia, LFT elevation	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 1–2 g IV every 12 hours; CrCl < 30 mL/min (0.50 mL/s): 1–2 g IV every 24 hours; CrCl < 10 mL/min (0.17 mL/s): 1 g IV every 24 hours *Hepatic*: No dose adjustment	
	Alternative Therapies Aztreonam *or* ciprofloxacin 400 mg IV every 8–12 hours (addition of aminoglycoside should be considered)	Nausea/vomiting/diarrhea, dizziness, headache, rash, confusion, seizures	Ciprofloxacin: *Renal*: CrCl < 30 mL/min (0.50 mL/s): 400 mg IV every 24 hours *or* 200 mg IV every 12 hours *Hepatic*: No dose adjustment	
Staphylococcus aureus	*Standard Therapy*			
Methicillin-susceptible	Nafcillin *or* oxacillin 2 g IV every 4 hours	Rash, nausea/vomiting/diarrhea, acute interstitial nephritis	*Renal*: No dose adjustment *Hepatic*: No dose adjustment (combined renal and hepatic impairment may require dose adjustment)	
	Alternative Therapies Vancomycin *or* meropenem	Rifampin: Hepatotoxicity, red-orange discoloration of body fluids, skin rash, hepatic enzyme induction		
Methicillin-resistant	*Standard Therapy* Vancomycin *plus* Rifampin 600 mg po *or* IV daily if shunt involved		*Renal*: No dose adjustment *Hepatic*: Caution in moderate/severe hepatic impairment	
	Alternative Therapies Linezolid 600 mg IV every 12 hours *or* trimethoprim-sulfamethoxazole	Linezolid: blood dyscrasias, myalgias, arthralgias, neuropathy	*Renal*: No dose adjustment *Hepatic*: No dose adjustment	
Staphylococcus epidermidis	*Standard Therapy* Vancomycin *plus* rifampin 600 mg po *or* IV daily if shunt involved			
	Alternative Therapies Linezolid			
Herpes simplex virus	*Standard Therapy* Acyclovir 10 mg/kg IV every 8 hours (adults); 20 mg/kg IV every 8 hours (neonates)	Nephrotoxicity, crystalluria, nausea/vomiting, neurotoxicity, phlebitis	*Renal*: CrCl < 50 mL/min (0.83 mL/s): 10 mg/kg IV every 12 hours; CrCl < 30 mL/min (0.50 mL/s): 10 mg/kg IV every 24 hours; CrCl < 10 mL/min (0.17 mL/s): 5 mg/kg IV every 24 hours *Hepatic*: No dose adjustment	

(*Continued*)

Table 70–3

Pathogen-Based Definitive Treatment for CNS Infections[11,24] (*Continued*)

Pathogen	Recommended and Alternative Antimicrobial Therapy (Adult Doses)	Adverse Effects/Safety Monitoring	Renal and Hepatic Dose Adjustment	Duration (Days)
	Alternative Therapy Foscarnet 120–200 mg/kg IV per day in divided doses every 8–12 hours	Nephrotoxicity, electrolyte imbalances, nausea/vomiting, headache, penile ulceration, thrombophlebitis, seizures	*Renal*: CrCl: 1.0–1.4 mL/min/kg (0.017–0.023 mL/s/kg): 70 mg/kg IV every 12 hours; CrCl: 0.8–1.0 mL/min/kg (0.013–0.017 mL/s/kg): 50 mg/kg IV every 12 hours; CrCl: 0.6–0.8 mL/min/kg (0.010–0.013 mL/s/kg): 80 mg/kg IV every 24 hours; CrCl: 0.5–0.6 mL/min/kg (0.008–0.010 mL/s/kg): 60 mg/kg IV every 24 hours; CrCl: 0.4–0.5 mL/min/kg (0.007–0.008 mL/s/kg): 50 mg/kg IV every 24 hours; CrCl < 0.4 mL/min/kg (0.007 mL/s/kg) *or* < 20 mL/min (0.33 mL/s) not recommended *Hepatic*: No dose adjustment	
Cryptococcus neoformans	Amphotericin B 0.7mg/kg IV daily *plus* flucytosine 100–150 mg/kg/day in divided doses every 6 hours (induction) Fluconazole 400–800 mg (maintenance) Fluconazole 200 mg (secondary prophylaxis)	Amphotericin: nephrotoxicity, electrolyte imbalances Flucytosine: bone marrow suppression, rash Fluconazole: transaminitis; QTc prolongation	*Renal*: Caution in severe renal dysfunction; consider alternative dosing strategy or change to lipid formulation *Hepatic*: No dose adjustment Flucytosine: *Renal*: CrCl 25–50 mL/min (0.42–0.83 mL/s): every 12 hours; CrCl 10–25 mL/min (0.17–0.42 mL/s) every 24 hours; CrCl < 10 mL/min (0.17 mL/s) 12.5 mg/kg every 24 hours *Hepatic*: No dose adjustment Fluconazole *Renal*: CrCl < 50 mL/min (0.83 mL/s) decrease dose by 50% *Hepatic*: Consider 50% reduction in mild-moderate hepatic insufficiency; risk-benefit in severe hepatic dysfunction	
Toxoplasmosis gondii	Pyrimethamine 200 mg po x 1, then 50 mg (< 60 kg) to 75 mg (≥ 60 kg) daily *plus* sulfadiazine 1000 mg (< 60 kg) to 1500 mg (≥ 60 kg) po every 6 hours plus leucovorin 10–25 mg po daily	Pyrimethamine: bone marrow suppression, high-risk for anemia Sulfadiazine: nephrotoxicity, bone marrow suppression, rash, SJS	*Renal*: No dose adjustment *Hepatic*: No dose adjustment *Renal*: CrCL 25–50 mL/min (0.42–0.83 mL/s): every 12 hours; CrCl 10–25 mL/min (0.17–0.42 mL/s) every 24 hours; CrCl less than 10ml/min (< 0.17 mL/s) caution use due to high risk of crystalluria *Hepatic*: No dose adjustment	

[a]Empiric therapy with a third-generation cephalosporin should be used until in vitro susceptibility data are known.

LFTs, liver function tests; MIC, minimum inhibitory concentration; SJS, Stevens-Johnson syndrome.

vancomycin. Treatment should be continued for 7 days, after which no further treatment is necessary.

Prevention of meningococcal disease by vaccination is a key to reducing the incidence of meningococcal meningitis. Routine vaccination should be administered between ages 11 and 12 years with a booster dose at age 16 with quadrivalent vaccine that provides protection against serogroups A, C, Y, and W.[20] Additional vaccination against serogroup B can be considered in all patients and is recommended in those with immunocompromising conditions. In addition, individuals aged 2 through 54 years who are immunocompromised (including those with complement deficiencies, who have HIV, or who have asplenia) or those with recent disease exposure during community outbreaks should receive the quadrivalent vaccine and the vaccine against Serogroup B is also recommended for immunocompromised individuals and during outbreaks.[20] Additionally, children less than 2 years may also need quadrivalent vaccine and serogroup B vaccine, depending on risk factors. The quadrivalent conjugate

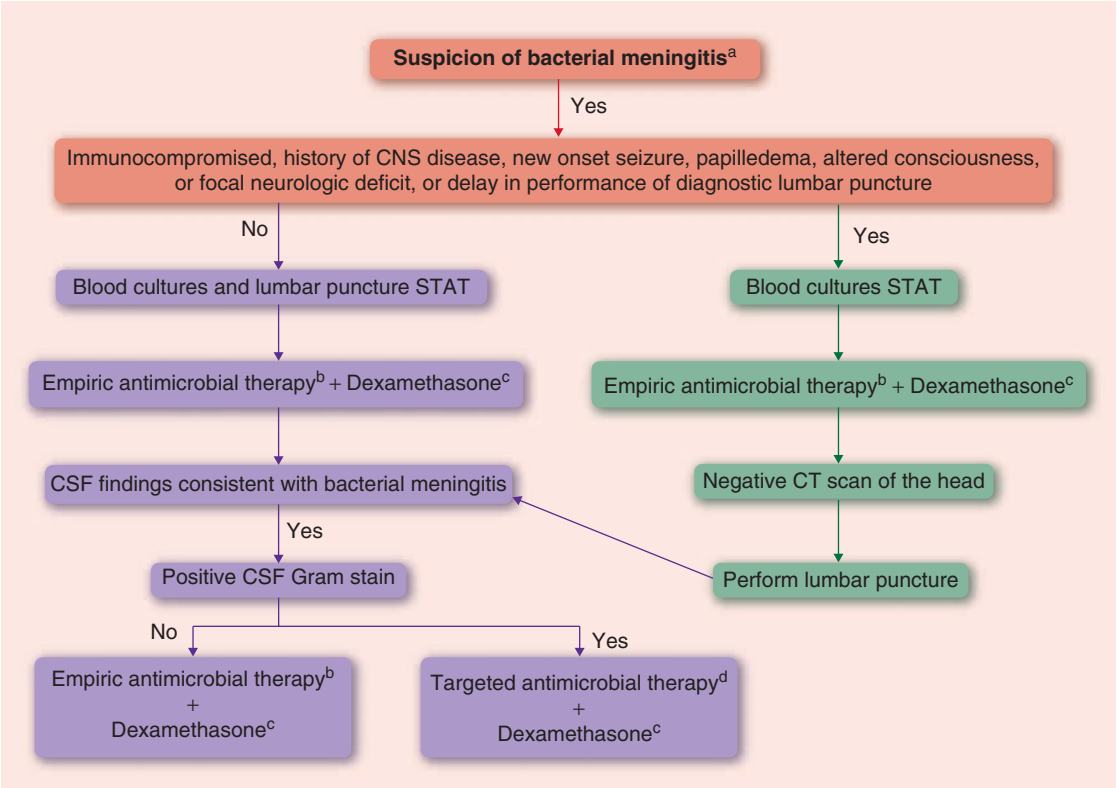

FIGURE 70–2. Management algorithm for adults with suspected bacterial meningitis. [a]Management algorithm is similar for infants and children with suspected bacterial meningitis. [b]See Table 70–1 for empirical treatment recommendations. [c]See text for specific recommendations for use of adjunctive dexamethasone in adults with bacterial meningitis. [d]See Table 70–3 for pathogen-based definitive treatment recommendations. (Adapted, with permission, from Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. Arch Intern Med. 1999;159:1185–1194.)

Table 70–4

Pediatric Doses of Selected Agents Used in Bacterial Meningitis Treatment

	Neonates, 0–7 Days	Neonates, 8–28 Days	Infants and Children
Ampicillin	150 mg/kg IV per day in divided doses every 8 hours	200 mg/kg IV per day in divided doses every 6–8 hours	300 mg/kg IV per day in divided doses every 8 hours
Cefepime	—	—	150 mg/kg/day in divided doses every 8 hours
Cefotaxime	100–150 mg/kg IV per day in divided doses every 8–12 hours	150–200 mg/kg IV per day in divided doses every 6–8 hours	225–300 mg/kg/day in divided doses every 6–8 hours
Ceftriaxone	—	—	80–100 mg/kg IV per day in divided doses every 12 hours
Gentamicin	5 mg/kg IV per day in divided doses every 12 hours (with dosing based on serum levels)	7.5 mg/kg IV per day in divided doses every 8 hours with dosing based on serum levels	7.5 mg/kg IV per day in divided doses every 8 hours based on serum levels
Meropenem	—	—	120 mg/kg IV per day in divided doses every 8 hours
Nafcillin/ oxacillin	75 mg/kg IV per day in divided doses every 8–12 hours	Nafcillin: 100–150 mg/kg IV per day in divided doses every 6–8 hours; Oxacillin: 150–200 mg/kg IV per day in divided doses every 6–8 hours	200 mg/kg IV per day in divided doses every 6 hours max, 2 g pediatrics > 3 months of age
Penicillin G	0.15 million units/kg IV per day in divided doses 8–12 hours	0.2 million units/kg IV per day in divided doses every 6–8 hours	0.3 million units/kg IV per day in divided doses every 4–6 hours
Vancomycin	20–30 mg/kg IV per day in divided doses every 8–12 hours	30–45 mg/kg IV per day in divided doses every 6–8 hours	60 mg/kg IV per day in divided doses every 6 hours

LFTs, liver function tests; MIC, minimum inhibitory concentration.

Adapted, with permission, from Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis 2002;186(Suppl 2):S225–S233.

meningococcal vaccine protects against four of the five serotypes causing invasive disease (A, C, Y, and W-135). A separate vaccine product confers protection against serogroup B. Meningococcal vaccines can be used in outbreak situations, with protective antibodies measurable within 7 to 10 days. KEY CONCEPT Close contacts of patients with meningococcal infections should be evaluated for antimicrobial prophylaxis. Close contacts include members of the same household, individuals who share sleeping quarters, daycare contacts, and individuals exposed to oral secretions of meningitis patients. After consultation with the local health department, close contacts should receive prophylactic antibiotics to eradicate nasopharyngeal carriage of the organism. Household contacts of patients with meningococcal meningitis have a 400- to 800-fold increased risk of developing meningitis.[23] Prophylactic antibiotics should be started as soon as possible, preferably within 24 hours of exposure and within 14 days. Recommended regimens, all of which are 90% to 95% effective, for adults include rifampin 600 mg orally every 12 hours for 2 days, ciprofloxacin 500 mg orally for one dose, or ceftriaxone 250 mg intramuscularly for one dose. Regimens for children include rifampin 5 mg/kg orally every 12 hours for 2 days (< 1 month of age), rifampin 10 mg/kg orally every 12 hours for 2 days (> 1 month of age), or ceftriaxone 125 mg intramuscularly for one dose (< 12 years of age).[11,23] It is not known whether close contacts who have been vaccinated will benefit from prophylaxis. Patients with meningococcal meningitis who are treated with antibiotics other than third-generation cephalosporins also should be considered for prophylaxis to eradicate the nasopharyngeal carrier state.[22]

LO 8

▶ *Streptococcus pneumoniae Meningitis*

S. pneumoniae is the most common cause of meningitis in adults and in children younger than 2 years of age. Pneumococcus is associated with the highest mortality observed with bacterial meningitis in adults (14%–18%), and coma and seizures are more common in pneumococcal meningitis.[1-3] Patients at high risk for pneumococcal meningitis include the elderly, alcoholics, splenectomized patients, patients with sickle cell disease, and patients with cochlear implants. At least 50% of pneumococcal meningitis cases are due to a primary infection of the ears, sinuses, or lungs.

Due to increases in pneumococcal resistance to high-dose penicillin G, the preferred empirical treatment now includes a third-generation cephalosporin in combination with vancomycin.[11] All CSF isolates should be tested for penicillin and cephalosporin resistance by methods endorsed by the CLSI. Once *in vitro* sensitivity results are known, therapy may be tailored (see Table 70–3). Patients with a history of type I penicillin or cephalosporin allergy may be treated with vancomycin. Treatment should be continued for 10 to 14 days, after which no further maintenance therapy is required. Antimicrobial prophylaxis is not indicated for close contacts.

Administration of vaccines to high-risk individuals is a key strategy to reduce the risk of invasive pneumococcal disease. However, 2013 reports note only 82% of children aged 35 months completed the full series of the pneumococcal conjugate vaccine.[25] The 23-valent pneumococcal vaccine targets serotypes that account for more than 90% of invasive disease in high-risk patients. However, the 23-valent vaccine does not produce a reliable immunologic response in children younger than 2 years, nor does it reduce pneumococcal carriage. The 7-valent pneumococcal protein-polysaccharide conjugate vaccine used between 2000 and 2010 targeted the seven most common serotypes in children and provided protection (94% reduction) against invasive pneumococcal disease (such as sepsis and meningitis) in children younger than 5 years.[4,26,27] Widespread administration of the 7-valent conjugate vaccine to children has also contributed to a 28% reduction in invasive pneumococcal disease in adults.[4] PCV13, a 13-valent vaccine introduced in 2010, confers protection against serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. It is intended for use in children younger than 18 years in the same schedule as the 7-valent conjugate vaccine.[27] PCV13 is specifically recommended for immunocompromised children aged 6 to 18 years.[28] Based on additional data, newer recommendations also recommend vaccination with PCV13 in addition to PPSV23 in adults older than age 65 and aged 18 to 64 with immunocompromising conditions. Additionally, immunization schedules provided by Centers for Disease Control and Prevention (CDC) are updated at least annually and should be consulted for more details.

▶ *Haemophilus influenzae Meningitis*

Prior to the introduction of the Hib conjugate vaccine, *H. influenzae* type B was the most common cause of bacterial meningitis in the United States.[3,4] Routine inoculation of pediatric patients against Hib has significantly reduced the incidence of Hib meningitis between 1998 and 2007.[3,4] The Hib vaccine is also recommended for patients undergoing splenectomy. Hib meningeal disease is often associated with a parameningeal focus such as a sinus or middle ear infection. Due to β-lactamase–mediated resistance, the empirical treatment of choice is third-generation cephalosporins (eg, ceftriaxone and cefotaxime). Treatment should be continued for 7 days, after which no further maintenance therapy is required.

KEY CONCEPT Close contacts of patients with H. influenzae type B meningitis should be evaluated for antimicrobial prophylaxis. The risk of Hib meningitis in close contacts may be up to 200- to 1000-fold higher than in the general population.[7] Invasive Hib disease, including meningitis, should be reported to the local health department and the CDC. Prophylaxis to eliminate nasal and oropharyngeal carriage of Hib in exposed individuals should be initiated after consultation with local health officials. Rifampin (600 mg/day for adults; 20 mg/kg/day for children, maximum of 600 mg/day) is administered for 4 days.[11,16] Rifampin prophylaxis is not necessary for individuals who have received the full Hib vaccine series. Exposed, unvaccinated children between 12 and 48 months of age should receive one dose of vaccine, and

Patient Encounter 2, Part 1

BB is an 18-year-old college freshman who is brought to the ED with a 1-day history of extreme fatigue and fever. Her roommate brought her to ED because of confusion and vomiting. Vital signs and laboratory values include a rectal temperature of 38.6°C (101.5°F), respirations 24 per minute, heart rate 119 beats/min, and peripheral WBC of 22.1 × 10^3/mm^3 (22.1 × 10^9/L), with 72% (0.72) PMNs. Physical examination reveals an unresponsive patient with nuchal rigidity.

What signs and symptoms consistent with meningitis are present in BB?

What clues to causative pathogen are present in BB?

What empiric antimicrobial regimen should be started?

Patient Encounter 2, Part 2

BB underwent lumbar puncture. Initial results from CSF studies are WBC 1.82 × 10^3/mm^3 (1.82 × 10^9/L) with 76% (0.76) PMNs, protein 255 mg/dL (2550 mg/L), glucose 30 mg/dL (1.7 mmol/L), with a concurrent serum glucose of 110 mg/dL (6.1 mmol/L). Gram stain shows gram-positive diplococci and culture results identify *Neisseria* infection with a penicillin MIC of 1 mg/L. The patient is admitted to an acute care unit and remains clinically stable.

What complications is BB at risk for acutely? What potential long-term complications may result?

How can her antibiotic regimen be streamlined at this time?

How long should the antibiotics be continued?

unvaccinated children 2 to 11 months of age should receive three doses of vaccine, as well as rifampin prophylaxis.[11,16] According to the CDC, up to 18% of children at 35 months have not completed the Hib vaccine series.[25]

▶ *Listeria monocytogenes* Meningitis

L. monocytogenes is an intracellular gram-positive bacillus that contaminates foods, such as soft cheese, unpasteurized milk, raw meats and fish, processed meats, and raw vegetables. Bacteria from contaminated foods colonize the GI tract, pass into the bloodstream, and overcome natural cellular immune responses to cause infection. *L. monocytogenes* meningitis, usually observed in patients at extremes of age and in immunocompromised patients with depressed cellular immunity (including patients with leukemia, solid-organ transplants, and HIV/AIDS) has an overall mortality rate of up to 30% and is associated with miscarriage when infection occurs during pregnancy.[29,30]

Only a limited number of antibiotics show bactericidal activity against *L. monocytogenes*. The combination of high-dose ampicillin or penicillin G and an aminoglycoside is synergistic and bactericidal against *L. monocytogenes*. A total treatment course of at least 3 weeks is required. Because of concerns about the risk of nephrotoxicity with an extended treatment course of aminoglycosides, patients are treated with combination therapy for 10 days and may finish out the remainder of their treatment with ampicillin or penicillin alone.[30] In penicillin-allergic patients, trimethoprim-sulfamethoxazole is the agent of choice due to documented *in vitro* bactericidal activity against *L. monocytogenes*, as well as good CNS penetration. Vancomycin and cephalosporins are not effective treatments for *L. monocytogenes* meningitis. Prophylaxis is not needed for close contacts, nor is suppressive therapy indicated. Patients with severe depression of cell-mediated immunity should be advised to avoid foods that may be contaminated with *L. monocytogenes.*

▶ Group B Streptococcus Meningitis

Infection with GBS (eg, *S. agalactiae*) is the most common cause of neonatal sepsis and meningitis. Around 15% to 35% of pregnant women are a carrier of GBS in the vagina or rectum. Group B streptococci can be acquired during childbirth after exposure to infected secretions from the mother's birth canal or rectum. Neonates born to women who are carriers are at very high risk (1 of every 100–200 babies) of developing invasive group B streptococcal disease.[31] Neonatal meningitis is associated with significant morbidity and mortality. Synergistic treatment with penicillin or ampicillin, plus gentamicin, for 14 to 21 days is recommended for group B streptococcal meningitis.[11]

To reduce the risk of clinical group B streptococcal disease in neonates, pregnant women should be screened at 35 to 37 weeks' gestation to determine whether they are carriers of group B streptococci.[31] Intrapartum antibiotics (eg, penicillin or ampicillin) are recommended for pregnant women with the following characteristics: group B streptococcal carrier state detected at screening, history of group B streptococcal bacteriuria at any time during pregnancy, and history of delivery of infant with invasive group B streptococcal disease.[31]

▶ Gram-Negative Bacillary Meningitis

Meningitis caused by enteric gram-negative bacilli is an important cause of morbidity and mortality in populations at risk, including those with diabetes, malignancy, cirrhosis, immunosuppression, advanced age, parameningeal infection, and/or a defect allowing communication from skin to CNS (eg, neurosurgery, congenital defects, cranial trauma).[7]

The optimal treatment for gram-negative bacillary meningitis is not well defined. The introduction of extended-spectrum cephalosporins has improved patient outcomes significantly. Although the third-generation cephalosporins ceftriaxone and cefotaxime provide good coverage for most Enterobacteriaceae, these antibiotics are not active against *P. aeruginosa*. Ceftazidime, cefepime, and carbapenems are effective in pseudomonal meningitis.[15,17] Addition of an aminoglycoside may improve treatment results; however, CNS penetration of aminoglycosides is extremely poor, even in the setting of inflamed meninges. Intrathecal or intraventricular administration of aminoglycosides may be useful, but intraventricular antibiotics have been associated with increased mortality in neonates.[15,32] Intrathecal therapy is accomplished by administering the antibiotic into the CSF via LP, whereas intraventricular therapy is usually administered into a reservoir implanted in the ventricles of the brain.

Initial therapy of suspected or documented pseudomonal meningitis should include an antipseudomonal β-lactam (eg, cefepime, meropenem) plus an aminoglycoside (eg, tobramycin, amikacin). Although the carbapenem imipenem-cilastatin has similar activity to these β-lactams, its use is not recommended in meningitis because of the risk of seizures. Aztreonam, high-dose ciprofloxacin, and colistin are alternative treatments for pseudomonal meningitis, although local susceptibility rates should be considered before initiating alternative therapy. Local therapy (ie, intrathecal or intraventricular therapy) may be indicated in patients with multidrug-resistant gram-negative bacillary meningitis or in patients who fail to improve on IV antibiotics alone. In cases of multidrug-resistant pathogens, alternative pharmacodynamic dosing strategies such as continuous or extended infusion of β-lactam antimicrobials may be considered to optimize target attainment (time greater than minimum inhibitory concentration [MIC]). Given the differences in local hospital resistance patterns, administration of pathogen-directed treatment is very important after microbiology results become available. Therapy for gram-negative bacillary meningitis should be continued for at least 21 days.

▶ Postoperative Infections in the Neurosurgical Patient and Shunt Infections

Patients who undergo neurosurgical procedures or have invasive or implanted foreign devices (eg, CSF shunts, intraspinal pumps or catheters, epidural catheters) are at risk for CNS infections. Key pathogens in postneurosurgical infections

include coagulase-negative staphylococci, *S. aureus*, streptococci, propionibacteria, and gram-negative bacilli, including *P. aeruginosa*. Clinical signs and symptoms may be similar to those of other CNS infections, and there also may be evidence of malfunction of implanted hardware or visible signs of a postoperative wound infection.

Empirical therapy for postoperative infections in neurosurgical patients (including patients with CSF shunts) should include vancomycin in combination with either cefepime, ceftazidime, or meropenem. Linezolid reaches adequate CSF concentrations and resolves cases of meningitis refractory to vancomycin.[30,33] However, data with linezolid are limited. The addition of rifampin may be considered for treatment of shunt infections. Removal of infected devices is desirable; aggressive antibiotic therapy (including high-dose IV antibiotic therapy plus intraventricular vancomycin and/or tobramycin) may be effective for patients in whom hardware removal is not possible.[34] If methicillin-resistant *S. aureus* is identified as the causative organism, daptomycin may be considered an alternative therapy.[35]

The use of prophylactic antibiotics against meningitis postcraniotomy remains controversial.[36,37] One meta-analysis suggests that prophylaxis reduces rates of postoperative meningitis by nearly one-half.[36] Breakthrough meningitis that does occur may be a result of drug-resistant pathogens.[37]

Brain abscesses are localized collections of pus within the cranium. These infections are difficult to treat due to the presence of walled-off infections in the brain tissue reducing antibiotic penetration. In addition to appropriate antimicrobial therapy (a discussion of which is beyond the scope of this chapter), surgical debridement is often required as an adjunctive measure. Surgical debridement may also be required in the management of neurosurgical postoperative infections.

► *Viral Encephalitis and Meningitis*

Viral encephalitis and meningitis may mimic bacterial meningitis on clinical presentation but often can be differentiated by CSF findings (see Table 70–2). The most common viral pathogens are enteroviruses, which cause approximately 85% of cases of viral CNS infections.[7] Other viruses that may cause CNS infections include arboviruses, HSV, cytomegalovirus, varicella-zoster virus, rotavirus, coronavirus, influenza viruses A and B, West Nile virus, and Epstein-Barr virus. Viral CNS infections are acquired through hematogenous or neuronal spread.[7] Most cases of enteroviral meningitis or encephalitis are self-limiting with supportive treatment.[38] However, arbovirus, West Nile virus, and Eastern equine virus infections are associated with a less favorable prognosis.

In contrast to other viral encephalitides, HSV type 1 and 2 encephalitis are treatable. Although rare (one case per 250,000 population per year in the United States), HSV encephalitis is a serious, life-threatening infection.[39] More than 90% of HSV encephalitis in adults is due to HSV type 1, whereas HSV type 2 predominates in neonatal HSV encephalitis (> 70%).[40] HSV encephalitis is the result of reactivation of a latent infection (two-thirds of cases) or a severe case of primary infection (one-third). Without effective treatment, the mortality rate may be as high as 85%, and survivors often have significant residual neurologic deficits. In accordance with 2008 IDSA guidelines, high-dose IV acyclovir is the drug of choice, given for 2 to 3 weeks at a dose of 10 mg/kg IV every 8 hours in adults, based on ideal body weight, and for 3 weeks at a dose of 20 mg/kg IV every 8 hours in neonates.[41] Patients receiving acyclovir should maintain adequate hydration (consider continuous IV hydration) to help prevent acute kidney injury secondary to crystal nephropathy.[41] Foscarnet 120 to 200 mg/kg/day divided every 8 to 12 hours for 2 to 3 weeks is the treatment of choice for acyclovir-resistant HSV.[41]

► *Opportunistic CNS Infections*

Cerebral Toxoplasmosis Across the globe, cerebral toxoplasmosis represents the most common focal brain infection in HIV-infected patients. Infection rates in the United States vary but are reported to be approximately 15% among patients with AIDS.[42] The majority of cases occur in patients with $CD4^+$ cell counts less than 100 cells/mm^3 (100×10^6/L). Potent antiretroviral therapy and primary prophylaxis (first-line option is sulfamethoxazole-trimethoprim) in IgG-positive patients has greatly reduced the disease burden.[43] First-line therapy in toxoplasmosis encephalitis is pyrimethamine plus sulfadiazine, given concomitantly with leucovorin to prevent severe hematologic adverse effects secondary to pyrimethamine (see tables for dosing).[43] Clindamycin may be substituted for sulfadiazine in cases of contraindications to sulfa-based therapy. Sulfamethoxazole-trimethoprim may also be an option, specifically in patients unable to take oral therapy. Adjunctive corticosteroids and anticonvulsant therapy should be considered to reduce sequelae from the inflammatory process and control active seizures, respectively.[43]

Cryptococcal Meningitis CNS disease secondary to *Cryptococcus neoformans* is primarily observed in severely immunocompromised hosts, such as those with HIV infection. Potent antiretroviral therapy has significantly reduced the disease burden from preantiretroviral therapy rates of 5% to 8% in developed countries. The majority of disease occurs in patients with $CD4^+$ cell counts less than 50 cells/mm^3 (50×10^6/L). First-line therapy is considered amphotericin B deoxycholate 0.7 mg/kg IV daily plus flucytosine 100 mg/kg/day orally in four divided doses for a minimum of 2 weeks.[43] Therapeutic drug monitoring may be considered for flucytosine to help reduce the risk of adverse effects. Development of renal dysfunction as a result of disease and/or drug toxicity should be closely monitored and may prompt dose reduction or possible switch to alternative lipid formulations of amphotericin, which may be less nephrotoxic. High-dose fluconazole is considered an alternative first-line therapy, especially in resource-limited areas. Secondary prophylaxis with fluconazole for an indefinite period is recommended following the completion of at least 2 weeks of induction therapy and 8 weeks of maintenance therapy with fluconazole.[43]

► *Adjunctive Dexamethasone Therapy*

The adjunctive agent dexamethasone improves outcomes in selected patient populations with bacterial meningitis. Dexamethasone inhibits the release of proinflammatory cytokines and limits the CNS inflammatory response stimulated by infection and antibiotic therapy.

Clinical benefit in reducing neurologic deficits (primarily by reducing hearing loss) has been observed in infants and children, if dexamethasone is initiated prior to antibiotic therapy.[1,44] The American Academy of Pediatrics recommends dexamethasone (0.15 mg/kg IV every 6 hours for 2 to 4 days) for infants and children at least 6 weeks of age with Hib meningitis and consideration of dexamethasone in pneumococcal meningitis.[11,45] In contrast to this recommendation, a large multicenter cohort study failed to show any mortality benefit of adjunctive dexamethasone therapy regardless of age or responsible pathogen

(*S. pneumoniae* or *N. meningitidis*).[46] Dexamethasone should be initiated 10 to 20 minutes before or no later than the time of initiation of antibiotic therapy; it is not recommended for infants and children who have already received antibiotic therapy because it is unlikely to improve treatment outcome in these patients. There are insufficient data to make a recommendation regarding the use of adjunctive dexamethasone therapy in neonatal meningitis.

In adults, a significant benefit was observed with dexamethasone in reducing meningitis complications, including death, particularly in patients with pneumococcal meningitis.[47] The IDSA recommends dexamethasone 0.15 mg/kg IV every 6 hours for 2 to 4 days (with the first dose administered 10–20 minutes before or with the first dose of antibiotics) in adults with suspected or proven pneumococcal meningitis.[11] Dexamethasone is not recommended for adults who have already received antibiotic therapy. Some clinicians would administer dexamethasone to all adults with meningitis pending results of laboratory tests. Benefit of dexamethasone in bacterial meningitis in an HIV-positive population has not been clearly established.[48]

There is controversy regarding the administration of dexamethasone to patients requiring vancomycin for pneumococcal meningitis. Animal models indicate that concurrent steroid use reduces vancomycin penetration into the CSF by 42% to 77% and delays CSF sterilization.[15] A prospective evaluation in patients with pneumococcal meningitis receiving vancomycin and adjunctive dexamethasone demonstrated that adequate concentrations of vancomycin (nearly 30% of serum concentrations) were achievable in the CSF, provided appropriate vancomycin dosage was utilized.[49] Treatment failures have been reported in adults with resistant pneumococcal meningitis who were treated with dexamethasone, but the risk–benefit of using dexamethasone in these patients cannot be defined at this time. Animal models indicate a benefit of adding rifampin in patients with resistant pneumococcal meningitis whenever dexamethasone is used.[15,17]

OUTCOME EVALUATION

Monitor patients with CNS infections continuously throughout their treatment course to evaluate their progress toward achieving treatment goals, including relief of symptoms, eradication of infection, and reduction of inflammation to prevent death and the development of neurologic deficits. These treatment goals are best achieved by appropriate parenteral antimicrobial therapy, including empirical therapy to cover the most likely pathogens, followed by directed therapy after culture and sensitivity results are known. KEY CONCEPT Components of a monitoring plan to assess efficacy and safety of antimicrobial therapy of CNS infections include clinical signs and symptoms and laboratory data (eg, CSF findings, culture, sensitivity data).

During the patient's treatment course, monitor clinical signs and symptoms at least three times daily. Trends are more important than one-time assessments. Expect fever, headache, nausea and vomiting, and malaise to begin to improve within 24 to 48 hours of initiation of antimicrobial therapy and supportive care. Evaluate the patient for resolution of neurologic signs and symptoms, such as altered mental status and nuchal rigidity, as the infection is eradicated and inflammation is reduced within the CNS. Expect improvement and subsequent resolution of signs and symptoms as the treatment course continues. At the time of hospital discharge, arrange outpatient follow-up for several weeks to months depending on the causative pathogen, clinical treatment course, and patient's underlying comorbidities.

Patient Encounter 2, Part 3

Upon review of her records, BB did not receive vaccination against *Neisseria meningitis* prior to college. In addition, her roommates are concerned about getting sick and inquire about measures to help prevent disease.

Who should receive antimicrobial prophylaxis for Neisseria?

Who should receive vaccination against meningococcal disease?

Patient Care Process

Collect Information:

- Obtain a complete patient allergy history, including details on the severity of reactions, and obtain a medication history
- Determine if patient has received recent antibiotics that may influence LP results or treatment decisions
- Review laboratory values, past medical history, and vaccination history

Assess the Information:

- Analyze CSF findings to determine the likely etiology of meningitis
- Assess the patient history for possible risk factors for specific etiologies of meningitis
- Determine from a medication history if any medicines may be associated with drug-induced aseptic meningitis

Develop a Care Plan:

- Based on patient-specific factors and local susceptibility patterns, determine appropriate empirical antimicrobial treatment plan
- Assess LP results, results of antigenic testing, and culture and susceptibility for additional data to help streamline therapy

Implement the Care Plan:

- Collaborate with treatment team to ensure timely administration of antibiotic in relation to performing LP and obtaining blood cultures
- Collaborate with treatment team to determine appropriate administration of adjunctive corticosteroid therapy

Follow-up: Monitor and Evaluate:

- Monitor patient for any antimicrobial-related adverse events. Provide recommendations for necessary prophylaxis based on causative pathogen and exposure history
- Determine appropriate length of therapy for diagnosed CNS infection
- Provide recommendations for outpatient parenteral therapy as needed upon discharge from acute care facility

Monitoring of laboratory tests is important in patients receiving treatment for CNS infections. Monitor CSF and blood cultures so that antimicrobial therapy can be tailored to the etiologic organisms. Follow-up cultures may be obtained to prove eradication of the organism(s) or treatment failure. Although repeat LP generally is not performed, consider repeat LP for patients who do not respond clinically after 48 hours of appropriate antimicrobial therapy, especially those with resistant pneumococcus who receive dexamethasone.[11] Other candidates for repeat LP include those with infection with gram-negative bacilli, prolonged fever, and recurrent meningitis. Repeat the LP in neonates to determine the duration of therapy. Repeat LP also may be performed to relieve elevated intracranial pressure. Expect repeat blood cultures to become negative quickly during therapy and the serum WBC count to improve and normalize with appropriate antimicrobial therapy.

Evaluate antimicrobial dosing regimens to ensure efficacy of the treatment regimen. Trough vancomycin concentrations of 15 to 20 mg/L (10–14 μmol/L) are recommended for the treatment of CNS infections.[44] Monitor patients for drug adverse effects, drug allergies, and drug interactions. The specific safety monitoring plan will depend on the antibiotic(s) used (Table 70–3). Pay close attention to concomitant medications in patients on rifampin for treatment or prophylaxis. Rifampin is a potent inducer of hepatic metabolism and may reduce the efficacy of other drugs metabolized by the cytochrome P-450 enzyme pathway.

Abbreviations Introduced in This Chapter

CDC	Centers for Disease Control and Prevention
CLSI	Clinical and Laboratory Standards Institute
CNS	Central nervous system
CSF	Cerebrospinal fluid
DIC	Disseminated intravascular coagulation
ESBL	Extended spectrum β-lactamase
GBS	Group B *Streptococcus*
Hib	*Haemophilus influenzae* type B
HSV	Herpes simplex virus
IDSA	Infectious Diseases Society of America
IL-1	Interleukin 1
LP	Lumbar puncture
MBC	Minimum bactericidal concentration
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
MRSE	Methicillin-resistant *Staphylococcus epidermidis*
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PMN	Polymorphonuclear cell
SJS	Stevens-Johnson Syndrome
TNF-α	Tumor necrosis factor-alpha

REFERENCES

1. van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2003;3:CD004405.
2. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med. 2011;364(21):2016–2025.
3. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis. 2014;14(9):813–819.
4. Levy C, Varon E, Picard C, et al. Trends of Pneumococcal meningitis in children after introduction of the 13-valent pneumococcal conjugate vaccine in France. Ped Infect Dis. 2014;33(12):1216–1221.
5. Marrie TJ, Tyrrell GJ, Majumdar SR, Eurich DT. The effect of age on the manifestations and outcomes of invasive pneumococcal disease in adults. Am J Med. 2018;131(1):100.e1–100.e7.
6. Sejvar JJ. The evolving epidemiology of viral encephalitis. Curr Opin Neurol. 2006;19:350–357.
7. Mitropoulous IF, Hermsen ED, Schafer JA, Rotschafer JC. Central nervous system infections. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 7th ed. New York City, NY: McGraw-Hill; 2008:1743–1760.
8. Khetsuriani N, Holman RC, Anderson LJ. Burden of encephalitis-associated hospitalizations in the United States, 1988–1997. Clin Infect Dis. 2002;35:175–182.
9. Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis. 2002;186(suppl 2):S225–S233.
10. Kim KS. Pathogenesis of bacterial meningitis: from bacteraemia to neuronal injury. Nat Rev Neurosci. 2003;4:376–385.
11. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis. 2004;39:1267–1284.
12. Lu CH, Huang CR, Chang WN, et al. Community-acquired bacterial meningitis in adults: the epidemiology, timing of appropriate antimicrobial therapy, and prognostic factors. Clin Neurol Neurosurg. 2002;104:352–358.
13. van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM. Community-acquired bacterial meningitis in adults. N Engl J Med. 2006;354:44–53.
14. Pankey GA, Sabath LR. Clinical relevance of bacterio-static versus bactericidal mechanisms of action in the treatment of gram-positive bacterial infections. Clin Infect Dis. 2004;38:864–870.
15. Sinner SW, Tunkel AR. Antimicrobial agents in the treatment of bacterial meningitis. Infect Dis Clin N Am. 2004;18:581–602.
16. Bashir HE, Laundy M, Booy R. Diagnosis and treatment of bacterial meningitis. Arch Dis Child. 2003;88:615–620.
17. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. N Engl J Med. 1997;336(10):708–716.
18. Tice AD, Strait K, Ramey R, et al. Outpatient parenteral antimicrobial therapy for central nervous system infections. Clin Infect Dis. 1999;29:1394–1399.
19. Jones ME, Draghi DC, Karlowsky JA, Sahm DF, Bradley JS. Prevalence of antimicrobial resistance in bacteria isolated from central nervous system specimens as reported by U.S. hospital laboratories from 2000 to 2002. Ann Clin Microb. 2004;3:3.
20. Patton ME, Stephens D, Moore K, MacNeil JR. Updated recommendations for Use of MenB-FHbp Serogroup B Meningococcal Vaccine—Advisory Committee on Immunization Practices. Morb Mortal Wkly Rep. 2017;66:509–513.
21. Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis. 2010;10(1):32–42.
22. Campos-Outcalt D. Meningococcal vaccine: new product, new recommendations. J Fam Pract. 2005;54(4):324–326.
23. Rosenstein NE, Perkins BA, Stephens DS, Popovic T, Hughes JM. Meningococcal disease. N Engl J Med. 2001;344(18):1378–1388.
24. Nudelman Y, Tunkel AR. Bacterial meningitis epidemiology, pathogenesis, and management update. Drugs. 2009;69(18): 2577–2596.
25. Centers for Disease Control and Prevention. National, state and selected local area vaccination coverage among children aged 19–35 months—United States, 2013. MMWR. 2014;63(No. RR#34):741–748.

26. Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥ 65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2014;63(37):822–825.
27. Advisory Committee on Immunization Practices (ACIP). Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. MMWR. 2011;59:RR-11.
28. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2013;62(25):521–524.
29. Mylonakis D, Hohmann EL, Calderwood SB. Central nervous system infection with Listeria monocytogenes: 33 years' experience at a general hospital and review of 776 episodes from the literature. Medicine. 1998;77(5):313–336.
30. Hof H. An update on the medical management of listeriosis. Expert Opin Pharmacother. 2004;5(8):1727–1735.
31. Department of Health and Human Services/CDC. Prevention of perinatal group B streptococcal disease. MMWR. 2010;59:RR-10.
32. Shah S, Ohlsson A, Shah V. Intraventricular antibiotics for bacterial meningitis in neonates. Cochrane Database Syst Rev. 2004;4:CD004496.
33. Villani P, Regazzi MB, Marubbi F, et al. Cerebrospinal fluid linezolid concentrations in postneurosurgical central nervous system infections. Antimicrob Agents Chemother. 2002;46(3):936–937.
34. Anderson EJ, Yogev R. A rational approach to the management of ventricular shunt infections. Pediatr Infect Dis J. 2005;24:557–558.
35. Lee DH, Palermo B, Chowdhury M. Successful treatment of methicillin-resistant *Staphylococcus aureus* meningitis with daptomycin. Clin Infect Dis. 2008;47:588–589.
36. Barker FG. Efficacy of prophylactic antibiotics against meningitis after craniotomy: a meta-analysis. Neurosurgery. 2007;60:887–894.
37. Korinek AM, Golmard JL, Elcheick A, et al. Risk factors for neurosurgical site infections after craniotomy: a critical reappraisal of antibiotic prophylaxis on 4,578 patients. Br J Neurosurg. 2005;19:155–162.
38. Sawyer MH. Enterovirus infections: diagnosis and treatment. Pediatr Infect Dis J. 1999;18(12):1033–1040.
39. Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. Herpes. 2004;11(suppl 2):57A–64A.
40. Kimberlin D. Herpes simplex virus, meningitis and encephalitis in neonates. Herpes. 2004;11(suppl 2):65A–76A.
41. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47:303–327.
42. Pereira-Chioccola VL, Vidal JE, Su C. Toxoplasma gondii infection and cerebral toxoplasmosis in HIV-infected patients. Future Microbiol. 2009;4(10):1363–1379.
43. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed August 21, 2014.
44. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. Arch Intern Med. 1999;159(11):1185–1194.
45. American Academy of Pediatrics. Pneumococcal infections. In: Pickering LK, ed. Red Book: 2003 Report of the Committee on Infectious Diseases, 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:490–500.
46. Mongelluzzo J, Mohamad Z, Ten Have TR, Shah SS. Corticosteroids and mortality in children with bacterial meningitis. JAMA. 2008;299(17):2048–2055.
47. de Gans J, van de Beek D, European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. Dexamethasone in adults with bacterial meningitis. N Engl J Med. 2002;347(20):1549–1556.
48. Scarborough M, Gordon SB, Whitty CJM, et al. Corticosteroids for bacterial meningitis in adults in Sub-Saharan Africa. N Engl J Med. 2007;357:2441–2450.
49. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. Clin Infect Dis. 2007;44:250–255.

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71 Lower Respiratory Tract Infections

Diane M. Cappelletty

LEARNING OBJECTIVES

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

LO

1. List the common pathogens that cause community-acquired pneumonia (CAP), aspiration pneumonia, ventilator-associated pneumonia (VAP), and hospital-associated pneumonia (HAP).
2. Explain the pathophysiology of pneumonia and associated host defenses.
3. List the signs and symptoms associated with CAP and VAP.
4. Identify patient and organism factors required to guide the selection of a specific antimicrobial regimen for an individual patient.
5. Design an appropriate empirical antimicrobial regimen based on patient-specific data for an individual with CAP, aspiration pneumonia, HAP, and VAP.
6. Design an appropriate antimicrobial regimen based on both patient- and organism-specific data.
7. Develop a monitoring plan based on patient-specific information for a patient with one of the four categories of pneumonia.
8. Apply the complete Patient Care Process to caring for patients with any type of pneumonia.
9. Formulate appropriate educational information to be provided to a patient with pneumonia.
10. Explain prevention of pneumonia via immunization and include who the appropriate patient groups are for receiving the various vaccines.

INTRODUCTION

Pneumonia is inflammation of the lung with consolidation. The cause of the inflammation is infection, which can be caused by a wide range of organisms. KEY CONCEPT There are four classifications of pneumonia: community-acquired, aspiration, hospital-acquired, and ventilator-associated. Patients who develop pneumonia in the outpatient setting and have not been in any health care facilities, which include wound care and hemodialysis clinics, have community-acquired pneumonia (CAP). Pneumonia can be caused by aspiration of either oropharyngeal or gastrointestinal contents. Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or more after admission.[1] Ventilator-associated pneumonia (VAP) requires endotracheal intubation for at least 48 hours before the onset of pneumonia.[1] Health care–associated pneumonia was addressed in the 2005 VAP and HAP guidelines but was eliminated in the 2016 guidelines due to the lack of resistant organisms associated as the cause.[2] The CAP guidelines might address health care–associated pneumonia; however, the updated guidelines will not be available until summer 2018 which is after the printing of this edition.

LO 1

EPIDEMIOLOGY AND ETIOLOGY

Etiology and Mortality Rates

KEY CONCEPT The etiology of bacterial pneumonia varies in accordance with the type of pneumonia. Table 71–1 lists the more common pathogens associated with the various types or classifications of pneumonia. *Streptococcus pneumoniae* colonizes the nasopharyngeal flora in up to 50% of healthy adults and may colonize the lower airways in individuals with chronic bronchitis.[2,3] It possesses many virulence factors, enhancing its ability to cause infection in the respiratory tract. KEY CONCEPT Therefore, it is not surprising that *S. pneumoniae* is the predominant bacterial pathogen associated with CAP. The second most common pathogen is one of the atypical organisms, *Mycoplasma pneumoniae*. Nontypeable *Haemophilus influenzae* intermittently colonizes about 80% of the population, and the incidence of permanent colonization increases in chronic obstructive pulmonary disease (COPD) patients and those with cystic fibrosis. Therefore, the likelihood of nontypeable *H. influenzae* causing pneumonia increases in COPD patients. *Moraxella catarrhalis* is a more common cause of pneumonia in the very young and the very old. *Chlamydophila pneumoniae* and *Legionella pneumophila* are less frequent causes than the other bacterial and atypical organisms. Community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is associated with necrotizing and severe pneumonia in healthy children and young adults. Less than 2% of all CA-MRSA infections are pneumonia (most are skin and soft tissue); however, the number of case reports of pneumonia are increasing.[4,5]

LO 1

LO 1

Viruses are a common cause of CAP in children (about 65%) and in adults ranging from 12% to 29%.[5-7] Mixed infections of viruses and bacteria have been increasingly identified in 11% to 56% of cases.[5-8] Viruses most often associated with pneumonia in adults include influenza A and B and rhinoviruses, but

Table 71–1

Common Pathogens by Type of Pneumonia

Type of Pneumonia	Common Pathogens
Community	Aerobic bacteria: *S. pneumoniae, H. influenzae, M. catarrhalis* Atypical: *M. pneumoniae, C. pneumoniae, L. pneumophila,* respiratory viruses (rhinoviruses and influenza most common)
Aspiration	Oral contents: Anaerobes, *Viridans* streptococci GI contents with pH increase Enteric gram-negative bacilli
Hospital	*S. pneumoniae,* MSSA, *E. coli, K. pneumoniae* (*M. pneumoniae, C. pneumoniae* are rare) (MDR pathogen risk factors present; MRSA, *P. aeruginosa*, extended-spectrum β-lactamase-producing gram-negative bacilli, carbapenemase-producing gram-negative bacilli)
Ventilator	MRSA, extended-spectrum β-lactamase-producing gram-negative bacilli, *P. aeruginosa, Acinetobacter* spp., carbapenemase-producing gram-negative bacilli

MDR, multi-drug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus.*

can be caused by adenoviruses, enteroviruses, cytomegalovirus, varicella-zoster virus, herpes simplex virus, and others. In children, viral pneumonia is more commonly caused by respiratory syncytial virus, influenza A, and parainfluenza, and less commonly by those listed previously for adults. Influenza is associated with seasonal local outbreaks (epidemics) and global outbreaks (pandemics). Influenza viruses are characterized and named for the hemagglutinin (H) and neuraminidase (N) proteins on the surface of the viruses. There are 16 hemagglutinin and 9 neuraminidase subtypes of influenza A, and H1–3 and N1 and 2 are the principal antigenic types found in humans.[9]

Mortality associated with CAP is dependent on the severity of the illness and the age of the patient. In elderly patients admitted to the hospital with severe pneumonia, the mortality rate is up to 40%.[10-13] In the outpatient setting (mild to moderate disease), the mortality rate is less than 5%.[14] Mortality among case reports of CA-MRSA necrotizing pneumonia is 42%.[4] Pneumonia owing to aspiration of oral contents is caused by a variety of anaerobes (*Bacteroides* spp., *Fusobacterium* spp., *Prevotella* spp., and anaerobic gram-positive cocci) as well as *Streptococcus* spp. *Moraxella catarrhalis* and *Eikenella corrodens* may be involved but much less frequently.[15,16] When gastric contents are aspirated, enteric gram-negative bacilli and *Staphylococcus aureus* are more commonly the pathogens.[16]

HAP and VAP may be caused by a wide spectrum of organisms. HAP and VAP pathogens are influenced by risk factors for multidrug-resistant (MDR) bacteria. These factors include: intravenous antibiotic use within the past 90 days, septic shock at the time of HAP or VAP, ARDS preceding VAP, five or more days of hospitalization, and acute renal replacement therapy.[1] MDR organisms include extended spectrum β-lactamase and/or carbapenemase-producing enteric gram-negative bacilli, *Pseudomonas aeruginosa*, *Acinetobacter* spp., or MRSA. The number of infections caused by MDR bacteria is increasing significantly in hospitalized patients.[1,5,13,17-19]

PATHOPHYSIOLOGY

Local Host Defenses

Local host defenses of both the upper and lower respiratory tract along with the anatomy of the airways are important in preventing infection. Upper respiratory defenses include the mucociliary apparatus of the nasopharynx, nasal hair, normal bacterial flora, IgA, and complement. Local host defenses of the lower respiratory tract include cough, mucociliary apparatus of the trachea and bronchi, antibodies (IgA, IgM, and IgG), complement, and alveolar macrophages. Mucous lines the cells of the respiratory tract, forming a protective barrier for the cells. This minimizes the ability of organisms to attach to the cells and initiate the infectious process. The squamous epithelial cells of the upper respiratory tract are not ciliated, but those of the columnar epithelial cells of the lower tract are. The cilia beat in a uniform fashion upward, moving particles up and out of the lower respiratory tract.

Particles greater than 10 microns (μm) are efficiently trapped by mechanisms of the upper airway and are removed from the nasopharynx either by swallowing or by expulsion. The mucociliary apparatus of the trachea and bronchi along with the sharp angles of the bronchi often are effective at trapping and eliminating particles that are 2 to 10 μm in size. Particles in the range of 0.5 to 1 μm may consistently reach the alveolar sacs of the lung. Microorganisms fall within this size range, and if they reach the alveolar sacs, then infection may result if alveolar macrophages and other defenses cannot contain the organisms.

Aspiration

Aspiration of the oropharyngeal or gastric contents may lead to aspiration pneumonia or chemical (acid) pneumonitis. Risk factors for aspiration include dysphagia, change in oropharyngeal colonization, gastroesophageal reflux (GER), and decreased host defenses.

Dysphagia can be caused by stroke or other neurologic disorders, seizures, alcoholism, and aging.[15] Oropharyngeal colonization may be altered by oral/dental disease, poor oral hygiene, tube feedings, or medications. This could result in a higher number of anaerobic organisms in the oral cavity or colonization with enteric gram-negative bacilli.[15] Acid suppression is an important factor in the treatment of GER disease, which may allow enteric gram-negative bacilli to colonize the gastric contents. Finally, impaired mucous production or cilia function, decreased immunoglobulin in secretions, and altered cough reflex may increase the likelihood of infection following an aspiration. The infection can result in a necrotizing pneumonia or lung abscess.

Inflammatory Response

Once breakdown of the local host defenses occurs and organisms invade the lung tissue, an inflammatory response is generated either by the organisms causing tissue damage or by the immune response to the presence of the organisms. This inflammatory

Patient Encounter 1

A 68-year-old woman, who only speaks Spanish, presents to your ED with difficulty breathing, coughing, and shortness of breath. It is late October and she collapsed in her front yard while raking leaves, her neighbors immediately called 911. Her physical examination reveals that she is easily confused and oriented name and place (×2), has decreased breath sounds on the right and left sides, and has rales and crackles in both lower lobes. Her temperature is 38.9°C (102.0°F), respiratory rate is 20 breaths/min, oxygen saturation 87% on room air, and blood pressure is 120/80 mm Hg. She is coughing up greenish sputum. The hospital interpreter is called to the ED to translate for this patient.

What are her signs and symptoms of pneumonia?

What are the top two bacterial organisms that could be causing the pneumonia?

What is the top atypical organism, as well as the top two viruses that could be causing the pneumonia?

What are the advantages and disadvantages of having a hospital employed interpreter for the patient?

response either can remain localized in the infected tissue or can become systemic. The role of the alveolar macrophages is twofold. First, to engulf the organisms to contain the infection, and second, to process the antigens for presentation in regional lymph nodes in order to generate a specific immune response by either the cell-mediated or humoral system, or both. The macrophages release cytokines in the area of the infection, which result in increased mucous production, constricting the local vasculature, and lymphatic vessels and attraction of other immune cells to the site. The increase in mucus is associated with symptoms such as cough and sputum production. If tumor necrosis factor alpha (TNF-α) and interleukins-1 and -6 are released systemically, then the symptoms become more severe and include hypotension, organ dysfunction, and/or a septic or septic-shock clinical presentation.

Patient Encounter 2

A 52-year-old man was admitted to the hospital for abdominal surgery. He developed complications postoperatively and was intubated 6 days ago. The nurses note an increase in the amount and purulence of his sputum. Attempts yesterday and today to wean the patient off the ventilator have failed. He is sedated but does respond to commands. His temperature is 38.4°C (101.1°F), blood pressure is 120/84 mm Hg, and white blood cell (WBC) 20.4 × 10^3/mm^3 (20.4 × 10^9/L) with a cell differential of 75% (0.75) neutrophils, 7% (0.07) bands, 15% (0.15) lymphocytes, and 3% (0.03) monocytes. The chest x-ray revealed left middle lobe infiltrates.

What are his signs and symptoms of pneumonia?

What are the top three bacterial organisms that could be causing the pneumonia?

CLINICAL PRESENTATION AND DIAGNOSIS

Several scoring systems are available for assessing the severity of the pneumonia: the Pneumonia Severity Index (PSI); confusion, uremia, respiratory rate, blood pressure (CURB); CURB-65 (for those ≥ 65 years of age), and systolic BP, oxygenation, age, and respiratory rate (SOAR).[10,13] These models are used to help determine the severity of illness, prognosis (mortality risk), and the need for hospitalization and then to help guide in the selection of antimicrobial therapy, along with the use of published guidelines.[10,13,14] For example, PSI or CURB-65 scores less than or equal to 70 and less than 2, respectively, correlate with mild disease that should be treated in the outpatient setting.

TREATMENT

LO 5

KEY CONCEPT The goal of antibiotic therapy is to eliminate the patient's symptoms, minimize or prevent complications, and decrease mortality. Potential complications secondary to pneumonia include further decline in pulmonary function in patients with underlying pulmonary disease, prolonged mechanical ventilation, bacteremia/sepsis/septic shock, and death. Use of an antimicrobial agent with the narrowest spectrum of activity that covers the suspected pathogen(s) without having activity against organisms not involved in the infection is preferred to minimize the development of resistance and secondary infections such as *Clostridium difficile* diarrhea/colitis.

General Approach to Treatment

Designing a therapeutic regimen for any patient with any type of pneumonia begins with three general categories of consideration:

1. Patient-specific factors that will impact therapy.
2. The top two to three organisms likely causing the infection and resistance issues associated with each organism.
3. The antimicrobials that will cover these organisms. Local resistance patterns, which can be obtained from hospital or clinic antibiograms, will influence the choice of antimicrobial. The spectrum should not be too broad or narrow; they should penetrate into the site of infection and be the most cost effective.

Patient factors that need to be considered include age, renal function, drug allergies and/or drug intolerances, immune status (diabetes, neutropenia, or immunocompromised host), cardiopulmonary disease, pregnancy, medical insurance and prescription coverage, exposure to resistant organisms, and prior antibiotic exposure(s).

- The most common pathogens vary with the type of pneumonia, and they are listed in Table 71–1. *M. pneumoniae* lack a cell wall; therefore, β-lactam drugs have no activity against this organism. The atypical organisms have not changed in recent years with respect to antibiotic resistance. β-Lactamase production in *H. influenzae* has remained relatively steady over the last 5 to 10 years, and the rate is approximately 25%.[20] *S. pneumoniae* has developed resistance mechanisms against many classes of antimicrobials, and the mechanisms include the following:
  - Alteration of the penicillin-binding proteins (PBPs), inactivating β-lactams

Clinical Presentation of CAP or Aspiration Pneumonia

General

Patients may experience nonrespiratory symptoms in addition to respiratory symptoms. With increasing age, both respiratory and nonrespiratory symptoms decrease in frequency.

LO 3

KEY CONCEPT **Symptoms**

- Respiratory—cough (productive or nonproductive), shortness of breath, and difficulty breathing
- Nonrespiratory—fever, fatigue, sweats, headache, myalgias, mental status changes

LO 3

KEY CONCEPT **Signs**

- Temperature may increase or decrease from baseline, but most often it is elevated. The temperature may be sustained or intermittent.
- Respiratory rate is often increased. Cyanosis, increased respiratory rate, and use of accessory muscles of respiration are suggestive of severe respiratory compromise.
- Breath sounds may be diminished. Rales or rhonchi may be heard.
- Confusion, lethargy, and disorientation are relatively common in elderly patients.

Diagnostic Tests

- Chest x-ray should reveal single or multiple infiltrates.
- Oxygen saturation on room air should be more than 90% (0.90), as determined by pulse oximetry.
- Arterial blood gases are beneficial primarily in patients with severe pneumonia.

Laboratory Tests

- The WBC may or may not be elevated. In elderly patients, a drop in WBCs also can be a sign of infection. The differential should show a predominance of neutrophils if a bacterial infection is present. The presence of bands also could be an indicator of bacterial infection. Elevated lymphocytes are an indication of viral infection.
- Blood urea nitrogen (BUN) and serum creatinine are needed to dose antibiotics appropriately and to minimize or prevent drug toxicity (especially in the elderly patient).

Microbiology Tests

- Sputum Gram stain should demonstrate the presence of WBCs and the absence of squamous epithelial cells. It may or may not show a predominance of one type of organism.
- Sputum culture and susceptibility are not obtained in the outpatient setting. The value of culturing is debated owing to the rapidity in which *S. pneumoniae* dies in transport media and the inability to reliably or routinely culture atypical organisms.
- Bronchoscopy may be performed to improve the ability to diagnose pneumonia. Tracheal secretions often are better specimens than sputum owing to the lack of oral contamination.
- Serology (IgM and IgG) is useful in determining the presence of atypical organisms such as *Mycoplasma* and *Chlamydia*.
- Urinary Legionella antigen is often used to diagnose *L. pneumophila*.
- Polymerase chain reaction (PCR) is being used more frequently to detect the DNA of respiratory pathogens.
- Blood cultures should be obtained in all patients admitted to the ICU with pneumonia. Positive blood cultures are present in about 1% to 20% of patients with CAP.

Clinical Presentation of Severe CAP or Aspiration Pneumonia

General

In approximately 10% of patients, CAP will be severe enough to require intensive care or mechanical ventilation.

LO 3

KEY CONCEPT **Symptoms**

Respiratory—cough (productive or nonproductive), shortness of breath, difficulty breathing

- Nonrespiratory—fever, fatigue, sweats, headache, myalgias, mental status changes

Signs

- Temperature may increase or decrease from baseline, but most often it is elevated. The temperature may be sustained or intermittent.
- Respiratory rate greater than 30 breaths/min, cyanosis and use of accessory muscles of respiration are suggestive of severe respiratory compromise.
- Hypotension (systolic blood pressure < 90 mm Hg or diastolic blood pressure < 60 mm Hg).
- Requirement for vasopressors.
- Breath sounds may be diminished. Rales or rhonchi may be heard.
- Urine output less than 20 mL/hour or less than 80 mL over 4 hours.
- Confusion, lethargy, and disorientation are relatively common in elderly patients.

Diagnostic Tests

As stated in the clinical presentation of community-acquired or aspiration pneumonia. Nasal swab MRSA PCR testing has a strong negative predictive value for MRSA pneumonia.

Laboratory Tests

As stated in the clinical presentation of community-acquired or aspiration pneumonia.

Microbiology Tests

As stated in the clinical presentation of community-acquired or aspiration pneumonia.

Diagnosis of VAP

Clinical Strategy

- Chest x-ray should reveal a new infiltrate *plus* two of the following:
  - Temperature greater than 38.0°C (100.4°F)
  - Leukocytosis or leukopenia
  - Purulent secretions
  - Semiquantitative cultures obtained identify the pathogen(s)
- Tracheal aspirates grow more organisms than invasive quantitative cultures and often result in overuse of antibiotics

- Efflux or methylation of the ribosome-inactivating macrolides
- Ribosome protection (tetM gene) inactivating tetracyclines
- Alteration of DNA gyrase or topoisomerase IV inactivating fluoroquinolones

S. pneumoniae resistance to commonly prescribed antimicrobials such as the penicillins and macrolides/azalides dramatically increased in the late 1980s through the mid- to late-1990s and has remained relatively flat in the 2000s. Resistance information collected nationally along with susceptibility testing for new antimicrobials demonstrates that average national rates of resistance to penicillin and macrolides were approximately 13% and 38%, respectively.[21,22] Resistance to trimethoprim/sulfamethoxazole is approximately 25%, and fluoroquinolone resistance remains less than 0.5%.[22]

For HAP, and VAP, the risk of infection from an MDR pathogen is relatively high. The number and type of organisms that are MDR vary from hospital to hospital, making it more difficult to generate guidelines for treatment. Therefore, the treatment recommendations may be too broad or too narrow for any given institution and local antibiogram data should influence the choice of therapeutic regimens. Risk factors for developing infection caused by a resistant pathogen are as follows:

- intravenous antibiotic use within the past 90 days
- septic shock at the time of HAP or VAP
- ARDS preceding VAP
- five or more days of hospitalization
- acute renal replacement therapy

The patient- and drug-related categories are common to all types of pneumonia, but the organisms vary with the type of pneumonia. Guidelines have been generated by experts in the field for all types of pneumonia. These guidelines were generated to provide practitioners with evidence-based therapeutic options for the management of patients with pneumonia.

Pharmacologic Therapy for CAP

LOS

KEY CONCEPT Treatment of CAP is predominantly empiric, that is, treatment is started without knowing the causative pathogen. The most recent guidelines are the result of collaboration between the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS).[23] The approach to patient care is based on the classification of patients into two broad categories, outpatient and inpatient, and then further dividing the groups by comorbid conditions and location in the hospital, respectively. These guidelines use patient-specific data along with predominant pathogen information to design appropriate empirical antimicrobial regimens. Table 71–2 summarizes these therapeutic options.

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

A 68-year-old woman, who only speaks Spanish, presents to your ED with difficulty breathing, coughing, and shortness of breath

PMH: Hypertension for 18 years, noninsulin dependent diabetes for 5 years, currently controlled

FH: Father died of lung cancer at the age of 68 years; mother died of natural causes

SH: Denies alcohol and tobacco use. Lives alone and has two children. She is 5′4″ (162.6 cm) and weighs 190 lb (86.4 kg)

Allergies: sulfa—hives, red-burning skin

Meds: Lisinopril 10 mg orally once daily; metformin ER 1000 mg orally twice daily

ROS: (+) difficulty breathing and shortness of breath; (–) chest pain, N/V/D, change in appetite

PE:

VS: BP 120/80 mm Hg, P 82 beats/min, RR 20 breaths/min, T 38.9°C (102.0°F)

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops

Lungs: Decreased breath sounds on both sides, rales and crackles in both lower lobes, greenish sputum production

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly, heme (–) stool

Neuro: Oriented to name and place, confused

Diagnostic Tests: Chest x-ray: left and right lower lobe infiltrates; oxygen saturation 87% (0.87) on room air

Labs: WBCs 18.6 × 10^3/mm^3 (18.6 × 10^9/L) with a cell differential of 70% (0.70) neutrophils, 2% (0.02) bands, 20% (0.20) lymphocytes, and 8% (0.08) monocytes; BUN 10 mg/dL (3.57 mmol/L), SCr 0.8 mg/dL (70.74 µmol/L), fasting glucose 110 mg/dL (6.1 mmol/L); sputum Gram stain: moderate gram-positive diplococci, few gram-negative bacilli, rare squamous epithelial cells, many WBCs; sputum culture is pending

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

What organisms should you include in your list of potential pathogens?

What pharmacologic agents are available for treating this patient?

Table 71–2

Summary of CAP Treatment

Adult outpatient otherwise healthy	*Monotherapy*
Empirical coverage against *S. pneumoniae, M. pneumoniae, C. pneumoniae,* and *H. influenzae*	Azithromycin, clarithromycin, erythromycin, doxycycline
Adult outpatient comorbidities	*Combination therapy*
Empirical coverage against *S. pneumoniae, M. pneumoniae, C. pneumoniae,* and *H. influenzae*	High-dose amoxicillin, or high-dose amoxicillin-clavulanate (alternatives are cefpodoxime, or cefuroxime, or ceftriaxone) *plus* azithromycin, or clarithromycin or, doxycycline
	Monotherapy
	Gemifloxacin, levofloxacin, moxifloxacin
Adult inpatient (non-ICU)	*Combination therapy*
Empirical coverage against *S. pneumoniae, H. influenzae, M. pneumoniae,* and *C. pneumoniae*	Cefotaxime, or ceftriaxone, or ampicillin-sulbactam, or ertapenem *plus* azithromycin, or clarithromycin, or doxycycline
	Monotherapy
	Gemifloxacin, levofloxacin, moxifloxacin
Adult inpatient ICU (*no* Pseudomonas)	*Combination therapy*
Empirical coverage against *S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, and *S. aureus*	Cefotaxime or ceftriaxone *plus* azithromycin, or levofloxacin, or moxifloxacin
Adult inpatient ICU (Pseudomonas is a concern)	*Combination therapy*
Empirical coverage against *P. aeruginosa, S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, and *S. aureus*	Cefepime, or ceftazidime, or piperacillin-tazobactam, or imipenem, or meropenem *plus* or ciprofloxacin or levofloxacin or an aminoglycoside
	If an aminoglycoside is chosen, then add azithromycin or levofloxacin or moxifloxacin
Adult inpatient non-ICU or ICU (MRSA is a concern)	
Empirical coverage against *S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, and *S. aureus (Pseudomonas* if ICU)	Add vancomycin or linezolid to the regimens listed above
Pediatric outpatient	*Monotherapy*
Empirical coverage against *S. pneumoniae, M. pneumoniae,* and *C. pneumoniae*	High-dose amoxicillin, or high-dose amoxicillin-clavulanate, or intramuscular ceftriaxone, or azithromycin, or clarithromycin
Pediatric inpatient (non-ICU)	*Monotherapy*
Empirical coverage against *S. pneumoniae*	Fully immunized child—ampicillin or penicillin G
	Partially immunized child—ceftriaxone or cefotaxime
	Combination therapy
Empirical coverage against *S. pneumoniae, H. influenzae, M. pneumoniae,* and *C. pneumoniae*	IV cefuroxime, or cefotaxime, or ceftriaxone, or ampicillin-sulbactam plus azithromycin, or clarithromycin
Pediatric inpatient ICU	*Combination therapy*
Empirical coverage against *S. pneumoniae, L. pneumophila, H. influenzae,* enteric GNB, and *S. aureus*	Cefotaxime, or ceftriaxone plus azithromycin, or clarithromycin

CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus;* GNB, gram-negative bacteria; ICU, intensive care unit.

Patient Encounter 2, Part 2: Medical History, Physical Examination, and Diagnostic Tests

A 52-year-old man was admitted to the hospital for abdominal surgery. He developed complications postoperatively and was intubated 6 days ago. The nurses note an increase in the amount and purulence of his sputum. Attempts yesterday and today to wean the patient off the ventilator have failed.

PMH: Hypertension for 15 years, currently controlled.

FH: Father and mother deceased from natural causes. Both had hypertension, mother had hypothyroidism.

SH: Smokes half a pack per day for 22 years, social alcohol two to three beers or liquor per week. He lives with his wife; truck driver. He is 5'11" (180.3 cm) and weighs 86.4 kg (190 lb).

Allergies: Penicillin—hives

Meds: Losartan 50 mg orally once daily

PE:

VS: BP 120/84 mm Hg, P 78 beats/min, T 38.4°C (101.1°F).

CV: RRR, normal S_1, S_2; no murmurs, rubs, or gallops.

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly.

Diagnostic Tests: Chest x-ray: left middle lobe infiltrate; oxygen saturation 98% (0.98) on ventilator.

Labs: WBC is $20.4 \times 10^3/mm^3$ ($20.4 \times 10^9/L$) with a cell differential of 75% (0.75) neutrophils, 7% (0.07) bands, 15% (0.15) lymphocytes, and 3% (0.03) monocytes; BUN 10 mg/dL (3.6 mmol/L), SCr 0.9 mg/dL (80 µmol/L); sputum Gram stain: many gram-negative bacilli, moderate gram-positive cocci in clusters, many WBCs; culture is pending.

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

What pharmacologic agents are available for treating this patient?

▶ Adult Outpatient Previously Healthy

First-line therapeutic options for treating previously healthy adults include use of a macrolide (erythromycin, clarithromycin) or an azalide (azithromycin) or doxycycline.[23] If a patient has failed therapy with a macrolide, azalide, or doxycycline, one has to consider why the patient failed. The most common reasons are either medication adherence issues or the presence of resistant organisms. If a resistant organism is suspected, then use of one of the respiratory fluoroquinolones active against *S. pneumoniae* (gemifloxacin, levofloxacin, or moxifloxacin) is warranted.

▶ Adult Outpatient with Comorbid Conditions

The comorbid conditions that can impact therapy and outcomes in patients with CAP include diabetes mellitus, COPD, chronic heart, liver, or renal disease, alcoholism, malignancy, asplenia, and immunosuppressive condition or use of immunosuppressive drugs.[23] If the patient did not receive antibiotics in the last 3 months, then either a respiratory fluoroquinolone alone or a combination of an oral β-lactam agent plus a macrolide or azalide is recommended. If the patient received an antibiotic in the last 3 months, the recommendation is to use an agent from a different class. Doxycycline is an acceptable alternative to a macrolide or azalide. The preferred β-lactam antimicrobial agents are high-dose (3 g daily) amoxicillin or high-dose (4 g daily) amoxicillin-clavulanate. Alternative β-lactams are second- and third-generation cephalosporins such as cefuroxime, cefpodoxime, or ceftriaxone intramuscular.

▶ Adult Inpatient Not in the ICU

For patients admitted to the hospital with CAP, the severity of illness is generally increased (caused either by the organism itself or underlying comorbidities in the patient), and the pathogens are essentially the same as in the outpatient setting. Recommendations are to use either a respiratory fluoroquinolone alone or a combination of an IV β-lactam antimicrobial agent plus an advanced macrolide/azalide (clarithromycin/azithromycin) or doxycycline. The recommended β-lactams include cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem.[23] The first antibiotic dose should be administered within the first 24 hours of admission. Conversion to oral therapy should occur when the patient is hemodynamically stable, improving clinically, and able to take oral medications, which often is within 48 to 72 hours for most patients. Discharge from the hospital should be as soon as the patient is stable and without other medical complications. The need to observe the patient in the hospital on their oral antibiotic is not necessary.[23]

▶ Adult Inpatient in the ICU

Patients admitted to the ICU have severe pneumonia, and the likely etiology includes *S. pneumoniae* and *H. influenzae* as in the other categories; however, the incidence of *L. pneumophila* increases in this setting and should be considered a potential pathogen. In addition, enteric gram-negative bacilli and *S. aureus* are more frequently the cause of the pneumonia in these patients. The recommendations are to treat with an IV β-lactam plus either azithromycin or a respiratory fluoroquinolone. These combination therapies minimize the risk of treatment failure due to a resistant pathogen as well as provide broad coverage.[23] The β-lactams are the same as for inpatient non-ICU treatment. If the patient is allergic to β-lactams, then aztreonam plus a respiratory fluoroquinolone are preferred.

If *P. aeruginosa* is suspected, then the antimicrobial treatment must be broadened to cover *Pseudomonas* as well as the organisms listed previously. Owing to the high resistance rates observed with *Pseudomonas*, the recommended regimens empirically double cover the *Pseudomonas* to ensure at least one of the antibiotics is active against it. The regimens include the use of an antipneumococcal, antipseudomonal β-lactam (cefepime, ceftazidime, piperacillin/tazobactam, imipenem, or meropenem), plus either ciprofloxacin or levofloxacin or an aminoglycoside. If the aminoglycoside is chosen, then either IV azithromycin or a respiratory fluoroquinolone should be added to cover the atypical bacterial organisms.[23]

If CA-MRSA is suspected in the patient (refer to Clinical Presentation of Severe CAP or Aspiration Pneumonia), then the addition of vancomycin or linezolid to the preceding regimen should be considered. Daptomycin cannot be used because surfactant in the lung inactivates the drug, thus rendering it ineffective for pneumonia. CA-MRSA can cause a necrotizing pneumonia, and the cause is believed to be due to its many virulence factors, including the Panton-Valentine leukocidin toxin.[4] In these patients the use of an agent that decreases toxin production may be beneficial. Linezolid decreases toxin production; the other recommended agents to decrease toxin production and added to vancomycin therapy are clindamycin or a respiratory fluoroquinolone.[23]

▶ Influenza

Influenza viruses A and B can cause pneumonia in pediatric and adult patients. Amantadine and rimantadine are available oral agents with activity against influenza virus type A. If started within 48 hours of the onset of the first symptoms, they reduce the duration of the illness by about 1.3 days. However, resistance to the adamantanes is over 90%.[24] Oseltamivir and zanamivir are oral agents active against both type A and B influenza that reduce the duration of the illness by about 1.3 days if initiated within 40 to 48 hours of the first symptoms.[25] Peramivir is an intravenous neuraminidase inhibitor approved as a single dose for adults with uncomplicated influenza. It may be used in hospitalized patients in whom oral therapy is contraindicated or not tolerated.[26] For active infection beyond the first 48 hours, none of these agents are effective in treating infection, and supportive care is the best treatment for these patients. Neuraminidase resistance rates in influenza A strains prevalent prior to 2009 were high and rates in strains prevalent after 2009 are low.[24] Seasonal information on resistance patterns and treatment recommendations should be evaluated.

▶ Aspiration

Anaerobes and *Streptococcus* spp. are the primary pathogens if a patient aspirates their oral contents and develops pneumonia. Antibiotics active against these organisms include penicillin G, ampicillin/sulbactam, metronidazole, and clindamycin. If the patient aspirates oral and gastric contents, then anaerobes and gram-negative bacilli are the primary pathogens. The preferred

Patient Encounter 1, Part 3: Creating a Care Plan

A 68-year-old woman, who only speaks Spanish, presents to your ED with difficulty breathing, coughing, and shortness of breath.

Based on the information presented, create a care plan for this patient's pneumonia. Your plan should include: (a) a statement of drug-related needs and/or problems; (b) a patient-specific detailed therapeutic plan; and (c) monitoring parameters to assess efficacy and safety.

Patient Encounter 2, Part 3: Creating a Care Plan

A 52-year-old man was admitted to the hospital for abdominal surgery. He developed complications postoperatively and was intubated 6 days ago. The nurses note an increase in the amount and purulence of his sputum. Attempts yesterday and today to wean the patient off the ventilator have failed. Your hospital antibiogram for gram-negative organisms is below; values are percentage of isolates susceptible to the antibiotic. Boxes without values indicate you should not use that antibiotic for that organism.

	Total # tested	Amikacin	Ampicillin	Amp/Sulbactam	Cefazolin	Cefepime	Ceftriaxone	Ciprofloxacin	Gentamicin	Imipenem/ Meropenem	Levofloxacin	Piperacillin/ Tazobactam	TMX/SMX	Tobramycin	Nitrofurantoin
Acinetobacter baumannii	29	62	0	69	0	45	17	34	48	66	38	55	41	62	
Citrobacter freundii complex	23		0	74	0	85	97	78	82	100	78	91	78	82	82
Enterobacter aerogenes	24		0	13	0	100	92	100	100	100	100	92	96	100	63
Enterobacter cloacae	61		0	9	0	95	82	80	87	100	74	79	82	84	79
Escherichia coli	375		2	40	63	93	90	65	88	96	65	72	60	90	98
Klebsiella pneumoniae	142		0	79	88	88	88	80	80	90	80	80	80	80	73
Proteus mirabilis	87		2	40	50	98	98	40	80	88	40	65	60	84	0
Serratia marcescens	31		6	29	0	100	100	97	100	100	97	97	97	81	3
Pseudomonas aeruginosa	132	88				88		45	50	70	45	90		63	

Based on the information presented, create a care plan for this patient's pneumonia. Your plan should include: (a) a statement of drug-related needs and/or problems; (b) a patient-specific detailed therapeutic plan; and (c) monitoring parameters to assess efficacy and safety.

treatment regimen is a β-lactam/β-lactamase inhibitor combination (ampicillin/sulbactam, amoxicillin/clavulanate, piperacillin/tazobactam, or ticarcillin/clavulanate).[23]

▶ *Pediatric Outpatient*

Guidelines have been published for treating CAP in children. The most predominant pathogens in preschool children in the outpatient setting are viruses, and often supportive therapy (maintaining hydration, antipyretics) is all that is needed.[27] For appropriately immunized infants, children, and adolescents with mild-to-moderate pneumonia in an area lacking high-level penicillin-resistant pneumococcus, high-dose amoxicillin is the recommended first-line therapy. If atypical organisms are considered likely, then a macrolide is recommended. If moderate to severe CAP is diagnosed and it is during influenza season, then treatment with oseltamivir, zanamivir (Relenza), amantadine, or rimantadine is recommended; however, seasonal resistance rates need to be evaluated.[27] Fluoroquinolones and tetracyclines should not be used in children younger than 5 years. Dosing of antibiotics for pediatric patients is presented in Table 71–3.

▶ *Pediatric Inpatient*

If the infant or child is fully immunized, then the guidelines recommend the use of IV penicillin G or ampicillin. Alternative β-lactams include IV cefotaxime or ceftriaxone. If the infant or child is not fully immunized, then the third-generation cephalosporins (cefotaxime or ceftriaxone) should be administered.[27] If atypical organisms are suspected, add azithromycin to the β-lactam. If community-acquired MRSA is suspected, then vancomycin or clindamycin should be added to the regimen.[27]

Pharmacologic Therapy for HAP/VAP

Nosocomial pneumonia has since been replaced by the terms *hospital-associated pneumonia*, and *ventilator-associated pneumonia*. KEY CONCEPT Empirical selection of antimicrobial therapy for ventilator- and hospital-associated pneumonia is broad spectrum; however, once culture and susceptibility information is available, the therapy should be narrowed (de-escalation) to cover the identified pathogen(s). Three factors important to the empirical selection of antibiotics for these types of pneumonia are risk of mortality, MRSA risk factors, and intravenous use of antibiotics in the prior 90 days.[1] MDR organisms that need to be considered include *P. aeruginosa*, extended-spectrum β-lactamase–producing *K. pneumoniae*, *Acinetobacter* spp., and MRSA. Empirical antibiotic selection must cover *P. aeruginosa*, which often then covers the other gram-negative pathogens. Empirical therapy for HAP and VAP is listed in Table 71–4 and is stratified by these three factors. If there is low risk of mortality and no MRSA

LOS

Table 71–3

CAP Antimicrobial Dosing in Pediatric Patients

	Body Weight < 2000 g		Body Weight > 2000 g		
Drug (Route)	**0–7 Days Old**	**7–28 Days Old**	**0–7 Days Old**	**7–28 Days Old**	**> 28 Days Old**
Amoxicillin (po)				15 mg/kg every 12 hours	17 mg/kg every 8 hours
Amoxicillin-clavulanate (po)			15 mg/kg every 12 hours	15 mg/kg every 12 hours	45 mg/kg every 12 hours
Cefotaxime (IV)	50 mg/kg every 12 hours	50 mg/kg every 8 hours	50 mg/kg every 12 hours	50 mg/kg every 8 hours	50 mg/kg every 8 hours
Ceftriaxone (IM/IV)	25 mg/kg every 24 hours	50 mg/kg every 24 hours	25 mg/kg every 24 hours	50 mg/kg every 24 hours	50 mg/kg every 24 hours
Cefuroxime (po)					15 mg/kg every 12 hours
Azithromycin (po/IV)	5 mg/kg every 24 hours	10 mg/kg every 24 hours	5 mg/kg every 24 hours	10 mg/kg every 24 hours	10 mg/kg every 24 hours
Clarithromycin (po)					7.5 mg/kg every 12 hours

risk factors then recommended antibiotics include cefepime, piperacillin/tazobactam, or levofloxacin. If risk of mortality is high or intravenous antibiotics have been used in the prior 90 days then double coverage for gram-negative bacilli including *P. aeruginosa* is recommended. If MRSA is suspected, then either vancomycin or linezolid should be added to the regimen.[1]

Currently there is debate over whether or not double coverage for *Pseudomonas* is required. In vitro studies have shown that aminoglycosides exhibit synergistic killing against gram-negative bacilli when combined with β-lactams. Dosing of the aminoglycosides is dependent on the patient's renal function. A high-dose once-daily regimen (eg, 4–7 mg/kg gentamicin or tobramycin or 15–20 mg/kg amikacin) can be utilized in patients with good renal function. Most of the studies enrolled patients with estimated creatinine clearances of at least 70 mL/min (1.17 mL/s). Meta-analyses have shown high-dose once-daily regimens to be as efficacious as and less toxic than divided daily dosing.[28-32] Divided daily dosing (eg, 1–2 mg/kg gentamicin or tobramycin or 7.5 mg/kg amikacin) has been utilized since the 1970s, and the dosing interval is based on the patient's renal

Table 71–4

Empirical Therapy HAP in Adults

Low Risk of Mortality and No Risk Factors for MRSA	Low Risk of Mortality with Risk Factors for MRSA	High Risk of Mortality or Received Intravenous Antibiotics in the Prior 90 Days
One of the following Piperacillin/tazobactam[c] 4.5 g IV q6h OR Cefepime[c] 2 g IV q8h OR Levofloxacin 750 mg PO/IV once daily	One of the following Piperacillin/tazobactam[c] 4.5 g IV q6h OR Cefepime[c] or Ceftazidime 2 g IV q8h OR Levofloxacin 750 mg PO/IV once daily Ciprofloxacin 400 mg IV q8h OR Imipenem[c] 500 mg IV q6h Meropenem[c] 1 g IV q8h OR Aztreonam[a] 2 g IV q8h PLUS Vancomycin[d] 15 mg/kg IV q8–12h OR Linezolid 600 mg IV/PO q12h	Two of the following Piperacillin/tazobactam[c] 4.5 g IV q6h OR Cefepime[c] or Ceftazidime 2 g IV q8h OR Levofloxacin 750 mg PO/IV once daily Ciprofloxacin 400 mg IV q8h OR Imipenem[c] 500 mg IV q6h Meropenem[c] 1 g IV q8h OR Aztreonam[a] 2 g IV q8h OR Amikacin[b] 15–20 mg/kg IV q24h Gentamicin[b] or Tobramycin[b] 5–7 mg/kg IV q24h PLUS Vancomycin[d] 15 mg/kg IV q8–12h OR Linezolid 600 mg IV/PO q12h

[a]Aztreonam should be reserved for a patient with a severe β-lactam allergy.

[b]Trough concentrations ideally should be nondetectable; < 1 mcg/mL for gentamicin and tobramycin (1 mg/L; 2 µmol/L) and < 4–5 mcg/mL (4–5 mg/L; 7–9 µmol/L) for amikacin.

[c]Extended infusions can be utilized.

[d]Target area under the curve (AUC) > 400 (400–650) or target trough concentration of 15–20 mcg/mL.

Table 71–5

Empirical Therapy VAP in Adults[a,b]

MRSA Coverage	Gram-Negative β-Lactam Antibiotics with Antipseudomonal Activity	Gram-Negative Non-β-Lactam Antibiotics with Antipseudomonal Activity
Vancomycin[c] 15 mg/kg IV q8–12h OR Linezolid 600 mg IV/PO q12h	Piperacillin/tazobactam[d] 4.5 g IV q6h OR Cefepime[e] or Ceftazidime 2 g IV q8h OR Imipenem[d] 500 mg IV q6h or Meropenem[d] 1 g IV q8h OR Aztreonam[f] 2 g IV q8h	Levofloxacin 750 mg PO/IV once daily Ciprofloxacin 400 mg IV q8h OR Amikacin[e] 15–20 mg/kg IV q24h Gentamicin[e] or Tobramycin[b] 5–7 mg/kg IV q24h OR Colistin 5 mg/kg IV ×1 followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h Polymyxin B 2.5–3 mg/kg/day IV divided in two daily doses

[a]Choose one agent for MRSA coverage PLUS one β-lactam antibiotic PLUS one non-β-lactam antibiotic.

[b]The hospital antibiogram or intensive care unit specific antibiogram should influence the selection from each column.

[c]Target area under the curve (AUC) > 400 (400–650) or target trough concentration of 15–20 mcg/mL.

[d]Extended infusions can be utilized.

[e]Trough concentrations ideally should be nondetectable; < 1 mcg/mL for gentamicin and tobramycin (1 mg/L; 2 µmol/L) and < 4–5 mcg/mL (4–5 mg/L; 7–9 µmol/L) for amikacin.

[f]Aztreonam should be reserved for a patient with a severe β-lactam allergy.

function to achieve a trough concentration of less than 2 mcg/mL (2 mg/L; 4 µmol/L) for gentamicin and tobramycin and less than 5 mcg/mL (5 mg/L; 9 µmol/L) for amikacin.

In addition to obtaining a synergistic effect, the primary reason for double coverage when treating VAP, or HAP is to broaden the coverage empirically to increase the likelihood of covering the majority of resistant pathogens. VAP is the most studied of these types of pneumonias and is often the most severe. There is an increase in mortality when inadequate therapy is initiated for VAP. Crude mortality ranges are quite large (35%–92%) compared with estimates of attributable mortality (approximately 9%); however, attributable mortality studies are limited by the large sample size needed to accurately measure this outcome.[33-35]

KEY CONCEPT Once a pathogen or pathogens have been identified, therapy should be narrowed (de-escalated) to cover only those pathogens. Use of broad-spectrum antibiotics for prolonged durations increases the risk of colonization with MDR pathogens.

LO 6

Duration of Antimicrobial Therapy

KEY CONCEPT The duration of therapy for pneumonia should be kept as short as possible and depends on several factors: type of pneumonia, inpatient or outpatient status, patient comorbidities, bacteremia/sepsis, and the antibiotic chosen. If the duration of therapy is too prolonged, then it can have a negative impact on the patient's normal flora in the respiratory and gastrointestinal tracts, vaginal tract of women, and on the skin. This can result in colonization with resistant pathogens, *Clostridium difficile* colitis, or overgrowth of yeast. In addition, the longer antibiotics are administered, the greater the chance for toxicity from the agent, as well as an increase in cost.

LO 6

The IDSA recommends treatment for CAP for a minimum of 5 days, and if the patient has been afebrile for 48 to 72 hours and has no more than 1 CAP-associated sign of instability (heart rate ≤ 100 beats/minute, respiratory rate ≤ 24 breaths/minute, systolic blood pressure ≥ 90 mm Hg, oxygen saturation ≥ 90% on room air, tolerating oral intake or normal mental status) then treatment can be discontinued.[23] For treatment of CAP in adult patients admitted to the hospital, the duration is dependent on whether or not blood cultures were positive. In the absence of positive blood cultures, the criteria for the 5-day duration of therapy listed above was validated for hospitalized patients and demonstrated similar clinical success as compared to longer durations of therapy.[36] If blood cultures were positive, the duration of therapy should be 2 weeks from the day blood cultures first became negative. The duration of therapy in pediatric patients is 10 days for uncomplicated CAP, with the exception of azithromycin, which is approved for 5 days.[27]

The duration of therapy cited in the literature for HAP or VAP ranges from 10 to 21 days. The ATS and IDSA guidelines (Table 71–5) recommend a shortened duration of therapy from the traditional 14 to 21 days to 7 days.[1] The ratings for the recommendations is a strong recommendation with moderate quality of evidence for VAP and a strong recommendation with very low quality of evidence for HAP.[1] Shorter or longer durations of therapy could be appropriate and should be based on the rate of improvement of clinical, radiological, and laboratory parameters. Shortening the duration of therapy was found to be beneficial with regard to secondary infections, colonization, toxicity, and cost issues. Several studies evaluated mortality, clinical success, recurrence, or the development of resistance with shorter courses of therapy for VAP and found no differences when compared with longer courses of therapy.[34,37]

OUTCOME EVALUATION

For CAP, outcomes include preventing hospitalization, shortening the duration of hospitalization, and minimizing mortality. Improvement of symptoms should occur within 24 to 72 hours after initiation of therapy for most patients with CAP. Response to therapy could be slowed in patients with underlying pulmonary disease such as moderate to severe asthma, COPD, or emphysema. In patients not responding to therapy consider patient comorbid conditions, other infectious and noninfectious reasons, and a drug-resistant pathogen as a causative agent. Noninfectious reasons to

consider include pulmonary embolus, congestive heart failure, carcinoma, lymphoma, intrapulmonary hemorrhage, and certain inflammatory lung diseases.

Outcome parameters for VAP and HAP are similar to those with CAP. Clinical improvement should occur within 48 to 72 hours of the start of therapy. If a patient is not responding to therapy, then, again, consider infectious and noninfectious reasons. Infectious explanations are the same as for CAP stated above, but noninfectious are not. They include atelectasis, acute respiratory distress syndrome (ARDS), pulmonary embolism or hemorrhage, cancer, empyema, or lung abscess.

PREVENTION

KEY CONCEPT Prevention of both pneumococcal and influenza pneumonia by use of vaccination is a national goal. Vaccination is used to prevent or minimize the severity of pneumonia caused by *S. pneumoniae* or the influenza virus. Further information on vaccination can be found in Chapter 86.

LO 10

The influenza vaccine is available in two forms: trivalent and quadrivalent. The trivalent vaccines are injectable, and inactivated consisting of 2 type A and 1 type B influenza viruses. There are several different formulations of the trivalent vaccine: standard dose, high dose, recombinant, and adjuvanted. Each manufacturer has different age approvals and should be evaluated prior to use in pediatric patients.[38] The high-dose influenza and standard dose adjuvanted vaccines are recommended for those 65 years of age and older.

The quadrivalent vaccines contain 2 type A and 2 type B influenza viruses. Each manufacturer has different age approvals and should be evaluated prior to use in pediatric patients.[37] Fluzone Quadrivalent is approved for use in people older than 6 months of age, including healthy people and people with chronic medical conditions. The quadrivalent nasal-spray influenza vaccine is made with live-attenuated influenza viruses that do not cause the influenza and is approved for use in healthy people 2 to 49 years of age who are not pregnant. The ability of influenza vaccine to protect a person depends on two key factors: the age and health status of the person getting the vaccine, and the similarity or "match" between the virus strains in the vaccine and those in circulation. Protective antibodies are detected approximately 2 weeks after vaccination. The Centers for Disease Control and Prevention (CDC) adopted a universal influenza vaccination policy, thus recommending all persons 6 months of age and older to be vaccinated annually prior to the start of during influenza season. Annual vaccination is recommended for individuals who are allergic to eggs. All licensed, age-appropriate vaccines can be used and it is no longer required to monitor the person for 30 minutes after the injection. If the person has a severe reaction to eggs, it is recommended they be vaccinated in a medical setting and supervised by a health care provider who can manage severe allergic reactions and conditions.[38]

Pneumococcal conjugate vaccine (PCV) is comprised of 13 serotypes and is recommended for all babies and children younger than 2 years old, all adults 65 years or older, and people 2 through 64 years old with certain medical conditions. Pneumococcal polysaccharide vaccine (PSV) is comprised of 23 serotypes and is recommended for all adults 65 years or older, people 2 through 64 years old who are at increased risk for disease due to certain medical conditions, and adults 19 through 64 years old who smoke cigarettes. The serotypes in the PCV13 are the most common disease-causing strains of pneumococcus.[39,40] A reliable immunologic response to the PCV13 has been demonstrated, along with a favorable safety profile.[40,41] One dose of PCV13 is recommended for children 6 through 18 years old and adults 19 through 64 years old with the following medical conditions that put them at increased risk for pneumococcal disease: cerebrospinal fluid (CSF) leaks (leak in fluid around the brain and spine), cochlear implant(s) (electronic medical device that replaces the function of a damaged inner ear), sickle cell disease and other hemoglobinopathies (blood disorders), functional or anatomic asplenia (a spleen that is damaged or removed), congenital or acquired immunodeficiencies, HIV infection, chronic renal failure, nephrotic syndrome, leukemia, Hodgkin disease, generalized malignancy, long-term immunosuppressive therapy, solid organ transplant, or multiple myeloma.[42] The 23 capsular types in the PPSV23 represent at least 85% to 90% of the serotypes that cause invasive pneumococcal infections among children and adults in the United States. Ten years after vaccination, a sample of elderly individuals demonstrated significant quantity of protective antibodies.[43] Individuals aged 2 to 64 years of age with one of the above disorders should receive 1 dose of the PCV13 and 5 years later receive the PSV23. Individuals 65 years and older should receive the PSV23 vaccine every 5 years for a maximum of three doses.[42] Additional information on these vaccines is available on the CDC website, Advisory Committee on Immunization Practices (ACIP; https://www.cdc.gov/vaccines/acip/index.html).

Patient Care Process

KEY CONCEPT Monitoring response to therapy is essential for determining efficacy, identifying adverse reactions, and determining the duration of therapy.

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Identify allergies to medications, including the reaction.
- Review the medical history and physical assessment findings.
- Speak with the patient (except for VAP patients) to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Evaluate the symptoms, and status (ie, inpatient, outpatient, or intubated) to determine the type of pneumonia.
- Identify comorbid conditions of asthma, COPD, or emphysema, smoking history to determine if there are factors that could slow or alter the rate of response to therapy due to bronchial or lung damage or impact the pathogen list.
- Review chest x-ray, pulse oximetry, laboratory values, microbiology data, and vital signs available.
- Assess allergies and drug intolerances, noting the severity of the reaction.
- Identify any significant drug interactions or adverse drug effects.

(*Continued*)

Patient Care Process (*Continued*)

Develop a Care Plan:

- Determine the top two to three organisms associated with the type of pneumonia for the patient (Table 71–1).
- Select an appropriate empirical antibiotic regimen for the patient and type of pneumonia, ensuring that the doses are correct for renal function and medication allergies or intolerances (see Tables 71–2 and 71–3).

Implement the Care Plan:

- Educate the patient on the importance of completing their antibiotic therapy, medication adverse effects, and drug interactions.
- Address any patient concerns regarding their pneumonia and its management.
- Determine whether the patient has insurance coverage or if the recommended agent(s) are included on the institution's formulary.

Follow-up: Monitor and Evaluate:

- Assess the effectiveness of the antibiotic therapy after 24 to 72 hours looking for improvement in signs and symptoms.
- If the patient responds to therapy within the first 72 hours, consider a 5- to 7-day course of therapy for CAP and HAP/VAP, respectively. If inpatient status, assess the patient for conversion from IV to oral therapy.
- If the patient is not improving, then reevaluate the diagnosis and pathogen list, and make appropriate changes to therapy.
- Assess the patient for the presence of adverse drug reactions, drug allergies, and drug interactions.
- Discuss with the patient the value of vaccination against *S. pneumoniae* and/or influenza. Recommend and administer vaccinations annually during the season for influenza and as appropriate for the patient for *S. pneumoniae*.

Abbreviations Introduced in This Chapter

ARDS	Acute respiratory distress syndrome
ATS	American Thoracic Society
BUN	Blood urea nitrogen
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
DFA	Direct fluorescence antigen
GER(D)	Gastroesophageal reflux (disease)
H	Hemagglutinin
HAP	Hospital-acquired pneumonia
IDSA	Infectious Diseases Society of America
MDR	Multidrug resistant
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
N	Neuraminidase
PBP	Penicillin-binding protein
PCR	Polymerase chain reaction
PCV13	Pneumococcal 13-valent conjugated vaccine
PPSV23	Purified-capsular polysaccharide 23 antigen vaccine
TNF-α	Tumor necrosis factor alpha
VAP	Ventilator-associated pneumonia

REFERENCES

1. Niederman MS, Craven DE. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. Clin Infect Dis. 2016;63(5):e61–e111.
2. Lees AW, McNaught W. Bacteriology of lower-respiratory-tract secretions, sputum, and upper-respiratory-tract secretions in "normals" and chronic bronchitics. Lancet. 1959;2:1112–1115.
3. Hendley JO, Sande MA, Stewart PM, Gwaltney JMJ. Spread of *Streptococcus pneumoniae* in families. I. Carriage rates and distribution of types. J Infect Dis. 1975;132(1):55–61.
4. Wallin TR, Hern HG, Frazee BW. Community-associated methicillin-resistant *Staphylococcus aureus*. Emerg Med Clin North Am. 2008;26(2):431–455, ix.
5. Cilloniz C, Martin-Loeches I, Garcia-Vidal C, et al. Microbial etiology of pneumonia: epidemiology, diagnosis and resistance patterns. Int J Mol Sci. 2016;17:2120–2138.
6. Jennings LC, Anderson TP, Beynon KA, et al. Incidence and characteristics of viral community-acquired pneumonia. Thorax. 2008;63:42–48.
7. Van Gageldonk-Lafeber AB, Wever PC, van der Lubben IM, et al. The aetiology of community-acquired pneumonia and implications for patient management. J Med. 2013;71(7):418–425.
8. Self WH, Balk RA, Griljava CG, et al. Procalcitonin as a marker of etiology in hospitalized patients with community-acquired pneumonia. Clin Infect Dis. 2017;65(2):183–190.
9. Petric M, Comanor L, Petti C. Role of the laboratory in diagnosis of influenza during seasonal epidemics and potential pandemics. J Infect Dis. 2006;194(suppl 2):S98.
10. Barlow GD, Lamping DL, Davey PG, Nathwani D. Evaluation of outcomes in community-acquired pneumonia: a guide for patients, physicians, and policy-makers. Lancet Infect Dis. 2003;3(8):476–488.
11. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58(5):377–382.
12. Ewig S, de Roux A, Bauer T, et al. Validation of predictive rules and indices of severity for community acquired pneumonia. Thorax. 2004;59(5):421–427.
13. Myint PK, Kamath AV, Vowler SL, Maisey DN, Harrison BDW. Severity assessment criteria recommended by the British Thoracic Society (BTS) for community-acquired pneumonia (CAP) and older patients. Should SOAR (systolic blood pressure, oxygenation, age and respiratory rate) criteria be used in older people? A compilation study of two prospective cohorts. Age Ageing. 2006;35(3):286–291.
14. Aujesky D, Auble TE, Yealy DM, et al. Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia. Am J Med. 2005;118(4):384–392.
15. Kikawada M, Iwamoto T, Takasaki M. Aspiration and infection in the elderly: epidemiology, diagnosis and management. Drugs Aging. 2005;22(2):115–130.

16. Allewelt M, Schuler P, Bolcskei PL, Mauch H, Lode H. Ampicillin + sulbactam vs clindamycin +/− cephalosporin for the treatment of aspiration pneumonia and primary lung abscess. Clin Microbiol Infect. 2004;10(2):163–170.
17. Wunderink RG. Nosocomial pneumonia, including ventilator-associated pneumonia. Proc Am Thorac Soc. 2005;2(5):440–444.
18. Edwards JR, Peterson KD, Andrus ML, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. Am J Infect Control. 2007;35(5):290–301.
19. Hidron A, Edwards J, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol. 2008;29(11):996–1011.
20. Darabi A, Hocquet D, Dowzicky MJ. Antimicrobial activity against Streptococcus pneumoniae and Haemophilus influenzae collected globally between 2004 and 2008 as part of the Tigecycline Evaluation and Surveillance Trial. Diagnost Microbiol Infect Dis. 2010;67(1):78–86.
21. Feldman C, Anderson R. Epidemiology, virulence factors and management of pneumococcus. F1000Res. 2016;5:2320. eCollection 2016.
22. Jones R, Farrell D, Mendes R, Sader H. Comparative ceftaroline activity tested against pathogens associated with community-acquired pneumonia: results from an international surveillance study. J Antimicrobiol Chemother. 2011;66(suppl 3):iii69.
23. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(suppl 2):S27–S72.
24. Hussein M, Galvin HD, Haw TY, et al. Drug resistance in influenza A virus: the epidemiology and management. Infect Drug Resis. 2017;10:121–134.
25. Clark N, Lynch J. Influenza: epidemiology, clinical features, therapy, and prevention. Semin Resp Crit Care Med. 2011;32(4):373–392.
26. Ison MG, Hui DS, Clezy K, et al. A clinical trial of intravenous peramivir compared with oral oseltamivir for the treatment of seasonal influenza in hospitalized adults. Antivir Ther. 2013;18(5):651–661.
27. Bradley J, Byington C, Shah S, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the pediatric infectious diseases society and the infectious diseases society of America. Clin Infect Dis. 2011;53(7):e25–e76.
28. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JPA. Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics. 2004;114(1):e111–e118.
29. Ferriols-Lisart R, Alos-Alminana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. Am J Health-Sys Pharm. 1996;53(10):1141–1150.
30. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. Ann Intern Med. 1996;124(8):717–725.
31. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. J Antimicrob Chemother. 1996;37(4):645–663.
32. Nestaas E, Bangstad HJ, Sandvik L, Wathne KO. Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. Arch Dis Child. 2005;90(4):F294–F300.
33. Melsen WG, Rovers MM, Koeman M, Bonten MJM. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. Crit Care Med. 2011;39:2736–2742.
34. Chastre J, Wolff M, Fagon J, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA. 2003;290(19):2588–2598.
35. Klompas M, Khan Y, Kleinman K, et al. Multicenter evaluation of a novel surveillance paradigm for complications of mechanical ventilation. PLoS ONE. 2011;6(3):e18062.
36. Uranga A, Espana PP, Bilboa A, et al. Duration of antibiotic treatment in community-acquired pneumonia. JAMA Intern Med. 2016;17(9):1257–1265.
37. Pugh RJ, Cooke RPD, Dempsey G. Short course antibiotic therapy for Gram-negative hospital-acquired pneumonia in the critically ill. J Hosp Infect. 2010;74(4):337–343.
38. Seasonal Influenza. Centers for Disease Control and Prevention. Available from: www.cdc.gov/flu. Accessed August 14, 2017.
39. Greenberg D. The shifting dynamics of pneumococcal invasive disease after the introduction of the pneumococcal 7-valent conjugated vaccine: toward the new pneumococcal conjugated vaccines. Clin Infect Dis. 2009;49(2):213–215.
40. Paradiso PR. Advances in pneumococcal disease prevention: 13-valent pneumococcal conjugate vaccine for infants and children. Clin Infect Dis. 2011;52(10):1241–1247.
41. Nunes M, Madhi S. Review on the immunogenicity and safety of PCV-13 in infants and toddlers. Exp Rev Vac. 2011;10(7):951–980.
42. Pneumococcal vaccination. Centers for Disease Control and Prevention. Available from: www.cdc.gov/vaccines/vpd/pneumo/index.html. Accessed August 14, 2017.
43. Musher D, Manoff S, McFetridge R, et al. Antibody persistence 10 years after 1st and 2nd doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of 2nd and 3rd doses in older adults. Hum Vaccin. 2011;7(9):919–926.

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72 Upper Respiratory Tract Infections

Heather L. Girand

LEARNING OBJECTIVES

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

1. List common bacteria that cause acute otitis media (AOM), acute bacterial rhinosinusitis (ABRS), and acute pharyngitis.
2. Explain the pathophysiology of and risk factors for AOM, ABRS, and streptococcal pharyngitis.
3. Identify clinical signs and symptoms associated with AOM, ABRS, streptococcal pharyngitis, and the common cold.
4. List treatment goals for AOM, ABRS, streptococcal pharyngitis, and the common cold.
5. Develop a treatment plan for a patient with an upper respiratory tract infection (URI) based on patient-specific information.
6. Create a monitoring plan for a patient with a URI based on patient-specific information and the treatment regimen.
7. Formulate appropriate educational information for patients about URIs and proper antibiotic use.

INTRODUCTION

Upper respiratory tract infection (URI) is a comprehensive term for upper airway infections, including otitis media, sinusitis, pharyngitis, laryngitis, and the common cold. Over 1 billion URIs occur annually in the United States, triggering millions of antibiotic prescriptions each year, of which up to 50% are considered inappropriate for use for acute respiratory conditions.[1] KEY CONCEPT Most URIs are caused by viruses, have nonspecific symptoms, and resolve spontaneously.[2] Antibiotics are not effective for viral URIs, and their excessive use has contributed to resistance, which has prompted development of clinical guidelines and national campaigns to reduce inappropriate prescribing.[3-7] This chapter focuses on acute otitis media (AOM), sinusitis, and pharyngitis, which are frequently caused by viruses but may be caused by bacteria. Proper management of the common cold is also reviewed.

OTITIS MEDIA

Otitis media, or middle ear inflammation, is the most common childhood illness treated with antibiotics. It usually results from a nasopharyngeal viral infection and can be subclassified as AOM or otitis media with effusion (OME). AOM is a rapid, symptomatic infection with effusion, or fluid, in the middle ear. OME is not an acute illness but is characterized by noninfectious middle ear effusion. Antibiotics are only useful for the treatment of AOM.

Epidemiology and Etiology

LO 2

AOM occurs in all ages but is most common between 6 and 18 months of age. By 3 years of age, about 60% of children have had at least one episode of AOM and nearly 25% have had at least 3 episodes of AOM.[8] Many risk factors (Table 72–1) predispose children to otitis media.[8,9] While the use of antibiotics for otitis media has declined since the mid-1990s, the proportion of health care visits resulting in antibiotic prescriptions for AOM remains high between 60% and 80%.[1,10]

LO 1

Although AOM occurs frequently with viral URIs, bacteria are isolated from middle ear fluid in 70% to 90% of children with AOM.[3,8] Historically, *Streptococcus pneumoniae* was the most common organism, responsible for up to half of bacterial cases.[3,8] *Haemophilus influenzae* and *Moraxella catarrhalis* caused up to 30% and 20% of cases, respectively. Routine childhood pneumococcal vaccination has altered the microbiology such that *H. influenzae* is now responsible for up to 60% of bacterial cases.[8,11] Viruses are isolated from middle ear fluid with or without concomitant bacteria in up to 70% of cases.[12] Lack of improvement with antibiotics is usually a result of viral infection and subsequent inflammation rather than antibiotic resistance.

Antibiotic resistance heavily influences the treatment options for AOM. Penicillin-resistant *S. pneumoniae* (PRSP) exhibit intermediate resistance (minimum inhibitory concentrations [MIC] between 0.12 and 1.0 mcg/mL [0.12 and 1.0 mg/L]) or high-level resistance (MIC of 2.0 mcg/mL [2.0 mg/L] and higher). Altered penicillin-binding proteins cause resistance in 35% to 44% of pneumococci with up to half of these strains exhibiting high-level resistance.[8,13,14] Recent data show that the prevalence of high-level penicillin resistance is less than 5% in pneumococci obtained from children.[14] Amoxicillin resistance is less common than penicillin resistance, occurring in 2% to 19% of pneumococci.[13,15] PRSP are frequently resistant to other drug classes, including sulfonamides, macrolides, and clindamycin, but are usually susceptible to levofloxacin. Treatment should be aimed at *S. pneumoniae* because pneumococcal AOM is unlikely to resolve spontaneously and commonly results in more ear pain and fever.[3,11] β-Lactamase production occurs in 20% to 45% of *H. influenzae* and 90% to 100% of *M. catarrhalis* strains.[8,11] Although

Table 72–1

Risk Factors for Otitis Media[8,9]

Atopy	Pacifier use
Craniofacial defects	Positive family history/genetic predisposition
Daycare attendance	Siblings
Gastroesophageal reflux	Tobacco smoke exposure
Immunodeficiency	Viral respiratory tract infection/winter season
Lack of breast-feeding	Young age at first diagnosis
Male sex	
Non-Hispanic white race	

infections caused by these organisms are more likely to resolve without treatment, they should be considered when failure occurs or when there is recurrent disease.[3,11]

Pathophysiology

LO 2

AOM is caused by an interplay of factors. Viral URIs impair eustachian tube function and cause mucosal inflammation, impairing mucociliary clearance and promoting bacterial proliferation and infection. Children are predisposed because they have shorter, more flaccid, and more horizontal eustachian tubes than adults, which are less functional for middle ear drainage and protection. Clinical manifestations of AOM result from host immune response and cellular damage from inflammatory mediators released by bacteria.

LO 2

Viscous effusions caused by allergy or irritant exposure contribute to impaired mucociliary clearance and AOM in susceptible individuals. Effusions can persist for up to 6 months after an episode of AOM. Atopic children experience chronic OME that may require tympanostomy tube placement to reduce complications such as hearing and speech impairment and recurrent AOM.

Patient Encounter 1, Part 1

A 12-month-old girl presents to the pediatrician's office with 36 hours of fever (maximum temperature of 39.1°C [102.4°F]) and fussiness and 2 to 3 days of rhinorrhea. Her mother reports that she was rubbing both of her ears throughout the day yesterday. She states that her daughter is irritable and was crying intermittently throughout last night. She has not eaten well today. She attends daycare 5 days a week.

What information is suggestive of acute otitis media (AOM)?

What risk factors does this child have for AOM?

Is there any additional information you need to know before recommending a treatment plan?

Treatment

LO 4

The goals of treatment are to alleviate ear pain and fever, if present; eradicate infection; prevent complications; and avoid unnecessary antibiotic use.

▶ *General Approach to Treatment*

Most uncomplicated cases of AOM do not require antibiotic treatment and will resolve spontaneously. Untreated AOM improves in over 80% of children between days 2 and 3 of illness without increasing complications.[16] Antibiotics improve otalgia in only 5% of children between days 2 and 7 of therapy while *increasing* the risk of adverse events by 38%.[16] Antibiotics significantly improve recovery in children younger than 2 years with bilateral AOM and in those with AOM and otorrhea.[16] Children younger than 2 years have a higher incidence of PRSP infections, and children between 6 months and 3 years have

Clinical Presentation and Diagnosis of AOM

Patients with AOM usually have cold symptoms, including rhinorrhea, cough, or nasal congestion, before or at diagnosis.

Symptoms

- Young children: ear tugging or rubbing, irritable, poor sleeping and eating
- Older patients: ear pain, ear fullness, hearing impairment

Signs[3]

- Fever: not common in older children; often in younger children
- Middle ear effusion
- Otorrhea with tympanic membrane perforation
- Bulging tympanic membrane
- Limited or absent mobility of tympanic membrane
- Distinct erythema of tympanic membrane
- Opaque tympanic membrane that obscures middle ear visibility

Laboratory Tests

- Gram stain, culture, and sensitivities of ear fluid if draining spontaneously or obtained via tympanocentesis (not performed routinely in practice)

Complications

- Infectious: mastoiditis, meningitis, osteomyelitis, intracranial abscess
- Structural: perforated eardrum, cholesteatoma
- Hearing and/or speech impairment

Diagnosis[3]

AOM should be diagnosed if any of the following is met:

- Moderate to severe bulging of tympanic membrane (usually with impaired mobility as assessed by pneumatic otoscopy)
- Mild bulging of tympanic membrane *and* recent onset (< 48 hours) of otalgia (or ear rubbing/tugging in nonverbal child) or intense erythema of tympanic membrane
- New onset otorrhea not caused by acute otitis externa
- Severe AOM: Moderate to severe otalgia or otalgia for at least 48 hours *or* temperature of 39.0°C (102.2°F) or greater

higher clinical and bacteriologic failure rates and complications without initial antibiotic treatment as compared with older children.[3,17] Patients with severe AOM have lower spontaneous recovery rates than those with less severe disease, particularly in children less than 2 years.[3,18] KEY CONCEPT Therefore, antibiotics should be reserved for patients most likely to benefit, which is dependent on proper diagnosis, patient age, and illness severity. Current guidelines stratify patients using these criteria in order to identify those most likely to benefit from antibiotics.[3]

▶ *Nonpharmacologic Therapy*

Watchful waiting and "safety-net" antibiotic prescriptions (prescription given to the patient but only filled if symptoms persist or worsen within 48–72 hours after diagnosis) are approaches used to attenuate microbial resistance and avoid unnecessary antibiotic adverse events and costs. Initial observation and use of delayed prescriptions in older children and those with less severe disease can reduce antibiotic use by 60% without increasing complications.[16,19] These approaches should only be considered in otherwise healthy children (Figure 72–1) as a joint decision between the clinician and the parent/caregiver and only if close follow-up and good communication exist.[3]

Children with recurrent AOM or chronic OME with impaired hearing or speech may benefit from surgery (tympanostomy tube placement with or without adenoidectomy).

▶ *Pharmacologic Therapy*

Adjunctive Therapy Pain is a central feature of AOM but it is often overlooked. Analgesics provide relief within 24 hours and should be used regardless of antibiotic therapy.[3] Acetaminophen and ibuprofen are commonly used for mild to moderate pain. Ibuprofen provides longer relief than acetaminophen but should be avoided in children younger than 6 months because of increased toxicity concerns. Alternating ibuprofen with acetaminophen is not recommended because of the potential for dosing error in ambulatory settings and a lack of safety and efficacy data. Myringotomy provides immediate relief but is rarely performed. Decongestants, antihistamines, and corticosteroids have no role in AOM treatment and can prolong effusion duration.[3,20] Data are lacking on the safety and efficacy of complementary and alternative treatments.

Antibiotic Therapy When antibiotics are necessary, clinicians must consider drug factors (eg, antimicrobial spectrum, likelihood of response, middle ear fluid penetration, side effects, drug interactions, cost) and patient factors (eg, risk factors for resistance, allergies, regimen complexity, medication palatability, and presence of other medical conditions). Studies in uncomplicated AOM have not revealed significant differences between antibiotics in clinical response rates, but most were confounded by spontaneous resolution in children likely to have had viral URIs. Bacteriologic response varies among antibiotics and does not always correlate well with clinical response but is considered important when selecting therapy.[3]

The American Academy of Pediatrics (AAP) developed clinical guidelines for healthy children between 6 months and 12 years of age with uncomplicated AOM (Figure 72–2).[3] KEY CONCEPT Amoxicillin is the drug of choice in most patients because of its proven effectiveness, high middle ear concentrations, excellent safety profile, low cost, palatable suspension, and relatively narrow spectrum (Table 72–2). High-dose amoxicillin (80–90 mg/kg/day) is preferred over conventional doses (40–45 mg/kg/day) because higher middle ear fluid concentrations can overcome pneumococcal penicillin resistance without substantially increasing adverse effects.[3,21] High dose amoxicillin-clavulanate is preferred for children who received amoxicillin in the previous 30 days, have concurrent purulent conjunctivitis, have a history of recurrent AOM unresponsive to amoxicillin, and when coverage for β-lactamase-producing organisms is desired. Despite reported high rates of penicillin allergies, only those with immunologic penicillin or amoxicillin allergies, such as hives, require alternative therapy

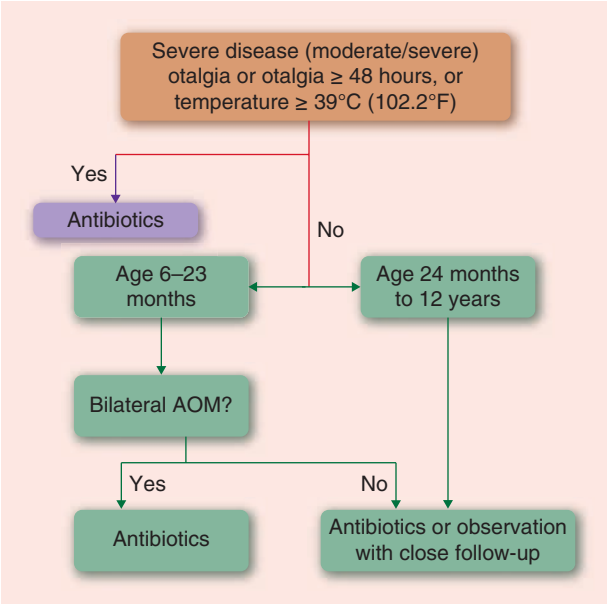

FIGURE 72–1. Treatment algorithm for initial antibiotics or observation in children 6 months to 12 years of age with uncomplicated AOM. (Data from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–e999.)

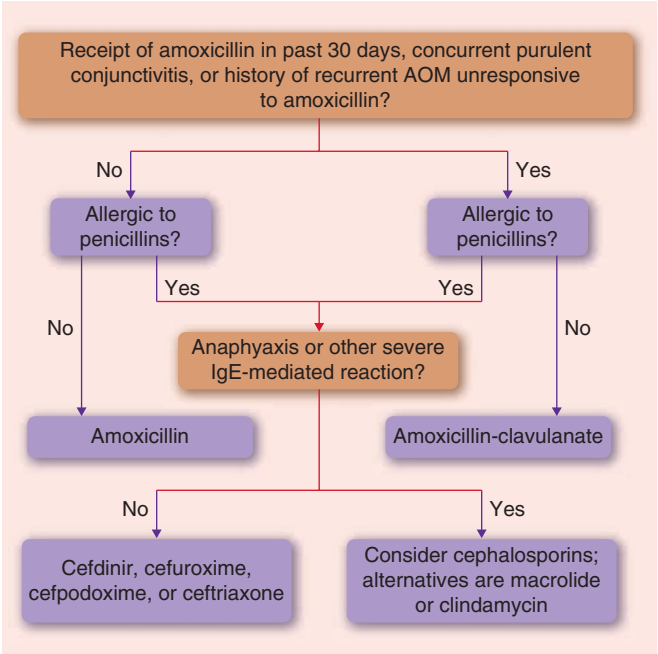

FIGURE 72–2. Treatment algorithm for uncomplicated AOM in children 6 months to 12 years of age. (Data from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–e999.)

Table 72–2

Antibiotics[a] for the Treatment of Acute Otitis Media

Drug	Usual Dose and Schedule	Common Adverse Effects	Relative Cost[b]	Comments
Amoxicillin	80–90 mg/kg/day divided in two doses (adult: 875 mg twice daily)	Nausea, vomiting, diarrhea, rash	$	Drug of choice for AOM; experts recommend high dose to overcome penicillin resistance
Amoxicillin-clavulanate	90 mg/kg/day divided in two doses (adult: 875 mg twice daily)	Nausea, vomiting, diarrhea, rash, diaper rash	$$–$$$	More diarrhea than amoxicillin; amoxicillin:clavulanate ratio of 14:1 preferred because of lower daily clavulanate component
Cefdinir	14 mg/kg/day divided in one to two doses (adult: 300 mg twice daily or 600 mg once daily)	Diarrhea, rash, vomiting, diaper rash, yeast infections	$$–$$$	Preferred oral cephalosporin (pleasant taste); separate from Fe supplements by 3 hours
Cefpodoxime proxetil	10 mg/kg/day divided in two doses (adult: 200 mg twice daily)	Diarrhea, diaper rash, vomiting, rash, yeast infections	$$$–$$$$	Suspension is bitter tasting
Ceftriaxone	50 mg/kg IM or IV for 1 or 3 days (max 1 g/dose)	Injection site pain, swelling, or erythema; diarrhea, rash	$$$–$$$$	3-day regimen preferred for PRSP
Cefuroxime axetil	30 mg/kg/day divided in two doses (adult: 250 mg twice daily)	Nausea, vomiting, diarrhea, rash, diaper rash	$$–$$$	Suspension is no longer available in the United States

[a]Other FDA-approved antibiotics for AOM not recommended in AAP guidelines: azithromycin, cefaclor, cefixime, cefprozil, ceftibuten, cephalexin, clarithromycin, erythromycin-sulfisoxazole, and trimethoprim-sulfamethoxazole.

[b]Approximate cost per course: $ (under $25), $$ ($25–$50), $$$ ($50–$100), $$$$ (over $100).

AAP, American Academy of Pediatrics AOM, acute otitis media; Fe, iron; IM, intramuscular; IV, intravenous; PRSP, penicillin-resistant *S. pneumoniae.*

Data from Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–e999.

(see Figure 72–2). There is limited cross-reactivity between penicillins and newer cephalosporins, which supports AAP recommendations to use cephalosporins in penicillin-allergic patients because they are more effective than alternatives.[3,22] Trimethoprim-sulfamethoxazole and macrolides are less active against *S. pneumoniae* and *H. influenzae* than the preferred cephalosporins, making them less appropriate for most penicillin-allergic patients.[3,14,23] Single-dose intramuscular ceftriaxone is effective for children who cannot tolerate oral medications, but a 3-day course may be preferred to prevent recurrence caused by resistant pneumococci and because of reported treatment failures with single doses.[3] Ototopical antibiotic and glucocorticoid combinations are more effective than systemic antibiotics for patients with acute otorrhea and tympanostomy tubes.[24]

If there is no improvement or worsening with initial therapy during the first 48 to 72 hours, proper diagnosis and antibiotic selection must be reassessed.[3] Tympanocentesis can assist with guiding therapy in difficult cases.

Duration of antimicrobial therapy depends on antibiotic selection, patient characteristics, and acceptability of failure if a short treatment course is used. The risk of treatment failure within 1 month is modestly higher with short-course therapy (3–5 day regimens) than standard-course therapy (minimum 7 days), but failure rates with short-course therapy are significantly higher in children with perforated eardrums.[25] Failure with short-course amoxicillin-clavulanate is also significantly more common in children 6 to 23 months of age as compared to 10 days of therapy.[26] Short-course regimens have not been proven to reduce the rates of adverse events or emergence of microbial resistance.[24,25] Standard 10-day regimens are recommended for all severe infections and for children younger than 2 years.[3] Seven-day regimens and five- to seven-day regimens can be considered for mild to moderate AOM in children 2 to 5 years and children 6 years and older, respectively.[3]

Prevention

Influenza vaccines and pneumococcal conjugate vaccines may prevent AOM in certain patients, but their benefits are small and they should not be administered solely for this purpose.[27,28] Antibiotic prophylaxis is not recommended because of selection pressure on microbial resistance. Exclusive breast-feeding for the first 6 months of life and avoidance of tobacco smoke are advised, but the effects of these interventions remain unproven.

Outcome Evaluation

Improvement of signs and symptoms (ie, pain, fever, and tympanic membrane inflammation) should be evident by 72 hours of proper therapy. Children can appear clinically worse during the first 24 hours but often stabilize during the second day. If symptoms persist or worsen, reevaluate the patient for the proper diagnosis and treatment. Counsel patients and caregivers regarding common antibiotic adverse effects such as rash, diarrhea, and vomiting that may prompt additional medical attention.

Presence of middle ear effusion in the absence of symptoms is not an indicator of treatment failure. Evaluate hearing in children who are otherwise healthy and have persistent effusion lasting 3 months in duration. Preschool-aged and younger children or those at risk for developmental difficulties may need reexamination earlier because speech and hearing impairment is more difficult to assess in these populations.

Patient Care Process for Upper Respiratory Tract Infections

Collect Information:

- Perform a medication history including prescription and nonprescription medications or therapies and dietary supplements. Identify allergies and adverse reactions to medications or other substances and document reaction(s) that occurred. Gather information on immunization history from the patient or patient's parent or caregiver and medical records including immunization registry, if applicable.
- Review the medical history and physical examination findings.
- Speak with the patient or patient's parent or caregiver to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on patient history and physical examination findings, determine if the patient has a bacterial infection and, if present, whether it is severe and/or recurrent.
- Determine if antibiotic therapy is indicated.
- Determine if the patient is current or behind on recommended immunizations.
- Determine if modifiable risk factors are present, such as exposure to tobacco smoke.
- Assess the effectiveness, safety, and patient adherence of current pharmacotherapy, where applicable.
- Identify comorbidities or conditions that may complicate the treatment plan or prompt referral to a specialist.

Develop a Care Plan:

- Select appropriate analgesic therapy that will provide optimal pain relief and appropriate adjunctive therapies to relieve symptoms.
- If appropriate, select antibiotic therapy that is likely to be effective and safe.
- Select an optimal antibiotic dose and an appropriate duration of treatment based on patient age and illness severity.

Implement the Care Plan:

- Discuss expectations for improvement of signs and symptoms with the patient, parent, or caregiver.
- Discuss importance of medication adherence to treat symptoms and infection.
- Discuss potential medication adverse effects and how to manage them.
- When appropriate, recommend and/or administer influenza and pneumococcal conjugate vaccinations to reduce risk for future infections.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist or worsen at any time.

Patient Encounter 1, Part 2

On further questioning, her mother states that she is "allergic" to amoxicillin-clavulanate. She was treated for a skin infection 3 months ago and experienced diarrhea while taking this antibiotic. She has not received antibiotics since that time, and this is her second ear infection. The first episode was diagnosed at 8 months of age.

Immunizations: Up-to-date

Meds: Ibuprofen 75 mg orally every 6 to 8 hours as needed for fever

ROS: (+) rhinorrhea and fever, (–) vomiting, diarrhea, or cough

PE:

Gen: Irritable child but consolable

VS: BP 90/55 mm Hg, P 140 beats/min, RR 24 breaths/min, T 38.6°C (101.5°F), Weight 9.5 kg

HEENT: Erythema, moderate bulging, and limited mobility of the left and right tympanic membranes

Identify your treatment goals for this child.

Given this information, what nonpharmacologic and pharmacologic therapy do you recommend?

Patient Care Process for Acute Otitis Media

See Patient Care Process for Upper Respiratory Tract Infections.

Assess the Information:

- Determine if antibiotic therapy is indicated or if observation can be employed (see Figure 72–1).

Develop a Care Plan:

- If appropriate, select an antibiotic (see Figure 72–2) and optimal dose and duration (see Table 72–2).

Implement the Care Plan:

- Educate parents or caregivers that pain, fever, and/or other symptoms should improve but may not resolve completely within 48 to 72 hours and can be present for up to 7 days or longer in some patients.
- After joint decision with parent or caregiver, refer children with recurrent AOM (three distinct episodes within 6 months or four episodes within 12 months with at least one episode in preceding 6 months) and/or chronic OME to an otolaryngologist for surgical evaluation and treatment.

Follow-up: Monitor and Evaluate:

- Reevaluate patient within 48 to 72 hours if symptoms persist or worsen at any time.
- Monitor for middle ear effusion resolution at an appropriate interval based on age and presence of conditions that interfere with recognition of hearing impairment.
- Evaluate hearing if middle ear effusion is present for 3 months in healthy children and earlier in children who are at risk for speech, language, or learning problems.

SINUSITIS

Sinusitis, or paranasal sinus inflammation, is often described as rhinosinusitis because it involves contiguous nasal mucosa and occurs in nearly all viral URIs. Acute rhinosinusitis is characterized by symptoms that persist for up to 4 weeks, whereas chronic rhinosinusitis lasts for more than 12 weeks. Acute bacterial rhinosinusitis (ABRS) refers to an acute bacterial sinus infection that occurs independently of or is superimposed on chronic sinusitis. This section will focus on ABRS.

Epidemiology and Etiology

Rhinosinusitis affects 12% of adults annually in the United States.[4] It is caused mainly by respiratory viruses but can also be triggered by allergies or environmental irritants. Viral rhinosinusitis is complicated by secondary bacterial infection in 0.2% to 2% of adults and 5% to 7% of children.[5,6] Sinusitis is the most common diagnosis associated with antibiotic prescriptions; they are used in 70% to 85% of cases, of which up to half are considered inappropriate.[1] URIs of less than 7 to 10 days' duration are usually viral, whereas more prolonged or severe symptoms are often caused by bacteria. Common risk factors for ABRS include prior viral URI, allergic rhinitis, and dental infections or procedures (Table 72–3).[6,29,30]

LO 2

LO 1

Bacteria that cause sinusitis are similar to those in AOM. *S. pneumoniae* and *H. influenzae* cause more than half of ABRS cases, with an additional 8% to 16% of cases caused by *M. catarrhalis*.[4-6] Similar to AOM, an increased prevalence of *H. influenzae* has been reported in ABRS, and certain factors predict the presence of drug-resistant pathogens.[4-6]

Pathophysiology

LO 2

Rhinosinusitis is typically caused by mucosal inflammation and mucociliary dysfunction from viral infection or allergy. Increased mucous production and reduced clearance lead to blockage of the sinus ostia. This environment is ideal for bacterial growth and promotes a cycle of local inflammation and mucosal injury characterized by increased concentrations of interleukins, interferons, and tumor necrosis factor.[31] Damage to the host defense system perpetuates bacterial overgrowth and persistence of infection.

Treatment

LO 4

The goals of treatment are to relieve symptoms; promote sinus drainage; avoid unnecessary antibiotic use or, when appropriate, use safe and effective antibiotics to eradicate bacterial infection and minimize resistance development; and prevent development of chronic disease or complications.

Table 72–3

Risk Factors for Acute Bacterial Rhinosinusitis[6,29,30]

Allergic or nonallergic rhinitis	Intranasal medications or illicit drugs
Anatomic defects (eg, septal deviation)	Mechanical ventilation
Aspirin allergy, nasal polyps, and asthma	Nasogastric tubes
Cystic fibrosis or ciliary dyskinesia	Swimming or diving
Dental infections or procedures	Tobacco smoke exposure
Immunodeficiency	Trauma or barotrauma
	Viral respiratory tract infection
	Winter season

Clinical Presentation and Diagnosis of Acute Bacterial Rhinosinusitis

Signs and Symptoms[4-6]

- *Adults:* Purulent nasal and/or postnasal discharge *plus* nasal congestion/obstruction and/or facial pain, pressure, or fullness; diminished sense of smell; fever; cough; maxillary tooth pain; fatigue; ear fullness, pressure, or pain
- *Children:* Persistent nasal or postnasal drainage; nasal congestion and mouth breathing; persistent cough (particularly at night) or throat clearing; fever; pharyngitis; ear discomfort; halitosis; morning periorbital edema or facial swelling; fatigue; facial or tooth pain

Laboratory Tests

- *Laboratory studies/nasopharyngeal cultures:* not recommended
- *Radiographic studies:* Useful for assessing presence of complications
- *Paranasal sinus puncture:* "Gold standard"; not routine but can be useful in complicated or chronic cases

Complications

- Orbital cellulitis or abscess, periorbital cellulitis, meningitis, cavernous sinus thrombosis, ethmoid or frontal sinus erosion, chronic sinusitis, and exacerbation of asthma or bronchitis

Diagnosis[4-6]

- *Clinical diagnosis:* Most common method; signs and symptoms that persist *without evidence of improvement* for at least 10 days *or* that worsen after initial improvement, *or* severe symptoms (fever ≥ 39.0°C [102.2°F] and purulent nasal discharge) for at least 3 to 4 days at illness onset. Respiratory secretion color is unreliable for diagnosis because neutrophil presence causes color and is found in viral sinusitis.[4]

▶ *General Approach to Treatment*

Initial management should focus on symptom relief and identification of patients with ABRS who are most likely to benefit from antibiotics. KEY CONCEPT Antibiotics should be prescribed only when ABRS is most likely and when the benefits of treatment outweigh the potential harms. ABRS is more likely than viral sinusitis in instances where symptoms persist without evidence of improvement for at least 10 days after the onset of illness; when symptoms suddenly worsen within 10 days after initial improvement; or when symptoms are severe in the first 3 to 4 days of illness onset.[4-6]

▶ *Nonpharmacologic Therapy*

Humidifiers, nasal saline sprays or drops, and nasal saline irrigation devices moisturize the nasal canal, impair crusting of secretions, and promote mucociliary clearance. Although many patients report benefit from these therapies, few controlled studies exist to support their efficacy in acute sinusitis.[32] Nasal irrigation with isotonic or hypertonic saline may reduce medication use and improve symptoms, especially in patients with allergic rhinitis and recurrent or chronic sinusitis, and it has a low risk of adverse reactions.[33,34]

▶ *Pharmacologic Therapy*

Adjunctive Therapy Medications that target rhinosinusitis symptoms are commonly used despite a lack of published evidence supporting their efficacy.[4] Analgesics/antipyretics may be used to treat facial pain and fever. Oral decongestants relieve congestion but should be avoided in children younger than 4 years and patients with ischemic heart disease or uncontrolled hypertension. Intranasal decongestants can be used for severe congestion in patients 6 years of age or older, but use should be limited to 3 to 5 days to avoid rebound nasal congestion. Avoid antihistamines because they thicken mucus and impair clearance, but they may be useful in patients with allergic rhinitis or chronic sinusitis.[29] Similarly, intranasal corticosteroids usually are reserved for patients with allergies or chronic sinusitis, but they may be beneficial as monotherapy or with antibiotics in ABRS if the clinician and patient agree that their modest benefits after 15 to 21 days of use outweigh their cost and minor adverse events (epistaxis, nasal itching, headache).[4,5,35] There is no evidence to support the use of guaifenesin in ABRS.

Antibiotic Therapy Because diagnosis is usually based on clinical presentation, clinicians must differentiate ABRS from viral rhinosinusitis in order to minimize inappropriate antibiotic use. In addition, recent evidence suggests that ABRS resolves spontaneously in many cases. Studies in adults with clinically diagnosed nonsevere sinusitis report cure rates of 50% to 90% by 7 to 15 days with no statistical differences between antibiotics and placebo, but there are significantly more adverse effects with antibiotics (27%) as compared to placebo (15%).[4,36] Studies in children with persistent nasal discharge for at least 10 days report modest benefits with antibiotic therapy.[37] In some studies, antibiotics led to faster symptom resolution with lower failure rates compared with no treatment, particularly with more severe infection.[5,6]

Treatment guidelines outline management approaches that include watchful waiting with close follow-up for uncomplicated infections (eg, those that do not extend beyond the sinuses or nasal cavity) or the use of antibiotics, depending on patient characteristics and illness presentation.[4-6] In adults, some experts recommend the use of watchful waiting for up to 7 days after ABRS is diagnosed, but only through shared decision making with patients and only if follow-up is available during this timeframe.[4] If symptoms worsen or fail to improve by 7 days post diagnosis, reevaluation should occur and antibiotics should be initiated (either with a repeat office visit or via use of a safety-net antibiotic prescription). Alternatively, antibiotics may be prescribed at the time of diagnosis for adults who are willing to accept the risk of adverse effects and cost of therapy in exchange for the small benefit that antibiotics provide. Other experts recommend prompt antibiotic therapy in all patients when the diagnosis of ABRS is confirmed with use of strict diagnostic criteria.[5] In children, 3 days of watchful waiting with close follow-up is an alternative approach for patients with persistent illness without symptom improvement for at least 10 days.[6] Severe or complicated infections should be treated in conjunction with specialists such as otolaryngologists or infectious diseases physicians.

When antibiotics are prescribed, empiric selection of an agent that is likely to result in favorable clinical and bacteriologic outcomes is recommended (Figure 72–3). Antibiotics (Table 72–4) should target *S. pneumoniae* and *H. influenzae*, but consideration must also be given to local resistance patterns and other bacteria.

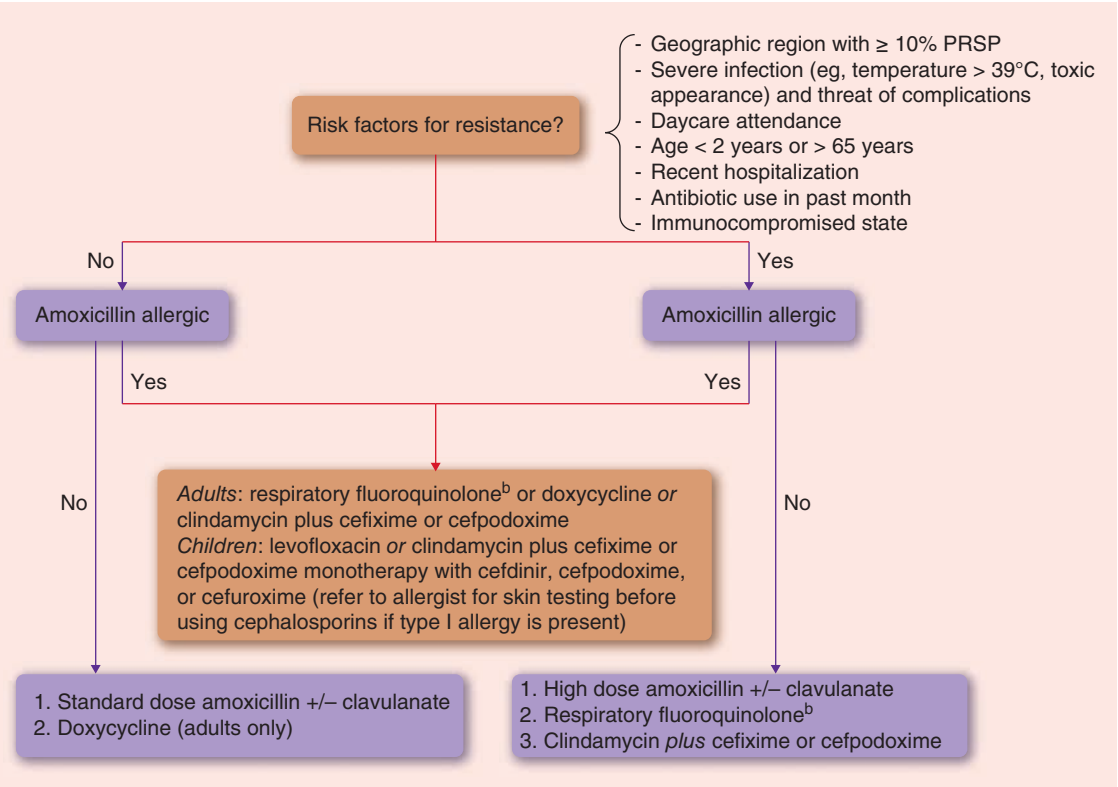

FIGURE 72–3. Treatment algorithm[a] for ABRS. [a]Antibiotics are listed in order of preference based on predicted clinical and bacteriologic efficacy rates, clinical studies, safety, and tolerability. Doses can be found in Table 72–4. [b]Respiratory fluoroquinolone = levofloxacin, moxifloxacin.[4-6]

Table 72–4

Antibiotics[a] for the Treatment of Acute Bacterial Rhinosinusitis[4-6]

Drug	Adult Dose	Pediatric Dose[b]	Relative Cost[c]	Comments
Amoxicillin	1.5–4 g/day divided in two to three doses	45–90 mg/kg/day divided in two doses	$	Lacks coverage against β-lactamase producers
Amoxicillin-clavulanate	1.5–4 g/day divided in two to three doses	45–90 mg/kg/day divided in two doses	$$–$$$	Broad coverage particularly with high doses; Augmentin XR (2 g every 12 hours) targeted toward PRSP
Cefdinir	600 mg/day divided in one to two doses	14 mg/kg/day divided in one to two doses	$$–$$$	Preferred oral liquid cephalosporin owing to good palatability
Cefixime	200 mg twice daily	8 mg/kg/day divided in two doses	$$$$	IDSA recommends use only in combination with clindamycin
Cefpodoxime proxetil	200 mg twice daily	10 mg/kg/day divided in two doses	$$$–$$$$	IDSA recommends use only in combination with clindamycin
Cefuroxime axetil	250–500 mg twice daily	15–30 mg/kg/day divided in two doses	$$–$$$	Only included as an option in AAP guideline
Ceftriaxone	1 g IM/IV every 24 hours	50 mg/kg IM/IV every 24 hours	$$$$	Experts recommend a 5-day treatment course; useful for patients who are vomiting and cannot tolerate oral therapy
Doxycycline	100 mg twice daily	Avoid in children < 8 years	$–$$$	Can cause photosensitivity, GI problems, tooth staining in young children; many drug–drug interactions (antacids, iron, calcium)
Levofloxacin	500–750 mg once daily (750 mg × 5 days)	10 mg/kg/dose every 12–24 hours	$–$$$$	Common fluoroquinolone side effects are nausea, vaginitis, diarrhea, dizziness; many drug–drug interactions (antacids, iron, calcium); tendon rupture, photosensitivity, QT prolongation possible
Moxifloxacin	400 mg once daily	Not available	$$$–$$$$	
Clindamycin	300–450 mg three times daily	30–40 mg/kg/day divided in three doses	$–$$$	No Gram-negative coverage; use only in combination with cephalosporin

[a]Refer to Table 72–2 for more information on antibiotics. Other FDA-approved antibiotics for ABRS not included in the Infectious Diseases Society of America, American Academy of Pediatrics, or American Academy of Otolaryngology-Head and Neck Surgery Foundation guidelines: azithromycin, cefaclor, cefprozil, clarithromycin, ciprofloxacin, erythromycin, and trimethoprim-sulfamethoxazole.

[b]Maximum dose not to exceed adult dose.

[c]Approximate cost per course: $ (under $25), $$ ($25–$50), $$$ ($50–$100), $$$$ (over $100).

AAP, American Academy of Pediatrics; ABRS, acute bacterial rhinosinusitis; IDSA, Infectious Diseases Society of America; IM, intramuscular; PRSP, penicillin-resistant *S. pneumoniae*.

Patient Encounter 2

A 45-year-old woman presents to her primary care physician with purulent postnasal discharge, nasal congestion, headache, and fatigue. She reports that her symptoms began 12 days ago and have worsened over the past 2 days. She states that her headache gets worse when she bends forward and she noticed that her upper molars ache when she eats or brushes her teeth. She tried acetaminophen and phenylephrine but received little to no relief. She has sinus infections every 3 to 4 years. Her last course of antibiotics was 2 years ago when she received amoxicillin for streptococcal pharyngitis. She has two daughters (12 years and 16 years of age).

Immunizations: Up-to-date; she has received the influenza vaccine this season

Allergies: Dust mites; cat and dog dander

Meds: Cetirizine 10 mg orally once daily; intranasal fluticasone one spray each nostril twice daily; acetaminophen 500 mg orally every 6 hours as needed; phenylephrine 10 mg orally every 4 hours as needed

PE:

Gen: Tired-appearing, moderate distress, appears uncomfortable

VS: BP 105/68 mm Hg, P 62 beats/min, RR 14 breaths/min, T 38.0°C (100.4°F), Wt 54.1 kg (119 lb)

HEENT: Thick, purulent brown/green postnasal discharge; nasal mucosal edema; bilateral maxillary facial pain and upper molar hypersensitivity upon tapping; no oral lesions; erythematous pharynx with no tonsillar hypertrophy

What information is suggestive of acute bacterial rhinosinusitis (ABRS)?

What risk factors are present?

What other diagnostic studies, if any, should be performed?

What are the treatment goals for this patient?

Create a care plan for this patient that includes nonpharmacologic and pharmacologic therapies and a monitoring plan.

KEY CONCEPT Standard dose amoxicillin or amoxicillin-clavulanate is recommended for most patients.[4-6] Amoxicillin is effective for most infections and is less expensive and better tolerated than amoxicillin-clavulanate, which provides expanded coverage against β-lactamase–producers. Amoxicillin-clavulanate should be considered in patients who are at risk for infection with an amoxicillin-resistant organism, such as recent antibiotic use in the previous month. High-dose amoxicillin or amoxicillin-clavulanate is recommended for patients who are at high risk for infection from resistant bacteria, such as those who attend daycare, have moderate to severe illness, and when PRSP and other resistant bacteria are frequent in a community (see Figure 72–3). Patients with penicillin allergies can be treated with an appropriate cephalosporin, doxycycline, or a respiratory fluoroquinolone depending on age and allergy severity. Cephalosporin monotherapy is less desirable because of increased pneumococcal resistance, so combination therapy may be required to optimize coverage for PRSP and β-lactamase producers, especially in moderate to severe illness.[4-6] Macrolides and trimethoprim-sulfamethoxazole are not recommended because of high pneumococcal and *H. influenzae* resistance. For uncomplicated infections, treatment duration ranges from 5 to 10 days in adults and 10 to 14 days in children.[4-6] While short-course therapy with some fluoroquinolones and β-lactams are as effective as longer courses in adults with uncomplicated ABRS, data are lacking to support shorter courses in more severe infections or in children.[38]

Failure to improve within 7 days of therapy or worsening at any time requires reevaluation to confirm the diagnosis, consider changing antibiotics, and examine for complications.[4]

Outcome Evaluation

Clinical improvement (eg, defervescence, reduced nasal congestion and discharge, improvements in pain or facial pressure) should be evident within 7 days of therapy. Monitor for common adverse effects and refer to a specialist if clinical response is not obtained with first- or second-line therapy. Referral is also important for severe, recurrent, or chronic infection. Surgery may be indicated in complicated cases.

Patient Care Process for Acute Bacterial Rhinosinusitis

See Patient Care Process for Upper Respiratory Tract Infections.

Develop a Care Plan:

- If appropriate, select an antibiotic (see Figure 72–3) and optimal dose and duration (see Table 72–4).

Implement the Care Plan:

- Educate patient or patient's parent or caregiver that symptoms may resolve slowly and can be present for up to 7 days (or longer) after diagnosis, even if antibiotics are initiated.
- Manage patients with severe infection or complications in conjunction with otolaryngologists and/or infectious diseases physicians.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist beyond 7 days or worsen at any time.
- If patient does not respond to first- or second-line therapy, refer to an otolaryngologist or infectious diseases physician.
- If recurrent infections or chronic sinusitis develop, refer to an otolaryngologist.

PHARYNGITIS

Pharyngitis is an inflammation of the throat often caused by infection. Most infections are viral and self-limited, but antibiotics are frequently prescribed because of difficulty in clinically distinguishing between viral and bacterial infection and the fear of untreated streptococcal illness.

Epidemiology and Etiology

LO 1 LO 2 Pharyngitis is a common manifestation of viral URIs. *Streptococcus pyogenes* (Group A streptococci) is the most common bacterial cause, responsible for 20% to 30% of cases in children and 5% to 15% of adult infections.[7,39] It is most common in late winter and early spring and spreads easily through direct contact with contaminated secretions. Children between 5 and 15 years have the highest incidence of streptococcal pharyngitis. Clusters of infection are common within families, classrooms, and other crowded settings.

Pathophysiology

LO 2 Group A streptococcal pharyngeal colonization occurs in up to 20% of children and is a risk factor for developing pharyngitis if there is disruption in mucosal integrity.[7] Symptoms of streptococcal pharyngitis usually are self-limited and resolve within a few days of onset *without* antibiotic treatment.[7] Historically, untreated or inappropriately treated infection caused acute rheumatic fever, heart valve damage, and other infectious complications. Antibiotic therapy given up to 9 days after symptom onset can prevent these sequelae. Proper diagnosis of streptococcal pharyngitis is important to minimize inappropriate antibiotic use for viral infections and prevent complications of untreated streptococcal infection.[7,39]

Treatment

LO 4 KEY CONCEPT The goals of therapy for streptococcal pharyngitis are to shorten the disease course, reduce spread, and prevent complications. Certain immune-mediated complications such as glomerulonephritis and reactive arthritis are not impacted by antibiotics.[7]

▶ *Nonpharmacologic Therapy*

Pain and throat irritation are key features of pharyngitis. Consumption of warm fluids, such as tea or soup, or cold items, such as ice chips or popsicles, can soothe dry throat tissue and provide hydration. Food items that coat the throat, such as honey or hard candies, can provide temporary relief of throat pain. Environmental approaches, such as adjusting room humidity to avoid a dry environment and avoiding smoke exposure, and warm saline gargles can also relieve throat irritation.

▶ *Pharmacologic Therapy*

Adjunctive Therapy Oral analgesics provide pain relief within 1 to 2 hours and can allow patients to maintain normal eating and drinking habits. Topical therapies, including medicated lozenges or sprays, provide quicker but temporary relief of throat pain and can be used in conjunction with oral analgesics. There is no evidence to support enhanced efficacy of one type of lozenge

Clinical Presentation and Diagnosis of Streptococcal Pharyngitis

Signs and Symptoms of Streptococcal Pharyngitis[7,39]

- Sudden sore throat with severe pain while swallowing
- Fever
- Headache, abdominal pain, nausea, or vomiting (especially children)
- Tonsillopharyngeal erythema with or without exudates
- Tender, anterior cervical lymphadenitis
- Swollen erythematous uvula
- Halitosis
- Soft palate petechiae
- Scarlatiniform rash
- Absence of conjunctivitis, hoarseness, cough, rhinorrhea, discrete ulcerations, and diarrhea (suggestive of viral etiology)
- Centor criteria: tonsillar exudates; tender anterior cervical adenopathy; fever; absence of cough

Complications

- Nonsuppurative: acute rheumatic fever, scarlet fever, streptococcal toxic shock syndrome, poststreptococcal glomerulonephritis or reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS)
- Suppurative: peritonsillar or retropharyngeal abscesses, cervical lymphadenitis, otitis media, sinusitis, necrotizing fasciitis

Diagnosis[7,39]

- Tests should be performed *only* when there is clinical suspicion for streptococcal pharyngitis. The likelihood of having streptococcal infection increases with the number of Centor criteria that are present. Centor criteria are most useful for identifying patients for whom testing and antimicrobial therapy are unnecessary (ie, fewer than three criteria). Pharyngeal streptococcal carriage occurs in up to 20% of healthy children.
- Rapid antigen detection test (RADT): 70% to 90% sensitivity; results available within minutes.
- Throat culture: "gold standard"; results available within 24 to 48 hours. Should be performed after all negative RADTs in children and adolescents, and adults with significant pediatric contact. Also recommended in outbreaks and to monitor for resistance.

or spray over another; however, benzocaine should be avoided because of rare but serious reports of **methemoglobinemia** associated with benzocaine sprays.

Antibiotic Therapy KEY CONCEPT Antibiotics should be used only in cases of laboratory-confirmed streptococcal pharyngitis with associated clinical symptoms (Figure 72–4).[7,39] Effective therapy (Table 72–5) reduces the infectious period from approximately 10 days to 24 hours and results in clinical improvement in 1 to 2 days.[2,7,39] KEY CONCEPT Penicillin is the drug of choice because of its narrow spectrum, documented safety and efficacy in nasopharyngeal streptococcal eradication, and low cost.[7,39] Amoxicillin is an alternative agent, particularly for children

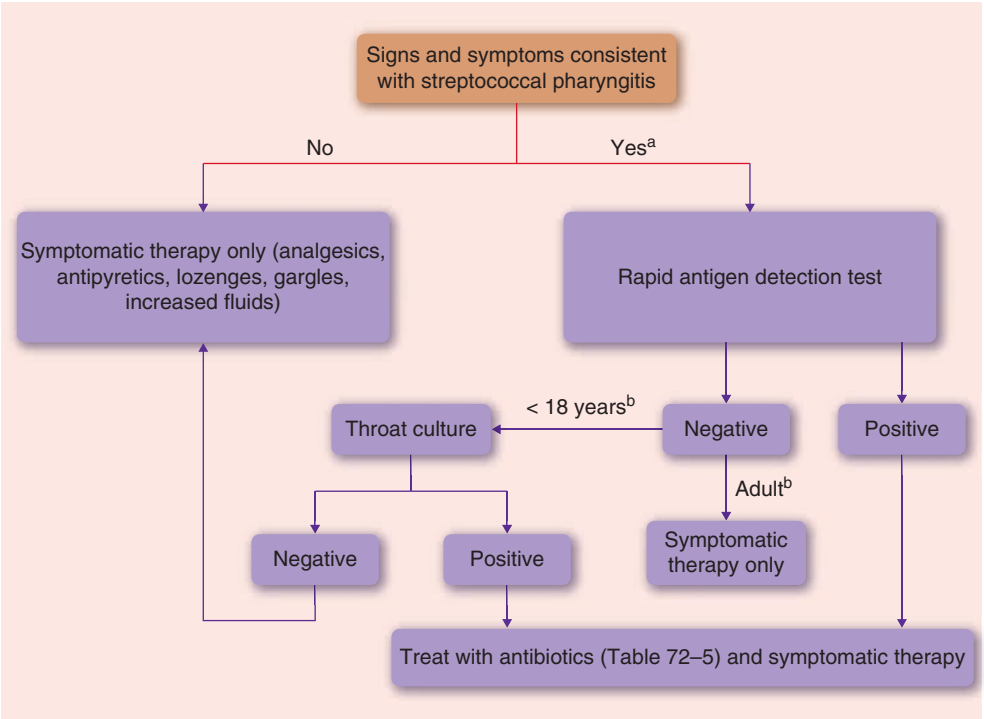

FIGURE 72–4. Treatment algorithm for management of pharyngitis in children and adults. [a]Rapid antigen detection tests (RADTs) are preferred if the test sensitivity exceeds 80%. [b]It is the clinician's discretion to perform a throat culture in adults who have a negative RADT.[7,39]

Table 72–5

Antibiotics[a] for the Treatment of Streptococcal Pharyngitis[7,39]

Drug	Adult Dose	Pediatric Dose[b]	Duration	Relative Cost[c]	Comments
Penicillin V	500 mg two to three times daily	250 mg two to three times daily (if ≤ 27 kg), 500 mg two to three times daily (if > 27 kg)	10 days	$	Drug of choice but increasing reports of treatment failures
Penicillin G benzathine	1.2 million units	600,000 units (if ≤ 27 kg); 1.2 million units (if > 27 kg)	1 IM dose	$$$$	Useful for patients with poor adherence or emesis; painful injection but pain can be reduced if warmed to room temperature prior to administration
Amoxicillin	775 mg to 1 g once daily[d]	50 mg/kg once daily; max 1 g	10 days	$ ($$$$[d])	Preferred drug for young children because of improved palatability and once daily dosing
Cephalexin	500 mg twice daily	25–50 mg/kg/day divided in two doses	10 days	$–$$	Recommended in non–type I penicillin allergy
Cefadroxil	1 g once daily	30 mg/kg once daily	10 days	$–$$	Recommended in non–type I penicillin allergy
Cefuroxime axetil	250 mg twice daily	20 mg/kg/day divided in two doses	10 days	$$–$$$	
Cefdinir	300 mg twice daily or 600 mg once daily	14 mg/kg/day divided in one to two doses	5–10 days	$$–$$$	Broad spectrum; expensive
Azithromycin	500 mg once daily	12 mg/kg once daily	5 days	$–$$	Recommended in immediate-type penicillin hypersensitivity; increasing resistance
Clindamycin	300 mg 3 times daily	20 mg/kg/day divided in three doses	10 days	$–$$$	Recommended in immediate-type penicillin hypersensitivity; useful for recurrent infections

[a]Other FDA-approved agents include amoxicillin-clavulanate, cefixime, cefaclor, cefprozil, cefpodoxime, erythromycin, clarithromycin, and others.

[b]Maximum dose not to exceed adult dose.

[c]Approximate cost per course: $ (under $25), $$ ($25–$50), $$$ ($50–$100), $$$$ (over $100).

[d]Moxatag 775 mg is a time-released formulation given once daily for patients 12 years of age and older

IM, intramuscular.

because of its improved taste and its enhanced adherence with once-daily dosing.[7,39] Cephalosporins may be more effective than penicillin for relapse prevention and nasopharyngeal eradication, particularly in asymptomatic carriers and adults.[39,40] Usual duration of therapy is 10 days, but shorter courses (5 days) of some cephalosporins, such as cefpodoxime and cefdinir, are as effective for streptococcal eradication and clinical improvement in children as 10 days of penicillin.[41]

Resistance plays a smaller role in pharyngitis treatment compared with other URIs. KEY CONCEPT Penicillin resistance is extremely rare in group A streptococci, but resistance and clinical failures occur more frequently with tetracyclines, trimethoprim-sulfamethoxazole, and to a lesser degree macrolides. Patients with penicillin allergies should be treated with a first-generation cephalosporin (if non–type I allergy), a macrolide/azalide, or clindamycin.[7,39] Recurrent infections or treatment failures can be retreated with the same initial antibiotic or treated with amoxicillin-clavulanate, a first-generation cephalosporin, clindamycin, or penicillin G benzathine.[7,39]

Outcome Evaluation

Antibiotics relieve symptoms of streptococcal pharyngitis within 3 to 5 days, and patients can return to work or school if improved after the first 24 hours of therapy. Lack of improvement or worsening after 72 hours of therapy requires reevaluation. Follow-up throat cultures are not recommended unless symptoms persist or recur. Recurrent symptoms following an appropriate treatment course should prompt reevaluation for possible retreatment.

Patient Encounter 3

A 9-year-old boy presents to the pediatrician with a sore throat and fever of 38.7°C (101.7°F) that has worsened over the past 24 hours. He says his "throat burns" when swallowing, so he is not able to eat or drink like usual. He also complains of a "tummy ache." He has no other symptoms and takes no medications. He is allergic to sulfonamides (rash). His mother reports that his 6-year-old sister had "strep throat" earlier in the week. Physical examination reveals pharyngeal and tonsillar erythema with exudates, swollen red uvula, soft palate petechiae, and tender cervical lymphadenopathy.

Does this child have streptococcal pharyngitis?

Is antibiotic therapy indicated? If so, what agent should be initiated and for how long?

What education should be provided to his mother regarding treatment?

Patient Care Process for Streptococcal Pharyngitis

See Patient Care Process for Upper Respiratory Tract Infections.

Assess the Information:

- If streptococcal pharyngitis is likely, perform an RADT and follow-up throat culture (if necessary) to confirm the diagnosis.
- Determine if antibiotic therapy is indicated based on diagnostic testing (see Figure 72–4).

Develop a Care Plan:

- If streptococcal pharyngitis is confirmed with laboratory testing, select antibiotic therapy that is likely to be effective and safe (Table 72–5).

Implement the Care Plan:

- Educate patient or patient's parent or caregiver that symptoms should improve within 1 to 2 days and resolve completely within 3 to 5 days with appropriate antibiotic therapy (if streptococcal pharyngitis is confirmed).
- Discuss the need to avoid close contact with others for 24 hours to minimize spread.
- Discuss importance of medication adherence to treat infection, minimize spread, and reduce chances of recurrence.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist after 72 hours or worsen at any time.
- Reevaluate patient if symptoms recur after completion of therapy.

COMMON COLD

The common cold is a viral URI associated with significant health care resource utilization, including physician office and emergency department visits and nearly universal use of cough and cold medication for treatment or prevention.[42,43] Clinicians must be aware of evidence regarding the use of cough and cold products in order to make appropriate recommendations for this commonly encountered condition.

Epidemiology and Etiology

Many viruses cause the common cold, including rhinoviruses (most common), coronaviruses, parainfluenza viruses, respiratory syncytial virus, and adenoviruses. Infection rates increase during the fall through spring seasons and are highest in the winter months. Adults experience 2 to 3 colds each year, whereas children have about 6 colds per year.[43] Colds usually resolve over 10 to 14 days but can be complicated by bacterial superinfections, including AOM and ABRS. Factors associated with an increased incidence of colds are young age, daycare attendance, contact with school-age children, crowded conditions and poorly ventilated areas, and cigarette smoking. Children are more likely than adults to transmit viruses because of poorer hand hygiene, closer casual contacts, and sharing of toys. Viral antigenic drifts and host immune system evasion contribute to the persistence of URIs in the community.

Pathophysiology

Viruses enter the respiratory tract mucosa via inhalation of aerosols or infected droplets or direct contact with contaminated secretions. After cell entry, viral replication and shedding occur for several days to weeks. Symptoms arise from epithelial cell damage, inflammation, vasodilation, local tissue edema, increased mucous production, and impaired mucociliary clearance. Tracheobronchial inflammation and irritation induce cough via afferent nerve impulse transmission to the medulla. Antibody production halts viral replication and inflammation as symptoms diminish.

Treatment

LO 4

The treatment goal is to minimize discomfort from symptoms to allow patients to function as normally as possible. Preventative measures are also important to limit the spread of infection. Antibiotics are not effective, but they are often prescribed to patients with viral URIs and purulent secretions, which have contributed to increased resistance.[1,2] Treatment should focus on symptom relief.

▶ *Nonpharmacologic Therapy*

Supportive measures include air humidification, intranasal saline drops or sprays with or without bulb suctioning, nasal saline irrigation, increased fluid intake, throat lozenges or saline gargles, and rest. Nasal strips may relieve congestion by lifting the nares and opening the anterior nasal passages. These nondrug measures are particularly important for children younger than 6 years and pregnant women, for whom medication safety is a significant concern. Although studies proving their benefits are lacking, these nondrug treatments are safe.

Clinical Presentation and Diagnosis of the Common Cold

Symptoms begin 24 to 72 hours after infectious contact. They peak at day 3 to 4, begin to wane by day 7, and resolve by day 10 to 14.

Signs and Symptoms[42,43]

- *Onset:* Malaise, fatigue, headache, pharyngitis, mildly elevated temperature (can be higher in infants and children)
- *Secondary:* Nasal and/or postnasal drainage (often clear at onset, but can become thick and purulent); congestion; cough and/or throat clearing; sneezing; conjunctivitis; irritability; impaired smell or taste

Complications

- AOM, ABRS, chronic bronchitis, bronchiolitis (in infants and children < 2 years), pneumonia, asthma exacerbation

Diagnosis

- *Clinical diagnosis:* Most common method; based on history, presence of symptoms, and physical examination
- *Radiographic studies:* Useful for assessing complications such as pneumonia
- *Laboratory studies:* Rapid viral antigen tests and nasopharyngeal cultures helpful for epidemiology and diagnosis in acutely ill young infants

▶ *Pharmacologic Therapy*

Nonprescription cough and cold preparations are used frequently despite a lack of evidence to support their safety and efficacy. Reports of serious adverse events and deaths led to efforts to eliminate use of these medications in young children.[44] Manufacturers have removed product labeling for all children younger than 4 years. Hundreds of products are available to manage cold symptoms. KEY CONCEPT Choice of therapy is influenced by patient age, presence of comorbid conditions, and balance of effectiveness and safety. Single-ingredient agents are preferred to target only symptoms that are present and to minimize toxicity that can result from confusion and lack of knowledge about active ingredients in multiple ingredient formulations. Cautious use of nonprescription products is warranted in certain patient populations: pregnant or lactating women, children, elderly, and patients with cardiovascular disease, diabetes, or glaucoma. Table 72–6 summarizes some of the available agents used for cold symptoms. Antipyretics

Table 72–6

Select Nonprescription Medications for the Common Cold for Patients 6 Years of Age and Older[42–44]

Class/Drug	Adults and Children > 12 Years of Age	Children 6–12 Years of Age[a]	Comments
Analgesics/Antipyretics			
Acetaminophen[b,c]	650 mg every 4–6 hours or 1000 mg every 6 hours as needed (max 3.25g/day or 4 g/day if directed by health care provider); extended-release 1300 mg every 8 hours as needed (max 3.9 g/day)	10–15 mg/kg/dose every 4–6 hours as needed (max 5 doses/day)	Use with caution in preexisting liver disease; monitor acetaminophen dose from all sources (prescription, nonprescription, and combination products)
Ibuprofen[d]	200–400 mg every 6–8 hours as needed (max 1200 mg/day)	5–10 mg/kg/dose every 6–8 hours as needed (max 4 doses/day)	Use with caution in cardiovascular disease and those with history of peptic ulcer disease or GI bleeding; avoid use in elderly, renal impairment, and heart failure; avoid in third trimester of pregnancy
Decongestants			
Intranasal:			
Oxymetazoline 0.05%[c]	Two to three sprays every 12 hours as needed (max 2 doses/24 hours)	One to two sprays every 12 hours as needed (max 2 doses/24 hours)	Limit use of intranasal decongestants to 3–5 days to minimize risk of rebound congestion; use with caution in patients with cardiovascular disease
Phenylephrine 0.25%, 0.5%, 1%	Two to three sprays no more than every 4 hours as needed	Two to three sprays no more than every 4 hours as needed (0.25% only)	
Systemic:			
Pseudoephedrine	60 mg every 4–6 hours as needed; extended release 120 mg every 12 hours or 240 mg every 24 hours as needed (max 240 mg/day)	30 mg every 4–6 hours as needed (max 120 mg/day)	Avoid use in patients with cardiovascular disease; children and elderly have increased risk of adverse effects (cardiovascular or CNS stimulation); use with caution in patients with diabetes, hyperthyroidism, prostatic hypertrophy; avoid in first trimester of pregnancy
Phenylephrine	10 mg every 4 hours as needed (max 60 mg/day)	5 mg every 4 hours as needed (max 30 mg/day)	
Cough Suppressants			
Dextromethorphan[c]	10–20 mg every 4 hours or 20–30 mg every 6–8 hours as needed; extended release 60 mg twice daily as needed (max 120 mg/day)	5–10 mg every 4 hours or 15 mg every 6–8 hours as needed; extended release 30 mg twice daily as needed (max 60 mg/day)	Increased adverse effects in children and poor metabolizers (5%–10% of white patients); can cause dysphoria and serotonin syndrome; use caution in those taking psychotropic medications
Expectorants			
Guaifenesin	200–400 mg every 4 hours as needed; extended release 600–1200 mg every 12 hours as needed (max 2.4 g/day)	100–200 mg every 4 hours as needed (max 1.2 g/day)	May cause nausea and abdominal pain, particularly in higher doses
Anticholinergics			
Intranasal ipratropium 0.06%[c]	Two sprays three to four times/day	Two sprays three times/day	Used for rhinorrhea only; does not improve congestion, postnasal drip, or sneezing; can cause epistaxis and nose/mouth dryness

[a]Maximum dose not to exceed adult dose.

[b]Preferred antipyretic/analgesic for children; can be used in newborns.

[c]Safe to use in pregnancy.

[d]Can be used in children older than 6 months of age.

and analgesics are used for fever, pain, and discomfort. Local anesthetics (eg, phenol, dyclonine) temporarily relieve throat pain and are available in lozenges and sprays. Decongestants cause vasoconstriction that can improve congestion, but use of intranasal products should be limited to 3 to 5 days to avoid rebound congestion.

Antihistamines should generally be avoided: first-generation agents may dry secretions through their anticholinergic effects, but they impair mucociliary clearance of thick mucus, which can worsen congestion, and there is not a clear benefit for cough or cold symptoms when these agents are used alone.[42,43] When used in combination with decongestants, antihistamines may provide some improvement in symptoms in adults and older children only but not in young children.[45] Cough suppressant use is not supported by strong evidence showing benefit.[46] They can cause significant neurologic adverse effects and have been linked to abuse by teens for their euphoric effects in high doses. Guaifenesin, an expectorant, may reduce sputum thickness in adults, but it has been poorly studied in children.[46] Regular high-dose vitamin C (> 200 mg/day) supplementation may result in mild reductions in cold severity or duration, but it is most useful for preventing colds in patients exposed to severe physical exercise or cold stress.[47] Echinacea has limited benefit for treatment in adults, and its use is discouraged for prevention and in all children because of adverse effects including gastrointestinal distress and rash.[48] Zinc lozenges are not consistently effective, but when used within 24 hours of symptom onset, they may slightly reduce the duration and severity of cold symptoms.[42,43]

Prevention

Prevention of the common cold is best achieved by minimizing contact with infected people and secretions. Frequent handwashing with soap and water or use of alcohol-based products is vital. Coughing and sneezing into the arm sleeve should be taught rather than using tissues or covering the mouth and nose with hands. Other methods that are advocated for preventing the spread include smoking cessation, maintenance of a healthy lifestyle through diet and exercise, and minimizing stress.

Outcome Evaluation

Most colds resolve within 7 to 10 days. Monitor patients for persistent symptoms lasting longer than 10 to 14 days, worsening symptoms, and complications such as wheezing, difficulty breathing, significant facial or ear pain, and high fevers. If complications are suspected, refer to a clinician for evaluation.

Patient Encounter 4

A 32-year-old man presents to his primary care provider's office with a "sinus infection." Four days ago, he developed a sore throat and a "runny nose." His throat pain has improved, but today his nasal discharge is thicker and yellow in color and he is congested. He took pseudoephedrine 60 mg this morning, which provided some relief. He has mild intermittent asthma and has had two sinus infections in the past (none for over 5 years). He is married with one daughter (2 years of age); both his wife and his daughter are ill with similar symptoms.

Immunizations: Up-to-date; needs influenza vaccine this season

Allergies: Amoxicillin (rash)

Meds: Albuterol inhaler as needed (hasn't used it for a few months)

PE:

Gen: No apparent distress

VS: BP 120/74 mm Hg, P 64 beats/min, RR 14 breaths/min, T 37.1°C (98.8°F), Wt 84.1 kg (185 lb)

HEENT: Conjunctiva clear; no photophobia; yellow nasal and postnasal discharge with swollen nasal mucosa; erythematous pharynx; no facial pain upon palpation; tympanic membranes normal appearing

Lungs: Clear to auscultation; no crackles

What signs and symptoms are suggestive of the common cold? Which are suggestive of ABRS?

What diagnostic studies should be performed?

Create a care plan that includes nonpharmacologic and pharmacologic therapies and a monitoring plan. Include preventative measures in your plan.

Patient Care Process for Common Cold

See Patient Care Process for Upper Respiratory Tract Infections

Assess the Information:

- Based on patient history, review of systems, and physical examination, determine if the presentation is consistent with the common cold.
- Determine if pharmacologic therapy is indicated or if nonpharmacologic measures alone can be employed.

Develop a Care Plan:

- Select nonpharmacologic and/or nonprescription therapies that will provide optimal relief of symptoms and that are safe for the patient.

Implement the Care Plan:

- Educate patient or patient's parent or caregiver that symptoms may resolve slowly and can be present for up to 10 to 14 days. If symptoms persist without improvement for longer than 10 days or worsen, refer the patient for medical evaluation.
- Discuss preventative measures for minimizing spread and future illnesses.

Follow-up: Monitor and Evaluate:

- Reevaluate patient if symptoms persist beyond 10 to 14 days or worsen at any time.
- If complications develop such as wheezing, difficulty breathing, significant facial or ear pain, or high fevers, refer to a clinician for evaluation.

Abbreviations Introduced in This Chapter

ABRS	Acute bacterial rhinosinusitis
AOM	Acute otitis media
OME	Otitis media with effusion
PRSP	Penicillin-resistant *S. pneumoniae*
RADT	Rapid antigen detection test
URI	Upper respiratory tract infection

REFERENCES

1. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. JAMA. 2016;315(17):1864–1873.
2. Hersh AL, Jackson MA, Hicks LA; American Academy of Pediatrics Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. Pediatrics. 2013;132(6):1146–1154.
3. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–e999.
4. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. 2015;152(suppl 2):S1–S39.
5. Chow AW, Benninger MS, Brook I, et al. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis. 2012;54(8):e72–e112.
6. Wald ER, Applegate KE, Bordley C, et al. Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics. 2013 Jul;132(1):e262–e280.
7. Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. Clin Infect Dis. 2012 (Nov 15);55(10):1279–1282.
8. Kaur R, Morris M, Pichichero ME. Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. Pediatrics. 2017 (Aug 7);e20170181. [Epub ahead of print.]
9. Harmes KM, Blackwood RA, Burrows HL, et al. Otitis media: diagnosis and treatment. Am Fam Physician. 2013;88(7):435–440.
10. McGrath LJ, Becker-Dreps S, Pate V, Brookhart MA. Trends in antibiotic treatment of acute otitis media and treatment failure in children, 2000-2011. PLoS One. 2013;8(12):e81210.
11. Van Dyke MK, Pirçon JY, Cohen R, et al. Etiology of acute otitis media in children less than 5 years of age: a pooled analysis of 10 similarly designed observational studies. Pediatr Infect Dis J. 2017;36(3):274–281.
12. Nokso-Koivisto J, Marom T, Chonmaitree T. Importance of viruses in acute otitis media. Curr Opin Pediatr. 2015;27(1):110–115.
13. Richter SS, Diekema DJ, Heilmann KP, et al. Changes in pneumococcal serotypes and antimicrobial resistance after introduction of the 13-valent conjugate vaccine in the United States. Antimicrob Agents Chemother. 2014;58(11):6484–6489.
14. Jones RN, Sader HS, Mendes RE, Flamm RK. Update on antimicrobial susceptibility trends among *Streptococcus pneumoniae* in the United States: report of ceftaroline activity from the SENTRY Antimicrobial Surveillance Program (1998–2011). Diagn Microbiol Infect Dis. 2013;75(1):107–109.
15. Kaur R, Casey JR, Pichichero ME. Emerging *Streptococcus pneumoniae* strains colonizing the nasopharynx in children after 13-valent pneumococcal conjugate vaccination in comparison to the 7-valent era, 2006–2015. Pediatr Infect Dis J. 2016;35(8):901–906.
16. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev. 2015;6:CD000219.
17. Tähtinen PA, Laine MK, Huovinen P, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med. 2011(Jan 13);364(2):116–126.
18. Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. N Engl J Med. 2011(Jan 13);364(2):105–115.
19. Sun D, McCarthy TJ, Liberman DB. Cost-effectiveness of watchful waiting in acute otitis media. Pediatrics. 2017;139(4):e20163086.
20. Bonney AG, Goldman RD. Antihistamines for children with otitis media. Can Fam Physician. 2014;60(1):43–46.
21. Piglansky L, Leibovitz E, Raiz S, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. Pediatr Infect Dis J. 2003;22(5):405–413.
22. Mirakian R, Leech SC, Krishna MT, et al. Management of allergy to penicillins and other beta-lactams. Clin Exp Allergy. 2015;45(2):300–327.
23. Pfaller MA, Farrell DJ, Sader HS, Jones RN. AWARE Ceftaroline Surveillance Program (2008-2010): trends in resistance patterns among *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States. Clin Infect Dis. 2012;55(suppl 3):S187–S193.
24. van Dongen TM, van der Heijden GJ, Venekamp RP, Rovers MM, Schilder AG. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med. 2014 (Feb 20);370(8):723–733.
25. Kozyrskyj AL, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. Cochrane Database Syst Rev. 2010;9:CD001095.
26. Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. N Engl J Med. 2016;375(25):2446–2456.
27. Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. Cochrane Database Syst Rev. 2015;3:CD010089.
28. Fortanier AC, Venekamp RP, Boonacker CW, et al. Pneumococcal conjugate vaccines for preventing otitis media. Cochrane Database Syst Rev. 2014;4:CD001480.
29. Aring AM, Chan MM. Current concepts in adult acute rhinosinusitis. Am Fam Physician. 2016;94(2):97–105.
30. Badr DT, Gaffin JM, Phipatanakul W. Pediatric rhinosinusitis. Curr Treat Options Allergy. 2016;3(3):268–281.
31. Scheckenbach K, Wagenmann M. Cytokine patterns and endotypes in acute and chronic rhinosinusitis. Curr Allergy Asthma Rep. 2016;16(1):3.
32. King D, Mitchell B, Williams CP, Spurling GK. Saline nasal irrigation for acute upper respiratory tract infections. Cochrane Database Syst Rev. 2015;4:CD006821.
33. Chong LY, Head K, Hopkins C, et al. Saline irrigation for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016;4:CD011995.
34. Achilles N, Mösges R. Nasal saline irrigations for the symptoms of acute and chronic rhinosinusitis. Curr Allergy Asthma Rep. 2013;13(2):229–235.
35. Zalmanovici Trestioreanu A, Yaphe J. Intranasal steroids for acute sinusitis. Cochrane Database Syst Rev. 2013;12:CD005149.
36. Lemiengre MB, van Driel ML, Merenstein D, et al. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. Cochrane Database Syst Rev. 2012;10:CD006089.
37. Smith MJ. Evidence for the diagnosis and treatment of acute uncomplicated sinusitis in children: a systematic review. Pediatrics. 2013;132(1):e284–e296.
38. Falagas ME, Karageorgopoulos DE, Grammatikos AP, Matthaiou DK. Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: A meta-analysis of randomized trials. Br J Clin Pharmacol. 2009;67(2):161–171.

39. Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis. A scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2009 (Mar 24);119(11):1541–1551.
40. van Driel ML, De Sutter AI, Habraken H, et al. Different antibiotic treatments for group A streptococcal pharyngitis. Cochrane Database Syst Rev. 2016;9:CD004406.
41. Altamimi S, Khalil A, Khalaiwi KA, et al. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. Cochrane Database Syst Rev. 2012;8:CD004872.
42. Fashner J, Ericson K, Werner S. Treatment of the common cold in children and adults. Am Fam Physician. 2012;86(2):153–159.
43. Allan GM, Arroll B. Prevention and treatment of the common cold: making sense of the evidence. CMAJ. 2014;186(3):190–199.
44. Yang M, So TY. Revisiting the safety of over-the-counter cough and cold medications in the pediatric population. Clin Pediatr (Phila). 2014;53(4):326–330.
45. De Sutter AI, van Driel ML, Kumar AA, et al. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane Database Syst Rev. 2012;2:CD004976.
46. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database Syst Rev. 2014;11:CD001831.
47. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 2013;1:CD000980.
48. Karsch-Völk M, Barrett B, Kiefer D, et al. Echinacea for preventing and treating the common cold. Cochrane Database Syst Rev. 2014;2:CD000530.

73 Skin and Skin Structure Infections

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LEARNING OBJECTIVES

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

1. Discuss skin structure and function responsible for preventing infection.
2. Describe the epidemiology, etiology, pathogenesis, diagnostic criteria, and clinical manifestations associated with acute bacterial skin and skin structure infections (ABSSSIs).
3. Identify goals of therapy associated with clinical response in patients with ABSSSI.
4. Recommend effective empiric and definitive antimicrobial regimens when given a diagnosis, patient history, physical examination, and laboratory findings.
5. Monitor chosen antimicrobial therapy for safety and efficacy.

INTRODUCTION

Skin and skin structure infections (SSSIs), also known as acute bacterial skin and skin structure infections (ABSSIs), are frequently encountered in both acute and ambulatory care settings, with outpatient visits and hospitalizations increasing annually.[1] ABSSSIs range in severity from mild, superficial, and self-limiting, to life-threatening deep tissue infections requiring intensive care, surgical intervention, and intravenous (IV) broad-spectrum antibiotics. Gram-positive pathogens, primarily *Staphylococcus aureus* and *Streptococcus* species, are the most common causative bacteria.[2-5] Polymicrobial infections are more likely in complicated or deeper infections and in persons with immune suppression, diabetes, vascular insufficiency, or recent surgery.[2,5]

The role of methicillin-resistant *S. aureus* (MRSA), particularly community-acquired methicillin-resistant *S. aureus* (CA-MRSA), in ABSSSI is of increasing importance. In many US cities, MRSA is the most frequently isolated pathogen from patients presenting to emergency departments with ABSSSI, and antimicrobial prescribing has largely shifted toward empiric use of MRSA-active agents.[3,6] Historically, MRSA infections were associated with health care exposure or defined populations such as injection drug users or athletes;[5,7] however, increasing MRSA prevalence in the community and its identification in otherwise healthy individuals means that risk stratification may be more difficult to perform. In areas with high rates of CA-MRSA, and in those with recurrent infections or infections that persist despite appropriate antimicrobial therapy, empiric therapy including antibiotics active against MRSA must be considered.[2,8] The general management of ABSSSIs is discussed throughout this chapter.

LO 1

Intact skin generally is resistant to infection. In addition to providing a mechanical barrier, its relative dryness, slightly acidic pH, colonizing bacteria, frequent desquamation, and production of various antimicrobial defense chemicals, including sweat (which contains IgG and IgA), prevent invasion by various microorganisms.[9] Conditions predisposing patients to ABSSSIs include: (a) high bacterial load (> 10^5 microorganisms); (b) excessive skin moisture; (c) decreased skin perfusion; (d) availability of bacterial nutrients; and (e) damage to the corneal layer of the skin.[10]

IMPETIGO

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Impetigo is a common skin infection that can occur in any age group, but most frequently affects children between 2 and 5 years.[11] β-Hemolytic streptococci (*Streptococcus pyogenes* or Group A *Streptococcus* [GAS]) and *S. aureus* are the most common pathogens.[5] Impetigo is a superficial infection and spreads easily, especially in settings of poor hygiene and crowding, and particularly during summer months. The offending microorganisms colonize the skin surface and invade through abrasions, insect bites, or trauma. The crusty eruption of impetigo ensues. These lesions may occur anywhere on the body, but are most common on the face and extremities.[12]

LO 2

CLINICAL PRESENTATION AND DIAGNOSIS

Impetigo lesions are numerous, well localized, and erythematous. KEY CONCEPT They begin as small, thin-walled blisters that quickly evolve into ruptured lesions, with the dried discharge forming a honey-colored crust reminiscent of cornflakes.[5] Impetigo lesions are rarely painful, but are pruritic. Scratching the lesions can spread the infection to other areas of the body. Scarring is rarely problematic, unless ulceration occurs, as in ecthyma.[5]

LO 2

In order to avoid further spread and complications, antibiotic therapy is usually indicated. Sequelae of impetigo are uncommon. Rare manifestations of disease include transformation into cellulitis, progression to sepsis requiring hospitalization, or development of glomerulonephritis secondary to GAS.[5]

TREATMENT

LO 3

The primary goals of impetigo therapy include preventing infection spread within the patient and to others, infection resolution, and preventing recurrence. Secondarily, symptom relief (eg, itching) and improving cosmetic appearance are important. Prevention of the rare, but serious complications of impetigo is an alternative goal.[13]

Nonpharmacologic Treatment

Because impetigo is rarely painful, there is often a delay in seeking medical attention. Lesions may improve with time and increased hygiene along with soaking and cleansing lesions with mild soap and water. The use of skin emollients to dry skin areas may reduce spread and urge to scratch itchy lesions.[13]

Pharmacologic Treatment

LO 4

Antibiotic therapy is recommended to prevent spread of infection and complications. Although GAS historically has been the primary causative organism and penicillin is recommended when cultures yield streptococci alone, KEY CONCEPT the incidence of *S. aureus* impetigo is common, and oral penicillinase-stable penicillins (such as *dicloxacillin*) or first-generation cephalosporins (such as *cephalexin*) are preferred. In skin cultures of children with impetigo, MRSA rates have only ranged from 7% to 10% of cases (other cases were due to GAS or Methicillin-sensitive *S. aureus* [MSSA]). Clindamycin, sulfamethoxazole-trimethoprim, or doxycycline is preferred for the treatment of MRSA impetigo. These are also alternative choices when penicillin allergy is a concern; however, tetracyclines should be avoided in children younger than 8 years. KEY CONCEPT Topical mupirocin or retapamulin twice daily for 5 days may be used alone in mild cases with few lesions or in individual outbreaks.[5,8]

FOLLICULITIS, FURUNCLES, AND CARBUNCLES

See Table 73–1 for summary.

CELLULITIS AND ERYSIPELAS

EPIDEMIOLOGY AND ETIOLOGY

Cellulitis and erysipelas are common bacterial infections involving the skin, with over 14 million cases annually.[14] KEY CONCEPT Cellulitis is an infection of the dermis and subcutaneous tissue, whereas erysipelas is a more superficial infection of the upper dermis and superficial lymphatics. Although both can occur on any part of the body, many infections involve the leg.[16,17] These infections develop after a break in skin integrity, resulting from trauma, surgery, ulceration, burns, tinea infection, or other skin disorder. However, they may occur after an inapparent break in the skin. In rare cases, cellulitis develops from bloodborne or contiguous spread of pathogens.[5,17]

Etiologic microorganisms vary according to the area involved, host factors, and exposures. KEY CONCEPT The predominant pathogens associated with cellulitis are streptococci, mainly group A, and less frequently *S. aureus*, including methicillin-resistant strains. Persons who are immunocompromised, have diabetes or vascular insufficiency, or use injection drugs are at risk for polymicrobial cellulitis.[5]

CLINICAL PRESENTATION AND DIAGNOSIS

LO 2

The manifestations of nonpurulent infections are compared to purulent infections in Table 73–2.

With early diagnosis and appropriate therapy, the prognoses for cellulitis and erysipelas are excellent. Severe or repeated episodes can cause lymphedema. Blood cultures are often obtained, though the rates of bacteremia range widely from 2% to 18.5% in patients with cellulitis.[18,19] Patients at higher risk for bacteremia from cellulitis include those with malignancy, signs of systemic infection (such as fever), animal bites, and the immunocompromised. Rare complications include the spread of infection to deeper skin and soft tissue layers and sepsis.[5]

Annual recurrence rates, especially for cellulitis of the leg, can be as high as 20%,[5] and over 50% within 3 years from the initial infection.[16] Cases often recur at the same site as previous infections. Vascular and lymphatic insufficiencies increase the risk of recurrences; obesity, tobacco use, history of cancer, and homelessness also increase risk.[5]

TREATMENT

LO 3

The goals of therapy for cellulitis and erysipelas are rapid and successful eradication of the infection and prevention of related complications.

Nonpharmacologic Treatment

Nonpharmacologic treatment includes elevating the involved limb to decrease swelling. Sterile saline dressings may be placed on open lesions to cleanse them of purulent materials. Surgical debridement may be indicated for severe infection and to assess for necrotizing infection. Incision and drainage of abscesses is imperative to achieving clinical cure and may be the only treatment necessary if abscesses are small (< 5 cm) with limited cellulitis.[5,17] The choice to treat with antibiotics after incision and drainage of an uncomplicated abscess is controversial.

Pharmacologic Treatment

Most patients with erysipelas or cellulitis are effectively treated with outpatient therapy. Hospitalization and treatment with IV antibiotics is recommended in the presence of systemic inflammatory response syndrome (SIRS) (eg, temperature > 38°C or < 36°C, tachypnea > 24 breaths/min, tachycardia > 90 beats/min, or white blood cell count > 12×10^3/mm^3 [12×10^9/L] or < 400/mm^3 [0.4×10^9/L]), altered mental status, or hemodynamic instability. Patients presenting with sepsis based on the Sepsis-3 definition and Sequential [Sepsis-related] Organ Failure Assessment (SOFA) should also be candidates for hospitalization and broad spectrum antimicrobials.[20] Further, inpatient therapy should be considered when suspecting deep or necrotizing infections, severely immunocompromised patients, failure of outpatient therapy, or poor adherence to therapy.[5]

Antibiotic choices for nonpurulent cellulitis should have activity against streptococci, and include penicillin, amoxicillin, amoxicillin-clavulanate, dicloxacillin, cephalexin, or clindamycin. In uncomplicated cases, a 5-day course is as effective as a 10-day course.[5] Monotherapy with a β-lactam is appropriate in uncomplicated cases.[21,22] As an example, when trimethoprim-sulfamethoxazole (TMP-SMX) was combined with cephalexin and compared to cephalexin monotherapy, a higher rate of clinical resolution was not seen in uncomplicated cellulitis.[22] TMP-SMX was also compared to clindamycin for uncomplicated cellulitis or abscess and found to have no significant difference in efficacy.[23] However, when purulent drainage, abscess, or ulcer is present, or in cases of penetrating trauma, particularly IV drug use, coverage for MRSA should be initiated.

Table 73–1

Folliculitis, Furuncles, and Carbuncles

	Folliculitis	Furuncles	Carbuncles
Epidemiology/ etiology	KEY CONCEPT Folliculitis is a superficial inflammatory reaction involving the hair follicle. The most familiar form of folliculitis is acne. It can be infectious, caused by microorganisms such as *S. aureus, Pseudomonas* spp., and *Candida* spp.	Also known as boils, furuncles might be described as a deep form of folliculitis. A furuncle is a bacterial infection that has spread into the subcutaneous skin layers but still only involves individual follicles. Furuncles occur primarily in young men. Diabetes and obesity are other predisposing factors. Staphylococci are the most common cause.	Carbuncles share all the characteristics of furuncles. However, a carbuncle is larger and involves several adjacent follicles and may extend into the subcutaneous fat. Carbuncles are more likely to occur in patients with diabetes and tend to form on the back of the neck.
Presentation and diagnosis	Folliculitis presents as small, pruritic, erythematous papules. Location of the lesions and patient history are often all that are required in the diagnosis of folliculitis. Although Gram stain and culture of the papules may be considered, they are not generally required as folliculitis typically resolves spontaneously.	Furuncles most commonly develop on the face, neck, axilla, and buttock. A furuncle typically starts as a small, red, tender nodule. Within a few days, the nodule becomes painful and pustular. Typically, a furuncle will spontaneously discharge pus, heal, and leave a small scar.	Carbuncles are similar to furuncles; only they are larger and exquisitely painful.
Desired outcomes	The goals of therapy for folliculitis, furuncles, and carbuncles are resolution of infection with no or minimal scarring. A secondary goal of therapy for larger furuncles and all carbuncles is to minimize the risk of endocarditis or osteomyelitis by reducing bloodstream invasion.		
Nonpharmacologic treatment	KEY CONCEPT Warm compresses are generally sufficient.	Moist heat is indicated to facilitate drainage. Large furuncles require incision and drainage.	Incision and drainage are indicated.
Pharmacologic treatment	KEY CONCEPT Often resolves spontaneously. A topical antibiotic or antifungal may be used to control the spread of infection but generally is unnecessary. For staphylococcal or streptococcal folliculitis, antibiotic ointments such as mupirocin might be administered. Antifungal shampoo can be used for dermatophytes.	Carbuncles and furuncles that are purulent with signs of infection (ie, fever) should be treated systemically with an antibiotic that will cover *S. aureus*, such as dicloxacillin or cephalexin. Trimethoprim-sulfamethoxazole or doxycycline is preferred if CA-MRSA is suspected or if the patient has a severe allergy to penicillin. Treatment should continue until acute inflammation has resolved, usually a 5- to 10-day course. Immunocompromised patients and severe infections or abscesses in patients who fail incision and drainage plus oral antibiotics should be treated empirically with vancomycin, daptomycin, linezolid, or ceftaroline. Prevention for recurrent episodes may be warranted, including adequate skin hygiene with the use of soap and water, and handwashing after contact with lesions. Proper care of clothing and dressings is also recommended to prevent autoinoculation.	

Data from Refs. 5, 12, and 14.

Patient Encounter 1, Part 1: Cellulitis

A 54-year-old man presents to the emergency department with a 5-day history of progressively worsening pain and swelling of his left lower extremity. Upon examination, you notice that in addition to the patient's complaints, the area is visibly erythematous. He has multiple purulent, weeping wounds along the left lower extremity. The left lower extremity also seems to have significant lymphedema when compared to the right lower extremity. When questioned, he indicates that he recently stepped on a shard of glass while barefoot inside his home. He reports using several rolls of paper towels to wrap and attempt to control the purulent discharge from his wounds. He reports running a low-grade fever and some feelings of fatigue, but otherwise feels fine. He has not seen a provider in over 10 years. His vital signs in the emergency department reveal a temperature of 38.8°C, pulse 98 beats/min, blood pressure 128/89 mm Hg, and respiratory rate 18 breaths/min. The physician diagnoses the patient with cellulitis and he is admitted to the inpatient care team.

What subjective and objective clinical manifestations are suggestive of cellulitis?

What additional information do you need before developing a therapeutic plan for this patient?

Table 73–2

Characteristics of Nonpurulent and Purulent ABSSSI

	Nonpurulent	Purulent
Clinical manifestation	Cellulitis, erysipelas	Abscess, carbuncle, furuncle
Initial presentation	Diffuse redness, edema, warmth, and tenderness	Painful and tender localized lesion
Microbiology	Often unable to obtain culture from infected area Blood cultures considered in complicated or severe cases	Often able to obtain culture data from localized lesion Blood cultures considered in complicated or severe cases
Nonpharmacologic management	Incision and drainage not recommended	Incision and drainage recommended
Common causative pathogens	*Streptococcus pyogenes*	*Staphylococcus aureus,* including MRSA

Data from Refs. 5 and 15.

Vancomycin continues to be the drug of choice for severe cellulitis due to MRSA because of its efficacy, safety, and low cost. Daptomycin, linezolid, or ceftaroline are also acceptable and should be considered over vancomycin when the isolated organism has a minimum inhibitory concentration (MIC) of greater than 2 mcg/mL (> 2 mg/L) (eg, vancomycin-intermediate *S. aureus* [VISA] or vancomycin-resistant *S. aureus* [VRSA]).[8] Newer agents for ABSSSI, including tedizolid, dalbavancin, and oritavancin, may have advantages over traditional therapy in terms of duration of activity and administration.[24,25] For less severe, uncomplicated infections, many CA-MRSA strains can be treated with clindamycin (isolates resistant to erythromycin should be evaluated with a **D-test**), doxycycline, or trimethoprim-sulfamethoxazole.[5,8] Trimethoprim-sulfamethoxazole and doxycycline should be empirically combined with a β-lactam if GAS is also a suspected causative organism, since the activity of these agents against β-hemolytic streptococci is unknown.[5] Linezolid is an additional oral option approved for ABSSI with activity against MRSA and Streptococci. It is available in both intravenous and oral formulations. It should be avoided in combination with medications that have serotonin or monoamine oxidase activity as it can precipitate serotonin syndrome.[26]

KEY CONCEPT In addition to coverage for staphylococcal and streptococcal ABSSSI, patients with severe infections should receive treatment for gram-negative bacilli such as *Escherichia coli* and *Pseudomonas aeruginosa*, with or without **anaerobic** coverage. Empiric broad-spectrum antimicrobial coverage, including coverage for resistant organisms such as health care–associated MRSA (HA-MRSA) and *P. aeruginosa*, is appropriate for severe ABSSSI and/or severe systemic illness. Broad spectrum antimicrobials, including activity against gram-negative bacteria, can also be considered in individuals who are neutropenic, receiving chemotherapy, or have an immunodeficiency.[5] Vancomycin with an antipseudomonal beta-lactam (ie, piperacillin-tazobactam, cefepime, meropenem) is recommended in these cases. Empiric therapy continuation is recommended in polymicrobial infections, whereas more defined therapy is recommended when a causative pathogen is isolated.[5]

LO 4

Patient Encounter 1, Part 2: Cellulitis: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension, obstructive sleep apnea.

FH: Father family history unknown. Mother passed away at 81 years of age due to complications of chronic obstructive pulmonary disease (COPD).

SH: Denies alcohol or tobacco use. Daily use of marijuana. Lives alone, works as a writer.

Meds: Lisinopril 20 mg daily; HCTZ 25 mg daily.

Allergies: No known drug allergies.

ROS: (+) chills, fatigue, rash, and swelling of lower extremity; (–) headache, chest pain, shortness of breath, cough, nausea, vomiting, diarrhea, and weight loss.

PE:

Gen: Patient is alert, awake, oriented. Wt 159 kg (350 lb); Ht 5′7″ (170 cm).

Chest: Lungs bilaterally clear to auscultation.

CV: Regular rate, rhythm. No murmurs/rubs/gallops.

Ext: Left lower extremity with significant lymphedema and approximately 3× larger than right lower extremity. Left lower extremity warm to touch and tender to palpation. He has sensation to light touch in bilateral lower extremity and is able to move toes bilaterally. Multiple actively weeping wounds with erythema present from above knee to toes. Right lower extremity within normal limits.

Imaging:

Foot x-ray of left lower extremity: Diffuse soft tissue swelling of the foot and ankle. No subcutaneous gas or foreign body. No fracture or arthritic change.

Tibia fibula x-ray of left lower extremity: No definitive fracture or other bone abnormalities identified.

Labs: WBC 15.8 × 10^3/mm^3 (15.8 × 10^9/L), serum creatinine 0.8 mg/dL (71 µmol/L).

What are the most likely causative organisms in this case of cellulitis?

What subjective or objective clinical criteria would be concerning for necrotizing fasciitis in this patient's presentation rather than the diagnosis of cellulitis?

What are the goals of therapy for this patient?

What nonpharmacologic interventions would you recommend for him?

What antimicrobial therapy would you recommend? Include drug, dosage, route, interval, and duration of therapy.

How would you monitor your selected regimen for safety and efficacy?

Table 73–3

Empiric Antimicrobial Therapy for Cellulitis

Host Factors	Probable Etiologic Bacteria	Mild Infection or Step-Down Therapy[a] (Oral Antibiotic Therapy)	Moderate–Severe Infection[a] (IV Antibiotic Therapy)
Previously healthy	MSSA GAS CA-MRSA	Dicloxacillin 500 mg every 6 hours Cephalexin 500 mg every 6 hours Clindamycin 300–450 mg q 6 hrs CA-MRSA suspected or allergy to PCNs: Clindamycin[b] 300–450 mg q 6 hrs Trimethoprim-sulfamethoxazole DS[c] one to two tablets every 12 hours Doxycycline[c] 100 mg every 12 hours Linezolid 600 mg every 12 hours	Nafcillin 1–2 g every 4 hours Cefazolin 1–2 g every 8 hours Clindamycin 600–900 mg every 8 hours CA-MRSA suspected or allergy to PCNs: Vancomycin 15–20 mg/kg every 8–12 hours (individualize dose to achieve a trough of 15–20 mcg/mL) Linezolid 600 mg every 12 hours Daptomycin 4 mg/kg every 24 hours Ceftaroline[f] 600 mg every 12 hours
Immunocompromise, diabetes mellitus, vascular insufficiency, pressure ulcer infection, or other polymicrobial infection suspected	MSSA HA-MRSA[g] CA-MRSA[g] Enterobacteriaceae *P. aeruginosa* Anaerobes	Amoxicillin-clavulanate[d,f] 875 mg every 12 hours Levofloxacin[e] 750 mg every 24 hours + clindamycin 300–600 mg every 6 hours Moxifloxacin[d] 400 mg every 24 hours	Vancomycin, daptomycin, or linezolid, in combination with one of the following choices: Piperacillin-tazobactam[e,f] 4.5 g every 6 hours Ampicillin-sulbactam[f] 3 g every 6 hours Imipenem-cilastatin[e,f] 500 mg every 6 hours Ertapenem[f] 1 g every 24 hours Meropenem[e,f] 1 g every 8 hours Cefepime[e,f] 2 g every 8 hours ± metronidazole 500 mg every 8 hours Ceftazidime[e,f] 2 g every 8 hours + clindamycin 600–900 mg every 8 hours OR Ceftaroline[f] 600 mg every 12 hours + clindamycin 600–900 mg every 8 hours or metronidazole 500 mg every 8 hours

[a]Doses given are for adults with normal renal function. IV therapy can be switched to oral therapy (as for mild infection) when the patient is afebrile and signs of infection are resolving. Extended infusion of beta-lactams can be considered per protocol of individual institution.

[b]CA-MRSA isolates resistant to erythromycin should be evaluated for inducible clindamycin resistance via a D-test.

[c]Limited clinical data exist for the treatment of MRSA infections. Poor activity against GAS; consider using in combination with clindamycin or cephalexin if empiric coverage for GAS is desired.

[d]If CA-MRSA suspected, clindamycin, trimethoprim-sulfamethoxazole, or doxycycline must be added to this regimen.

[e]*P. aeruginosa* generally is susceptible to this agent.

[f]Use caution in patients with known hypersensitivity to β-lactam antibiotics.

[g]MRSA coverage indicated for patients with severe cellulitis or systemic illness, who have risk factors for HA-MRSA or CA-MRSA infection, or reside in areas with high CA-MRSA prevalence. Otherwise, the broad-spectrum regimens listed in the table, without MRSA coverage, are appropriate.

Data from Refs. 5, 12, and 17.

LO 4

Table 73–3 lists some recommended antibiotic regimens for the treatment of ABSSSI. Because antimicrobial susceptibilities vary considerably between geographic locations, clinicians should select empiric treatment based on the antibiograms at their respective institutions. To decrease spread of resistance, antibiotic therapy should be narrowed based on culture and sensitivity results whenever possible. The duration of therapy for uncomplicated cellulitis typically ranges from 5 to 10 days. For complicated cellulitis, therapy with IV antibiotics is generally initiated, and a switch to oral therapy can be made once the patient is afebrile and skin findings begin to resolve. Typically, this is done after 3 to 5 days. The complete duration of therapy may extend beyond 10 days if the patient's infection has a slower clinical response within the first 5 days.[5]

Recurrent cellulitis can be problematic, and reducing risk factors, such as obesity, edema, or toe abnormalities, may help with prevention, especially in the lower extremities. For patients with recurrent abscesses due to *S. aureus*, decolonization regimens can be considered. These include intranasal mupirocin, chlorhexidine

Patient Encounter 1, Part 3: Cellulitis: Clinical Course

During the patient's hospitalization, his wound culture grows methicillin-sensitive *Staphylococcus aureus*. On day four of the patient's hospital stay, his cellulitis has significantly improved. The interdisciplinary team of clinicians is preparing the patient for discharge.

What would you suggest for modification of his antimicrobial regimen to an oral regimen?

What is the appropriate duration of his antibiotic course of therapy for his cellulitis?

How would you monitor his new regimen for safety and efficacy?

What are the patient's risk factors for recurrence of his cellulitis?

What strategies would you recommend to prevent recurrence of cellulitis?

rinses, and decontamination of towels or sheets. Efficacy of decolonization has not been consistently proven to reduce rates of ABSSSIs.[5] Low-dose antibiotic prophylaxis with penicillin or erythromycin for up to 1 year may reduce recurrences, but the benefit subsides when therapy is discontinued.[5,16]

NECROTIZING FASCIITIS

EPIDEMIOLOGY AND ETIOLOGY

LO 2

Necrotizing fasciitis (NF) is a rapidly progressive, life-threatening infection causing necrosis of subcutaneous tissue and fascia. When due to GAS infection, its associated mortality rate approaches 25%.[27] NF can affect any age group. Although the risk of NF is higher in injection drug users and in patients with diabetes or vascular insufficiency, healthy hosts can become infected as well.[5]

NF typically erupts after an initial trauma, which can range from a small abrasion to a deep penetrating wound. The infection begins in the fascia, where bacteria replicate and release toxins facilitating spread.[5]

NF may be monomicrobial, most often involving *S. pyogenes, S. aureus, Vibrio vulnificus, Aeromonas hydrophilia*, or anaerobic streptococci (*Peptostreptococcus*). Polymicrobial NF develops in the following clinical settings: after surgery or deep penetrating wounds involving the bowel; from decubitus ulcer, perianal, or vulvovaginal infection; or from the injection site in an IV drug user.[5]

CLINICAL PRESENTATION AND DIAGNOSIS

Patient outcomes rely on the clinician's ability to recognize NF early in the course of disease. This is often difficult because early disease tends to be indistinguishable from cellulitis. The clinical presentation of NF is presented in Table 73–4.

Table 73–4

Presentation of Necrotizing Fasciitis

Symptoms
- Early: Severe pain that is disproportionate to clinical signs and extends beyond the margins of the infected area.
- Late: Area may become numb secondary to muscle and nerve involvement.

Signs
- Early: Skin is erythematous, edematous, and warm; the clinical presentation is similar to that of cellulitis.
- Intermediate (within 24–48 hours): Blisters and bullae indicate severe skin and tissue ischemia.
- Late: The skin becomes violaceous and progressively gangrenous, and subcutaneous tissues have wooden-hard induration; hemorrhagic bullae may be present. Systemic signs may include fever, tachycardia, hypotension, and shock.

Laboratory Tests
- White blood count, serum creatinine, and C-reactive protein may be elevated.
- Deep tissue specimens obtained during surgical irrigation and debridement should be sent for Gram stain, culture, and sensitivity.

Imaging Studies
- MRI and CT scans may reveal fluid and gas along fascial planes.
- Typically, imaging studies are avoided when making a diagnosis because they may delay surgical intervention and increase mortality.

Data from Refs. 5 and 28.

NF is perhaps the most devastating ABSSSI. Left untreated, it can invade the muscles and circulation, resulting in myonecrosis and septic shock, respectively. Half of the cases caused by GAS are accompanied by GAS toxic shock–like syndrome. The syndrome is endotoxin mediated, manifested by hypotension and multiorgan dysfunction, and highly lethal.[28] Amputation is common in patients with extremity infections. Once the patient recovers from acute NF, he or she often requires skin and/or muscle grafting and consequent physical rehabilitation depending on the amount and types of tissues removed during surgical intervention and the duration of hospital stay.[29]

TREATMENT

LO 3

The goals of therapy for NF include eradication of infection and reduction of related morbidity and mortality.

Nonpharmacologic Treatment

LO 4

KEY CONCEPT *After resuscitation and hemodynamic stabilization*, prompt surgical intervention is key in the treatment of NF. Delayed operative debridement increases mortality, and most patients should return to the operating room frequently until debridement is no longer indicated.[5,29]

Pharmacologic Treatment

As an adjunct to surgery, high-dose, broad-spectrum IV antibiotic therapy should be initiated immediately in patients with NF until the patient has improved clinically and is afebrile for 48 to 72 hours, and no further need for debridement exists. Piperacillin-tazobactam, a carbapenem, ceftriaxone plus metronidazole, or a fluoroquinolone plus metronidazole is appropriate for empiric therapy. These agents should be used in combination with vancomycin, daptomycin, or linezolid until MRSA infection is ruled out.[5] Protein synthesis inhibitors, clindamycin or linezolid, are often utilized to decrease bacterial toxin production, thereby limiting tissue damage. This is particularly beneficial in streptococcal or clostridial infections.[28]

IV immunoglobulin (IVIG) dosed at 2 g/kg may also be a useful adjunctive treatment in patients with GAS NF who present with shock. Anecdotal evidence and data from small studies strongly support its use in improving 30-day survival and reducing mortality, although additional evidence is needed for a definitive recommendation.[5]

DIABETIC FOOT INFECTIONS

EPIDEMIOLOGY AND ETIOLOGY

LO 2

Foot ulcers and related infections are among the most common, severe, and costly complications of diabetes mellitus. For the approximately 25 million patients with diabetes in the United States, the lifetime risk of developing at least one foot ulcer is estimated at 25%.[30] In addition to significant morbidity, the health care costs associated with treating infected foot ulcers are enormous.

Infected diabetic foot ulcers typically contain a multitude of microorganisms. KEY CONCEPT Aerobic gram-positive cocci, such as *S. aureus* and β-hemolytic streptococci, are the predominant pathogens in acutely infected diabetic foot ulcers. However, severe, or more extensive chronically infected wounds are subject to polymicrobial infection. Clinicians should suspect gram-negative (such as *P. aeruginosa*) and possibly low-virulence pathogens (including enterococci and *S. epidermidis*) in polymicrobial infections. Foul-smelling, necrotic, or gangrenous wounds are also commonly infected with anaerobic bacteria.

LO 4

Patient Encounter 2, Part 1: Diabetic Foot Infection

A 69-year-old man presents to the emergency department with complaints of pain, redness, and swelling of his left foot. He has difficulty ambulating to the examination table because his foot is so sore. Upon examination, you see a purulent lesion on the plantar aspect of his left great toe approximately 3 cm (1.2 in) in diameter, and a smaller, more superficial ulcer near the heel. His foot is erythematous, warm, and foul-smelling, and cellulitis and lymphangitic streaking extend beyond his ankle. The patient has poorly controlled type 2 diabetes mellitus, and has not seen his primary care provider in over a year. Because of obesity, the patient admits that it is difficult for him to perform proper foot care at home. The patient is afebrile, and other vital signs are within normal limits.

What signs and symptoms present in this patient are indicative of a diabetic foot infection?

Based on presentation, classify this patient's diabetic foot infection using the PEDIS grading scale.

What additional information do you need before developing a therapeutic plan for this patient?

Patients recently hospitalized or treated with broad-spectrum antibiotics, or those with a previous history of MRSA infection are at risk for MRSA as a causative agent.[31]

PATHOPHYSIOLOGY

KEY CONCEPT The pathogenesis of diabetic foot infection stems from two key factors: peripheral neuropathy and ischemia from peripheral vascular disease.[30] Neuropathy, the most prominent risk factor for diabetic foot ulcers, develops when continuously high blood glucose levels damage motor, autonomic, and sensory nerves. Damage to motor neurons that supply the small intrinsic muscles of the foot causes deformation, resulting in altered muscular balance, abnormal areas of pressure on tissues and bone, and repetitive injuries. Damage to autonomic neurons results in the shunting of blood through direct arteriole-venous communications, thereby decreasing capillary flow. The secretion of sweat and oil is also diminished, producing dry, cracked skin that is more prone to infection. Finally, damage to sensory neurons produces a loss of protective sensation so that the patient becomes unaware of injury or ulceration.[30]

Dysfunction of the endothelial cells and abnormalities of the smooth muscles of the peripheral vessels is also the result of high blood glucose concentrations. Vasoconstriction can occur due to decreased levels of endothelium-derived vasodilators, as well as in the presence of other risk factors, including hypertension, dyslipidemia, and smoking. Together, ischemia and skin breakdown can occur as a cumulative result.[30]

Finally, persons with diabetes have altered immune function that predisposes them to infection. Leukocyte function, and cell-mediated and humoral immunity are compromised in poorly controlled disease.[31] Achieving and maintaining controlled blood glucose levels should be a component of the prevention and management of diabetic foot infections.

CLINICAL PRESENTATION AND DIAGNOSIS

Not all diabetic foot ulcers are infected. However, infection is often difficult to detect when perfusion and the inflammatory response are limited in the patient with diabetes. The common signs and symptoms (ie, pain, erythema, and edema) of infection may be absent.[32] Still, the diagnosis of diabetic foot infection depends mostly on clinical evaluation.

Patient Encounter 2, Part 2: Diabetic Foot Infection: Medical History, Physical Examination, and Diagnostic Tests

PMH: Type 2 diabetes mellitus × 14 years, hypertension, dyslipidemia, obesity, and GERD.

FH: Father died of lung cancer at age 70; mother (age 89) is living with type 2 diabetes mellitus, hypertension, and COPD. One sister alive with hypertension.

SH: Married, no children. Retired rancher. Denies alcohol and tobacco use.

Meds: Lantus 56 units at bedtime, metformin 1000 mg BID, lisinopril 20 mg daily, amlodipine 10 mg daily, atorvastatin 40 mg daily, omeprazole 20 mg daily, and aspirin 81 mg daily.

Allergies: penicillin (hives).

ROS: (+) left foot findings per HPI; (–) headache, chest pain, shortness of breath, cough, nausea, vomiting, diarrhea, and weight loss.

PE:

Gen: Patient is in no acute distress. Wt 154.3 kg (339.46 lb); Ht 6'1" in (185 cm).

Chest: CTAB.

CV: RRR. No murmurs/rubs/gallops.

Ext: 3-cm purulent, erythematous lesion present on the plantar aspect of the left great toe. 2+ edema in the left foot; diminished sensation bilaterally. Lymphangitic streaking present; wound probe 1.5 cm deep.

Labs: Most recent labs were drawn at last visit 8 months ago: BUN 13 mg/dL, SCr 1.1 mg/dL, Glu 239 mg/dL, A_{1C} 12.4%.

The patient is diagnosed with a diabetic foot infection and is admitted to the local hospital.

Explain the role of neuropathy, ischemia, and immunopathy in the development of this patient's diabetic foot infection.

What are the best preventative strategies for diabetic foot infections and complications such as lower extremity amputation?

Antimicrobial therapy for this patient's infection should provide coverage for which microorganisms?

What antimicrobial therapy would you recommend? Include drug, dosage, route, interval, and duration of therapy.

How would you monitor your selected regimen for safety and efficacy?

Purulent drainage from the ulcer is indicative of infection. When pus and inflammatory symptoms are not present, the clinician must be astute to more subtle findings. These include delayed healing, increase in lesion size, prolonged exudate production, malodor, and tissue friability. Abnormal granulation tissue also may be present, as evidenced by color change (from bright red to dark red, brown, or gray) and increased bleeding. The ability to probe the ulcer to the underlying bone is highly indicative of osteomyelitis.[32]

Diabetic foot infections are classified into four categories based on clinical presentation using the PEDIS scale (perfusion, extent/size, depth/tissue loss, infection, sensation). Grade 1 signifies no infection; grade 2, involvement of skin and subcutaneous tissue only; grade 3, extensive cellulitis or deeper infection; and grade 4, presence of SIRS.[31] Table 73–5 provides detailed information regarding these grades.

Imaging studies, such as x-ray and magnetic resonance imaging (MRI), can identify osteomyelitis. Blood cultures should be obtained from all patients with signs and symptoms of systemic illness. Deep tissue cultures may help to direct therapy. Bone also may be sent for culture in cases of osteomyelitis, as osteomyelitis is present in up to half of diabetic foot infections.[33] Superficial cultures of ulcers are unreliable and should be avoided.[31]

Spreading soft tissue infection and osteomyelitis are often the first complications that develop from diabetic foot infection. Some patients develop bacteremia and sepsis.

The most feared complication of infected diabetic foot ulcers is lower extremity amputation. More than 80% of all nontraumatic lower extremity amputations performed each year in the United States are linked to diabetic foot infections, about half of which could be potentially avoided.[30]

Table 73–5

Clinical Classification of a Diabetic Foot Infection

Infection Severity	PEDIS Grade	Clinical Manifestations of Infection
Uninfected	1	Wound lacking purulence or any manifestations of inflammation
Mild	2	Presence of at least two manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends no more than 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness
Moderate	3	Infection (as above) in a patient who is systemically well and metabolically stable but who has at least one of the following characteristics: cellulitis extending > 2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone
Severe	4	Infection in a patient with systemic toxicity or metabolic instability (eg, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)

From Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12)132–173.

Patient Encounter 2, Part 3: Diabetic Foot Infection: Clinical Course

The patient received the empiric therapy you recommended for his diabetic foot infection. Two days later, deep wound cultures were reported positive for *P. aeruginosa*. Blood cultures revealed no growth. The patient remained hospitalized for an additional week, during which time his cellulitis improved on directed antimicrobial therapy. He was discharged to complete his antibiotic therapy and to follow-up as an outpatient in 1 week.

What modifications would you make to this patient's antimicrobial regimen knowing that the causative agent is P. aeruginosa?

What individualized foot care strategies can you suggest to this patient to prevent further infections?

TREATMENT

LO 3

The goals of therapy for diabetic foot infection are eradication of the infection and avoidance of soft tissue loss and amputation.

Prevention

Comprehensive foot care programs and the utilization of multidisciplinary care teams can improve outcomes and decrease amputation rates.[31] Periodic foot examinations with monofilament testing and patient education regarding proper foot care, optimal glycemic control, and smoking cessation are key preventative strategies.

Nonpharmacologic Treatment

The nonpharmacologic treatment of diabetic foot ulcers may include debridement of necrotic or nonviable tissue, wound dressings, vascular or orthopedic surgery, and off-loading pressure from the wound.[31]

Pharmacologic Treatment

The severity of a patient's infection, based on the PEDIS scale, can help guide the selection of empiric antimicrobial therapy. Although most patients with grade 2 diabetic foot infections can be treated as outpatients with oral antimicrobial agents, all grade 4 and many grade 3 infections require hospitalization, stabilization of the patient, and broad-spectrum IV antibiotic therapy.[31]

LO 4

Multiple antibiotic options exist for the treatment of diabetic wound infections. Table 73–6 provides both general treatment strategies and specific, although not all-inclusive, antibiotic recommendations. The duration of therapy correlates with infection severity. Antibiotics should be continued until the infection has resolved, but not necessarily until the ulcer has healed. Milder infections generally require 7 to 14 days of therapy; more severe infections may necessitate treatment durations of 2 to 3 weeks, or longer with bone involvement. Patients with osteomyelitis may require weeks to months of antibiotic therapy depending on whether infected and necrotic bone is surgically debrided or amputated.[31]

Table 73–6

Empiric Pharmacologic Treatment of Diabetic Foot Infection

Infection Severity	PEDIS Grade	General Approach to Empiric Pharmacologic Treatment	Examples of Appropriate Empiric Antibiotics[a]
Uninfected	1	None. Avoid treating uninfected diabetic foot ulcers.	Not applicable
Mild	2	Oral, narrow-spectrum antibiotic therapy with activity against *S. aureus* and streptococcal species. Include coverage for MRSA according to patient history and resistance patterns in the area. Duration of antibiotics: 1–2 weeks, may extend to 4 weeks if slow resolution	MRSA not suspected: cephalexin, dicloxacillin, clindamycin, amoxicillin-clavulanate, levofloxacin MRSA suspected: clindamycin,[b] trimethoprim-sulfamethoxazole,[c] doxycycline,[c] or linezolid
Moderate	3	Difficult to define a general approach. In many patients, highly bioavailable oral therapy is appropriate. IV therapy should be initiated in patients with more extensive or chronic infections, or those with abscess, deep tissue or bone involvement, or gangrene. Duration of antibiotics: 1–3 weeks	Options for grade 3 infections: amoxicillin-clavulanate or ampicillin-sulbactam, cefoxitin, ceftriaxone, ertapenem, levofloxacin[d] + clindamycin, or moxifloxacin MRSA suspected: clindamycin,[b] doxycycline,[c] linezolid, daptomycin, trimethoprim-sulfamethoxazole,[c] or vancomycin
Severe	4	Parenteral, broad-spectrum antibiotic therapy should be initiated. Ideally, drugs with activity against gram-positive, gram-negative, and anaerobic bacteria (especially if wound is malodorous) should be selected. Include coverage for MRSA. Duration of antibiotics: 2–4 weeks	IV options for grade 3–4 infection: gram-negative/anaerobic activity: ampicillin-sulbactam, aztreonam, cefepime, ceftazidime, ceftriaxone, ertapenem, imipenem-cilastatin,[d] piperacillin-tazobactam, meropenem, moxifloxacin, levofloxacin[d] + clindamycin MRSA activity: vancomycin, daptomycin, or linezolid

[a]Please refer to Table 73–3 for dosing in adults with normal renal function.

[b]CA-MRSA isolates resistant to erythromycin should be evaluated for inducible clindamycin resistance via a D-test.

[c]Poor activity against GAS; consider using in combination with clindamycin or cephalexin if empiric coverage for GAS is desired.

[d]*P. aeruginosa* generally is susceptible to this agent.

Data from Williams DT, Hilton JR, Harding KG. Diagnosing foot infection in diabetes. Clin Infect Dis. 2004;39(2):S83–S86.

INFECTED BITE WOUNDS

EPIDEMIOLOGY AND ETIOLOGY

LO 2

Approximately 1 in 2 Americans will be bitten by an animal at least once during their lifetimes.[34] Bite wounds account for 5% of traumatic wounds in emergency departments and 1% of all emergency department visits.[34,35] Although most of these injuries are minor, some will require medical treatment.

Dogs cause most animal bites, typically open lacerations, of which approximately 20% become infected. Cat bites are the second most common animal bite, most often puncture wounds involving the hand. Because cat bites are deep and penetrating, up to 80% may become infected.[36]

Human bites are the third most common and the most serious. Before the availability of antibiotics, up to 20% resulted in amputation. Currently, human bite–associated amputation rates remain at 5%, secondary to vascular compromise and infectious complications.[37]

There are two types of human bite injuries. Occlusal injuries are inflicted by actual biting, whereas clenched-fist injuries are sustained when a person's closed fist hits another's teeth. Of the two, clenched-fist injuries typically are more prone to infectious complications.[36,37]

KEY CONCEPT Bite wound infections generally are polymicrobial.[5]

LO 4

Both the normal flora of the biter's mouth and that of the bite recipient's skin can be implicated. The bacteriology of the cat and dog mouth is quite similar. *Pasteurella multocida,* a gram-negative aerobe, is one of the predominant pathogens. Viridans streptococci are the most frequently cultured bacteria from human bite wounds, although empiric treatment should also provide coverage for *Eikenella corrodens*.[5,37] Table 73–7 provides a comprehensive list of cat-, dog-, and human bite-wound pathogens.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of infected bite wounds is presented in Table 73–7.

Table 73–7

Etiology and Presentation of Infected Bite Wounds

Bacterial Pathogens

- Dog and cat: *Pasteurella multocida,* staphylococci, streptococci *Moraxella* spp., *Eikenella corrodens, Capnocytophaga canimorsus, Actinomyces, Fusobacterium, Prevotella,* and *Porphyromonas* spp.
- Human: Viridans streptococci, *S. aureus, E. corrodens, Haemophilus influenzae,* and β-lactamase–producing anaerobic bacteria.

Signs and Symptoms

- The onset of infectious symptomatology is typically 12–24 hours after the bite.
- Pain at the wound site is common.
- Erythema, edema, and purulent or malodorous drainage at the wound site are manifestations of infected wounds. The patient may be febrile.
- Limited range of motion may be present, especially if the hand is bitten.

Laboratory Tests

- Leukocytosis may be present.
- The clinician should obtain anaerobic and aerobic wound cultures only if the wound appears clinically infected.

Imaging Studies

- Radiographs should be obtained if the bite is on the hand, could have damaged bone or joints, or if an embedded object or tooth fragment is suspected.

Data from Refs. 5 and 37.

Complications of infected bite wounds include lymphangitis, abscess, septic arthritis, tenosynovitis, and osteomyelitis. Bites to the hand are particularly complication-prone.[37]

TREATMENT

LO 3

The goals of therapy for an infected bite wound are rapid and successful eradication of infection and prevention of related complications.

Nonpharmacologic Treatment

LO 4

Thorough irrigation with normal saline is the first step in the care of an infected bite wound. The wound should be elevated and immobilized. Surgical closure may be advocated, especially for facial wounds. Wounds that are infected, at higher risk for infection, or older than 24 hours should be left open because premature closure can lead to disastrous infectious complications.[37]

Pharmacologic Treatment

Most bite wounds require antibiotic therapy only when clinical infection is present. *However, prophylactic therapy is recommended for wounds at higher risk for infection and bites requiring surgical repair.*[37] Bites to the hand or face and human bites may benefit the most from prophylaxis.[36] Other indications include immunocompromised state, asplenia, advanced liver disease, edema in the affected area, or injuries to the joint capsule.[5]

The most effective agent for the treatment (and prophylaxis) of human and animal bite-wound infections is amoxicillin-clavulanate. Alternatives include second-generation cephalosporins, such as cefuroxime, plus coverage for anaerobes, such as clindamycin or metronidazole. Moxifloxacin, doxycycline, or a carbapenem may also be used. The durations of prophylaxis and treatment are generally 3 to 5 days.[5] Consider rabies prophylaxis as appropriate, based on recommendations from the Centers for Disease Control and local health department.

If the wound is associated with significant cellulitis and edema, systemic signs of infection, or possible joint or bone involvement, hospitalization and IV antibiotics (typically ampicillin-sulbactam 3 g IV every 6 hours) should be initiated. Bone and joint infections will require longer durations of therapy of up to 6 weeks.[5,37]

OUTCOME EVALUATION

Education of the patient, caregivers, and household members is important to limit further spread of infection and is a key component in ABSSSI case management. Table 73–8 lists several key prevention messages for patients with ABSSSIs.

Table 73–8

Prevention Education for Patients with ABSSSIs

1. Draining wounds should be covered with clean, dry bandages.
2. Hands should be cleaned regularly with soap and water (or with alcohol-based hand gel if not visibly soiled) and immediately after touching infected skin or any item directly contacting a draining wound.
3. General hygiene should be maintained with regular bathing.
4. Items that may become contaminated with wound drainage or that directly touch the skin should not be shared.
5. Wash and dry thoroughly any clothing that has come in contact with wound drainage after each use.
6. If the wound is unable to be covered with a clean, dry bandage at all times, avoid activities with skin-to-skin contact until the wound is healed.
7. Equipment and environmental surfaces with bare skin contact should be cleaned with *S. aureus*—active detergents or disinfectants.

From Gorwitz RF, Jernigan DB, Powers JH, et al. Strategies for clinical management of MRSA in the community: summary of an experts' meeting convened by the Centers for Disease Control and Prevention [online]. 2006. [cited 2017 Sept 1]. http://www.cdc.gov/ncidod/dhqp/ar_mrsa_ca.html.

LO 5

Patients receiving antibiotic therapy for ABSSSIs require monitoring for efficacy and safety. Efficacy typically is manifested by reductions in temperature, white blood cell count, erythema, edema, and pain. Initially, signs and symptoms of infection may worsen owing to toxin release from certain organisms (ie, GAS); however, they should begin to resolve within 48 to 72 hours of treatment initiation. If no response or worsening infection is noted after the first 3 days of antibiotics, reevaluate the patient.[5] Lack of response may be due to a noninfectious or nonbacterial diagnosis, a pathogen not covered by or resistant to current antibiotic therapy, poor patient adherence, drug or disease interactions causing decreased antibiotic absorption or increased clearance, immunodeficiency, or the need for surgical intervention. To ensure the safety of the regimen, dose antibiotics according to renal and hepatic function as appropriate, and monitor for or minimize adverse drug reactions, allergic reactions, and drug interactions.

Patient Care Process

Collect Information:

- Review the medical history and physical assessment findings.
- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Based on physical examination and review of systems, determine whether the patient is experiencing signs or symptoms of an ABSSSI and if so, its severity.
- Based on the history and presentation, determine the most likely causative microorganism of the patient's infection to select treatment.
- Document current temperature, blood pressure, and heart rate.

(*Continued*)

Patient Care Process (*Continued*)

- Review relevant laboratory tests (eg, complete blood count, renal function, basic metabolic profile, and culture and sensitivity report).
- Identify any significant adverse drug effects or interactions with current drug therapy.

Develop a Care Plan:

- Determine the most appropriate nonpharmacologic or pharmacologic treatment option(s) for the patient's infection based on presentation and history.
- Select the most appropriate antibiotic therapy that is likely to be effective and safe.
- Choose medications, doses, routes, and treatment durations that are optimal for the patient and will result in resolution of infection. In pediatric patients especially, consider method and ease of administration, and palatability and tolerability of oral formulations.

Implement the Care Plan:

- Educate the patient about their drug therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about SSSI and its management.
- Discuss importance of medication adherence to improve resolution of infection and reduce antimicrobial resistance.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary.
- Abide by antimicrobial stewardship practices at the institution.

Follow-up: Monitor and Evaluate:

- Follow-up at an appropriate interval to ensure resolution of infection.
- Review physical examination, vital signs, and lab tests to assess changes in clinical status and resolution of infection.
- Narrow antibiotic coverage when possible with the use of culture and sensitivity data.
- Reinforce proper infection prevention strategies.

Abbreviations Introduced in This Chapter

ABSSSI	Acute bacterial skin and skin structure infection
CA-MRSA	Community-acquired methicillin-resistant *S. aureus*
GAS	Group A *Streptococcus* (also known as *Streptococcus pyogenes*, one of the β-hemolytic streptococci)
GERD	Gastroesophageal reflux disease
HA-MRSA	Health care–associated methicillin-resistant *S. aureus*
IVIG	Intravenous immunoglobulin
MIC	Minimum inhibitory concentration
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-sensitive *S. aureus*
NF	Necrotizing fasciitis
SIRS	Systemic inflammatory response syndrome
SSSI	Skin and skin structure infection
VISA	Vancomycin-intermediate *S. aureus*
VRSA	Vancomycin-resistant *S. aureus*

REFERENCES

1. Kaye KS, Patel DA, Stephens JM, Khachatryan A, Patel A, Johnson K. Rising United States hospital admissions for acute bacterial skin and skin structure infections: recent trends and economic impact. PLoS ONE. 2015;10(11):e0143276.
2. Amin AN, Cerceo EA, Deitelzweig SB, Pile JC, Rosenberg DJ, Sherman BM. Hospitalist perspective on the treatment of skin and soft tissue infections. May Clin Proc. 2014; 89(10):1–16.
3. Moran GJ, Abrahamian FM, LoVecchio F, et al. Acute bacterial skin infections: developments since the 2005 Infectious Diseases Society of America (IDSA) guidelines. J Emer Med. 2013;44(6):e397–e412.
4. Pallin DJ, Espinola JA, Leung DY, et al. Epidemiology of dermatitis and skin infections in United States physicians offices, 1993–2005. Clin Infect Dis. 2009;49:901–907.
5. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. Clin Infect Dis. 2014;41:1373–1406.
6. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infection among patients in the emergency department. N Engl J Med. 2006;355(7):666–674.
7. Jimenez-Truque N, Saye EJ, Soper N, et al. Association between contact sports and colonization with Staphylococcus aureus in a prospective cohort of collegiate athletes. Sports Med. 2017;47(5):1011–1019.
8. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Disease Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011;52:1–38.
9. Dieffenbach CW, Tramont EC, Plaeger SF. Innate (general or nonspecific) host defense mechanisms. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, PA: Elsevier; 2010:37–47.
10. Yagupski P. Bacteriologic aspects of skin and soft tissue infections. Pediatr Ann. 1993;22:217–224.
11. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. Clin Infect Dis. 2005;41:1373–1406.
12. Pasternack MS, Swartz MN. Cellulitis, necrotizing fasciitis, and subcutaneous tissue infections. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, PA: Elsevier; 2010:1289–1312.
13. Cole C, Gazewood J. Diagnosis and treatment of impetigo. Am Fam Physician. 2007;75:859–864, 868.
14. Luelmo-Aguilar J, Santandreu MS. Folliculitis: recognition and management. Am J Clin Dermatol. 2004;5(5):301–310.
15. Raff AB, Kroshinsky D. Cellulitis: a review. JAMA. 2016;316(3): 325–337.

16. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. N Engl J Med. 2013;368;(18):1695–1703.
17. Swartz MN. Clinical practice. Cellulitis. N Engl J Med. 2004;350(9):904–912.
18. Perl B, Gottehrer NP, Raveh D, Schlesinger Y, Rudensky B, Yinnon AM. Cost-effectiveness of blood cultures for adult patients with cellulitis. Clin Infect Dis. 1999;29:1483–1488.
19. Peralta G, Padron E, Roiz MP, et al. Risk factors for bacteremia in patients with limb cellulitis. Eur J Clin Microbiol Infect Dis. 2006;25(10):619–626.
20. Singer M, Deutschman CS, Seymour CW, et al. The third internation consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–810.
21. Pallin DJ, Binder WD, Allen MB, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. Clin Infect Dis. 2013;56: 1754–1762.
22. Moran GJ, Krishnadasan A, Mower WR, et al. Effect of cephalexin plus trimethoprim-sulfamethoxazole vs. cephalexin alone on clinical cure of uncomplicated cellulitis: a randomized clinical trial. JAMA. 2017;317(20):2088–2096.
23. Miller LG, Daum RS, Creech CB, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med. 2015;372(12):1093–1103.
24. Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med. 2014;370:2180–2190.
25. Boucher HW, Wilcox M, Talbot GH, et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med. 2014;370:2169–2179.
26. Lexicomp Online®, Lexi-Drugs®, Hudson, OHil: Lexi-Comp, Inc.; February 9, 2018.
27. Group A Streptococcal (GAS) Disease. Department of Health and Human Services, Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/groupastrep/diseases-hcp/index.html. Accessed February 9, 2018.
28. Anaya DA, Dellinger EP. Necrotizing soft-tissue infection: diagnosis and management. Clin Infect Dis. 2007;44:705–710.
29. Hakkarainen TW, Burkette Ikebata N, Bulger E, et al. Necrotizing soft tissue infections: review and current concepts in treatment, systems of care, and outcomes. Curr Prob Surg. 2014;51:344–362.
30. Clayton W, Elasy TA. A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients. Clin Diabetes. 2009;27:52–58.
31. Lipsky BA, Berendt AR, Cornia PB, et al. Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54(12):132–173.
32. Williams DT, Hilton JR, Harding KG. Diagnosing foot infection in diabetes. Clin Infect Dis. 2004;39(2):S83–S86.
33. Lavery LA, Peters EJ, Armstrong DG, et al. Risk factors for developing osteomyelitis in patients with diabetic foot wounds. Diabetes Res Clin Pract. 2009;83:347–352.
34. Goldstein EJC. Bite wounds and infection. Clin Infect Dis. 1992;14:633–640.
35. Hollander JE, Singer JS, Valentin S, Henry MC. Wound registry: development and validation. Ann Emerg Med. 1995;25:675–685.
36. Singer AJ, Dagum AB. Current management of acute cutaneous wounds. N Engl J Med. 2008;359:1037–1046.
37. Bower MG. Managing dog, cat, and human bite wounds. Nurs Pract. 2001;26(4):36–38, 41–42, 45.

74 Infective Endocarditis

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LEARNING OBJECTIVES

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

LO

1. Differentiate the causes and development of infective endocarditis (IE).
2. Identify the clinical presentation and laboratory evaluation for IE.
3. Assess diagnostic criteria used to evaluate a patient suspected of having IE.
4. Describe the most likely causative pathogens of IE, particularly in specific patient populations.
5. Develop appropriate pharmacologic treatment recommendations for patients with IE.
6. Define appropriate patient populations requiring prophylactic treatment, and differentiate appropriate drug regimens.
7. Devise a monitoring plan for patients with IE to determine treatment efficacy and discern any adverse effects.

INTRODUCTION

Infective endocarditis (IE) is a serious infection affecting the lining and valves of the heart. Although this disease is mostly associated with infection of the heart valves, septal defects may become involved in some cases. Infections also occur in patients with prosthetic or mechanical devices or who are intravenous drug users (IVDUs). Bacteria are the primary cause of IE; however, fungi and atypical organisms may also be responsible pathogens.

Typically, IE is classified into two categories: acute or subacute. Differences between the two categories are based on the progression and severity of the disease. Acute disease is more aggressive, characterized by high fevers, leukocytosis, and systemic toxicity, with death occurring within a few days to weeks. This type of IE is often caused by more virulent organisms, particularly *Staphylococcus aureus*. Subacute disease is often caused by less virulent organisms, such as viridans group streptococci, producing a slower and more subtle presentation. It is characterized by nonspecific symptoms including fatigue, low-grade fever, and weight loss, with death occurring in several months.

Successful management of patients with IE is based on proper diagnosis, treatment with appropriate therapy, and monitoring for complications, adverse events, or development of resistance. The treatment and management of IE are best determined through identification of the causative organism. IE has varied clinical presentations; therefore, patients with this infection may be found in any medical subspecialty (ie, medicine, surgery, critical care, etc).

EPIDEMIOLOGY AND ETIOLOGY

Despite IE being a fairly uncommon infection, in the United States, there are about 10,000 to 15,000 new cases annually, accounting for an incidence of approximately three to seven cases per 100,000 persons-years.[1,2] Although the exact number of cases is often difficult to determine, owing to the diagnostic criteria and reporting methods for this disease, its incidence remains similar overall but is increasing in older patients, those with prosthetic valves, and infections due to *S. aureus*. IE is now considered the fourth leading cause of serious infectious diseases syndromes following sepsis, pneumonia, and intraabdominal abscess.[3] Although IE occurs at any age, more than 50% of cases occur in patients older than 50 years.[1,2] IE in children continues to be uncommon and is mainly associated with underlying structural defects, surgical repair of the defects, or nosocomial catheter-related bacteremia.[1] With the increased use of mechanical valves, prosthetic-valve endocarditis (PVE) now accounts for approximately 10% to 33%.[1,4] Patients who are IVDUs are typically younger patients and also at an increased risk for IE, with 150 to 2000 cases per 100,000 persons per year accounting for 5% to 15% of infection-related hospital admissions.[1,5] Additionally, others at high risk for IE include patients with any congenital or structural cardiac defects, including valvular disease; long-term hemodialysis; diabetes mellitus; poor oral hygiene; major dental treatment; previous endocarditis; hypertrophic cardiomyopathy; and mitral valve prolapse with regurgitation.[3,6,7]

Although almost any type of microorganism is capable of causing IE, the majority of cases are caused by gram-positive bacteria. These consist primarily of streptococci, staphylococci, and enterococci. Consideration of gram-negative, fungal, and other atypical organisms must be taken into account in select patient populations. In Table 74–1, approximate percentages are given for each organism based on the type of IE, including native valve (community-acquired vs health care–associated), prosthetic valve (grouped by months postsurgery), and IVDUs.

PATHOPHYSIOLOGY

LO 1

KEY CONCEPT For IE to develop, the occurrence of several factors is required. Typically, there must be an alteration of the endothelial

Table 74–1

Etiologic Organisms of Infective Endocarditis

	Percentage of Cases							
	Native-Valve IE		PVE at Indicated Onset (Months) after Valve Surgery			IE in IVDU		
	Community-Acquired	Health Care–Associated	< 2	2–12	> 12	Right-sided	Left-sided	Total
Streptococci[a]	40	13	1	9	31	5	15	12
Pneumococci	2	—	—	—	—	—	—	—
Enterococci[b]	9	16	8	12	11	2	24	9
Staphylococcus aureus	28	52[c]	22	12	18	77	23	57
CoNS	5	11	33	32	11	—	—	—
HACEK group	3	—	—	—	6	—	—	—
Gram-negative bacilli	1	1	13	3	6	5	13	7
Fungi (*Candida* spp.)	< 1	1	8	12	1	—	12	4
Polymicrobial/ miscellaneous	3	3	3	6	5	8	10	7
Diphtheroids	—	< 1	6	—	3	—	—	0.1
Culture-negative	9	3	5	6	8	3	3	3

[a]Includes viridans group streptococci; *S. gallolyticus* (formerly *S. bovis*); other nongroup A, groupable streptococci; and *Abiotrophia* and *Granulicatella* spp. (nutritionally variant streptococci).

[b]Primarily *E. faecalis* or nonspeciated isolates, occasionally *E. faecium*.

[c]Methicillin resistance is common among these *S. aureus* strains.

CoNS, coagulase-negative staphylococci; HACEK, *Haemophilus* spp. (primarily *H. paraphrophilus, H. parainfluenzae*, and *H. aphrophilus*), *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*.

Modified from Karchmer AW. Infective endocarditis. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, eds. Harrison's Principles of Internal Medicine, 19th ed. New York: McGraw Hill; 2014: Chap. 155.

surfaces of the heart valves to allow for organism attachment and colonization. These alterations may be produced by an inflammatory process such as rheumatic heart disease or by injury from turbulent blood flow. Platelets and fibrin are then capable of depositing on the damaged valves, forming a **nonbacterial thrombotic endocarditis** (NBTE). At this point, bacteria, through hematogenous spread (ie, bacteremia), adhere to and colonize the **nidus**, forming a **vegetation**. Further deposits of platelets and fibrin cover the bacteria, providing a protective coating that allows for development of a suitable environment for continued organism and vegetation progression, often producing an organism density of 10^9 to 10^{10} **colony-forming units** (CFU) per gram.

Acquisition of PVE differs in early stages, where direct inoculation may occur during surgery rather than through hematogenous seeding. In addition, causative organisms in early PVE are typically nosocomial, with increased likelihood of being drug-resistant.[7,8] The prosthetic valve also has a greater propensity for organism colonization than native valves.[8] However, in late PVE, the process of colonization and vegetation formation is similar to that of native-valve IE, as described earlier.[7,8] Differentiation of native versus prosthetic valve IE is important in determining empiric therapy as well as impacting the risk of disease complications (discussed later).

Typically, vegetations are located on the line along valve closure on the atrial surface of the atrioventricular valves (tricuspid and mitral) or on the ventricular surface of the semilunar valves (pulmonary and aortic). The vegetations can vary significantly in size, ranging from millimeters to several centimeters and may be single or multiple masses. Often, destruction of underlying tissue occurs and may cause perforation of the valve leaflet or rupture of the chordae tendineae, interventricular septum, or papillary muscle. Valve ring abscesses may occur, resulting in fistulas penetrating into the myocardium or pericardial sac, particularly with staphylococcal endocarditis.

Patient Encounter Part 1

A 48-year-old woman with a history of Crohn disease, breast cancer, CHF, and HTN is brought to the emergency department after developing fever, chills, nausea, and vomiting. The patient was recently discharged (approximately 1 month ago) after a prolonged hospital stay with a complicated intraabdominal infection secondary to a perforated colon (blood cultures *E. coli* and urine culture *E. faecalis*). Postoperatively for a colon resection she received approximately 3 weeks of therapy, initially consisting of vancomycin, cefepime and metronidazole then narrowed down to oral ciprofloxacin once discharged. She reports losing about 10 pounds over the past few weeks and denies any use of alcohol or tobacco.

Does the patient have any specific presenting signs or symptoms that would make you suspect IE?

What, if any, risk factors does the patient have for developing IE?

Based on presentation, which causative organism(s) should be considered to empirically treat?

Is there any other information you would like to know before deciding on an empirical treatment for this patient?

Embolic events are also common. Embolization occurs as portions of the friable vegetation break loose and enter the bloodstream. These infected pieces are called **septic emboli**. Pulmonary abscesses are commonly formed as a result of septic emboli from right-sided IE (tricuspid and pulmonary valves). However, left-sided IE (mitral and aortic valves) is more likely to have an embolus travel to any organ, especially kidneys, spleen, and brain. Along with emboli, immune complex deposition may occur in organ systems, causing extracardiac manifestations of the disease. This commonly occurs in the kidneys, producing abscesses, infarction, or glomerulonephritis. Immune complexes or emboli may also produce skin manifestations of the disease, as seen with petechiae, Osler nodes, and Janeway lesions, or within the eye (eg, Roth spots).

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation for IE is quite variable and often nonspecific. KEY CONCEPT A fever is the most frequent and persistent symptom in patients but may be blunted with previous antibiotic use, congestive heart failure, chronic liver or renal failure, or infection caused by a less virulent organism (ie, subacute disease).[1,4] Other symptoms may include chills, weakness, night sweats, dyspnea, weight loss, and myalgias/arthralgias.

Historically, heart murmurs were frequently heard on auscultation (> 85% of cases), but recent data indicates that a new murmur or change/worsening in murmurs was only found in 48% or 20%, respectively.[1,9] Over 90% of patients with a new murmur will develop congestive heart failure, which is a major cause of morbidity and mortality. Splenomegaly and mycotic aneurysms are also noted in many cases of IE.

Peripheral manifestations may be found in up to one-half of adult patients with IE, although recently the prevalence of these findings has been decreasing and is rarely seen in children.[1,3,9]

- **Skin:** *Petechiae* are very small (usually < 3 mm), pinpoint, flat, red spots beneath the skin surface caused by microhemorrhaging. They occur in 10% to 40% of patients with chronic IE and are often found on the buccal mucosa, conjunctivae (Figure 74–1A), and extremities.[1,4] *Splinter hemorrhages* appear as small dark streaks beneath the fingernails or toenails and occur most commonly proximally with IE, typically as a result of local vasculitis or microemboli in about 5% to 15% of patients (Figure 74–1B). *Osler nodes* are small (usually 2–15 mm), painful, tender, subcutaneous nodules located on the pads of the fingers and toes (Figure 74–1D) caused primarily by either septic emboli or vasculitis. These nodes are rare in acute disease but are also nonspecific for IE despite occurring in 3% to 10% of all patients.[1,4] *Janeway lesions* are small, painless, hemorrhagic macular plaques on the palms of the hands or soles of the feet due to septic emboli (in ~5%–10% of patients) and more commonly associated with acute *S. aureus* IE (Figure 74–1E).
- **Extremities:** *Clubbing* of the finger tips typically occurs in long-standing illness and is present in approximately 10% to 20% of patients (Figure 74–1C).[1]
- **Eye:** *Roth spots* occur rarely (< 5% of IE cases) and are oval-shaped retinal hemorrhages with a pale center near the optic disc (Figure 74–1F).

Laboratory Studies

KEY CONCEPT Blood cultures are the essential laboratory test for the diagnosis and treatment of IE. Typically, patients with IE have a low-grade consistent bacteremia.[1] Blood culture results are critical for determining the causative organism, thus aids in selection of the most appropriate therapy. Three blood culture sets from different venipuncture sites should be drawn within 24 hours of initial evaluation to determine the etiologic organism. Approximately 90% of the first two cultures will yield a positive result. If a positive blood culture is not obtained from a patient with suspected IE, the microbiology laboratory should be notified to monitor cultures for growth of fastidious organisms (eg, HACEK) for up to 1 month if these organisms are suspected.

KEY CONCEPT Another important tool aiding in the diagnosis of IE is the echocardiogram. This imaging tool is used to visualize the heart valves to assess the presence of vegetations. Two methods of the echocardiogram are used: the **transthoracic echocardiogram** (TTE) and the **transesophageal echocardiogram** (TEE). The TTE has been used since the 1970s; however, it is less sensitive (historically 40%–60%, newer imaging for native-valve 82%) than

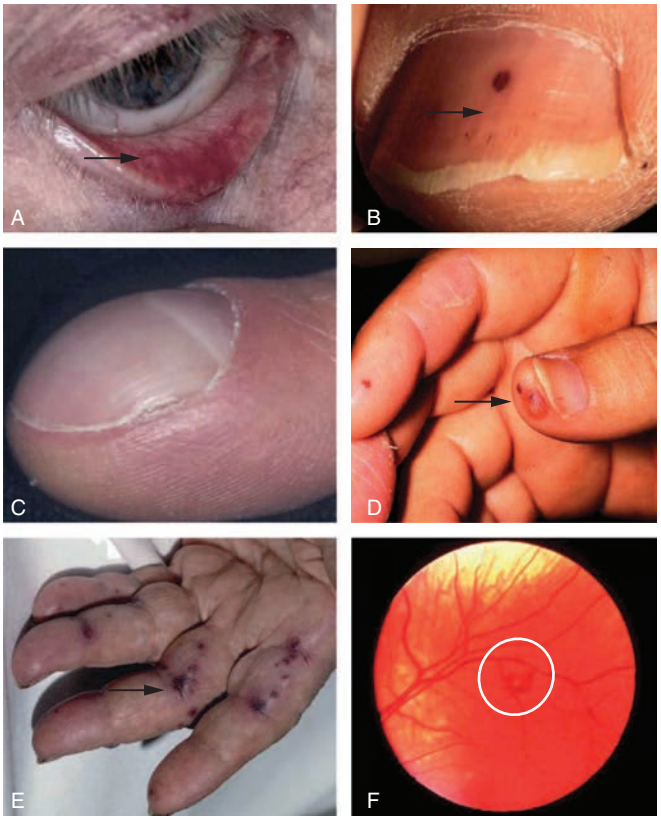

FIGURE 74–1. **(A)** Conjunctival petechiae. (From Wolff K, Johnson R, Saavedra AP, Roh EK. In: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York: McGraw Hill. Copyright 2016.) **(B)** Splinter hemorrhage. (From Knoop KJ, Stack LB, Storrow AB, Thurman AB. In: Atlas of Emergency Medicine. 4th ed. New York: McGraw Hill. Copyright 2016.) **(C)** Clubbing of finger. (From Tosti A, Piraccini BM. In: Fitzpatrick's Dermatology in General Medicine, 7th ed. New York: McGraw Hill. Copyright 2007.) **(D)** Osler nodes. (From Knoop KJ, Stack LB, Storrow AB, Thurman AB. In: Atlas of Emergency Medicine, 4th ed. New York: McGraw Hill. Copyright 2016.) **(E)** Janeway lesions. (From Wolff K, Johnson R, Saavedra AP, Roh EK. In: Fitzpatrick's Color Atlas & Synopsis of Clinical Dermatology, 8th ed. New York: McGraw Hill. Copyright 2016.) **(F)** Roth spots. (From Effron D, Forcier BC, Wyszynski RE. In: Atlas of Emergency Medicine, 4th ed. New York: McGraw Hill. Copyright 2016.)

the TEE (80%–95%).[4] Despite the TEE being more sensitive, use of the TTE for patients with suspected native-valve IE is usually sufficient for diagnosis.[10] The TEE may be used as a secondary test for patients whose TTE was negative in the setting of high clinical suspicion of IE and is often preferred in patients with complicated disease, including left-sided IE, prosthetic valves, or perivalvular extension of the vegetation.[10,11] Echocardiograms may also be employed to assess the need for surgical intervention or to determine the possible source of emboli.[10]

Additional nonspecific tests for IE may be performed. These include hematologic parameters to determine whether the patient is anemic (normochromic, normocytic), which occurs in the majority of patients. The white blood cells (WBCs) may be elevated in acute disease, but potentially normal in a subacute infection. Other nonspecific tests may also result in an increased **erythrocyte sedimentation rate** (ESR) or C-reactive protein, abnormal urinalysis (proteinuria or microscopic hematuria), or thrombocytopenia.

Diagnostic Criteria

A definitive pathological diagnosis of IE consists of invasive testing such as a biopsy or culture directly from specimens of the endocardium. Instead, the clinical diagnosis of IE relies on patient's presentation as well as laboratory and echocardiographic results. LO 3 To guide the clinical diagnosis of IE, major and minor criteria have been established (Table 74–2A).[12] The number of major or minor

Table 74–2

Modified Duke Criteria for IE

2A. Definitions of Modified Duke Criteria

Major Criteria

Blood culture positive for IE:

Typical microorganisms consistent with IE from two separate blood cultures:

Viridans streptococci, *S. bovis*, HACEK group, *S. aureus,* or community-acquired enterococci in the absence of a primary focus, or

Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:

At least two positive cultures of blood samples drawn > 12 hours apart, or

All of three or a majority of four separate cultures of blood (with first and last sample drawn at least 1 hour apart)

Single positive blood culture for *C. burnetii* or antiphase I IgG antibody titer > 1:800

Evidence of endocardial involvement:

Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:

Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant, or on implanted material in the absence of an alternative anatomic explanation, or

Abscess, or

New partial dehiscence of prosthetic valve

New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Minor Criteria

Predisposition: predisposing heart condition or injection drug use

Fever: temperature > 38°C (100.4°F)

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor

Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above[a] or serologic evidence of active infection with organism consistent with IE

2B. Modified Duke Criteria for the Diagnosis of IE

Definite IE

Pathologic criteria:

(1) Microorganisms demonstrated by culture or histologic examination of a vegetation that has embolized, or an intracardiac abscess specimen, or

(2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

Clinical criteria[b]:

(1) Two major criteria, or

(2) One major criterion and three minor criteria, or

(3) Five minor criteria

Possible IE

(1) One major criterion and one minor criterion, or

(2) Three minor criteria

Rejected

(1) Firm alternate diagnosis explaining evidence of IE, or

(2) Resolution of IE syndrome with antibiotic therapy for less than or equal to 4 days, or

(3) No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days, or

(4) Does not meet criteria for possible IE, as above

[a]Excludes single positive cultures for CNS and organisms that do not cause endocarditis.

[b]See above for definitions of major and minor criteria.

TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Data from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–638; by permission of Oxford University Press, 2000 by the Infectious Diseases Society of America.

criteria demonstrated by a specific patient leads to a classification of definite, possible, or rejected diagnosis of IE (Table 74–2B).

Causative Organisms

LO 4

Gram-positive bacteria are the most common causative organisms in IE. Streptococci and staphylococci species account for the majority of cases at more than 80% to 90%.[1,7] Viridans group streptococci are primary pathogens in community-acquired native-valve and pediatric IE. However, staphylococci are now considered the dominant causative organisms, with *S. aureus* being the most common in developed countries (see Table 74–1).[3,9,12] Other gram-positive, gram-negative, atypical, and fungal organisms are less common, but still must be considered in certain patient populations. General recommendations also encourage obtaining an infectious diseases consult to aid in selection of empirical regimen, diagnosis, treatment duration, and management regardless of organism or disease severity.

▶ *Streptococci*

Streptococci causing IE are typically a group of species called viridans group streptococci. The most common of this group are *Streptococcus salivarius, Streptococcus mutans, Streptococcus mitis/oralis*, and *Streptococcus sanguinis* (formerly *sanguis*). This group of bacteria is α-hemolytic and considered normal flora in the human mouth, with most clinical microbiology laboratories not differentiating to the exact species. These organisms may cause bacteremia after dental procedures, which can lead to the development of IE in at-risk patients. Viridans group streptococci are also a predominant pathogen of IE associated with mitral valve prolapse, IE of native valves, and in children.[1,13] Another streptococcal species commonly associated with IE is *Streptococcus gallolyticus* (formerly *bovis*), classified as group D streptococci which is frequently found in the gastrointestinal (GI) tract. However, owing to the similarities of these streptococci, including microbiologic susceptibility, treatment is similar regardless of species. Other streptococcal species (eg, *Streptococcus pneumoniae*, beta-hemolytic streptococci) are a rare cause of IE and would be treated based on susceptibility.

IE caused by these streptococci typically has a subacute clinical course. The current cure rate is often greater than 90% unless complications arise, which do occur in more than 30% of patients.[1,13] The majority of viridans group streptococci remain very susceptible to penicillin, with most strains having a *minimum inhibitory concentration* (MIC) of less than 0.12 mcg/mL (0.12 mg/L).[1,13] However, isolation of organisms with reduced penicillin susceptibilities is increasing. Therefore, antibiotic susceptibilities need to be assessed in order to determine the most appropriate treatment regimen.

▶ *Staphylococci*

Staphylococcal endocarditis continues to increase in prevalence, causing 30% or more of all cases of IE, with the majority (80%–90%) being due to *S. aureus* (coagulase-positive staphylococci).[1,3–5] This increase in staphylococci has been primarily attributed to expanded use of venous catheters, more frequent valve replacement, and increased IVDU.[1,3–5] Coagulase-negative staphylococci (CoNS) is also a cause IE. However, these organisms most frequently infect prosthetic valves over native valves or foreign material such as indwelling catheters, thus is the predominate causative pathogen in PVE.[1,8]

Patients with *S. aureus* bacteremia are at an increased risk of developing IE. *S. aureus* may infect "normal" heart valves (no prior detected valvular disease) in one-third of cases.[1,3] Therefore, it is imperative to assess these patients adequately for the presence of vegetations. Any heart valve may be affected; however, the mitral or aortic valve is most commonly involved, often resulting in extensive infection with a mortality rate of approximately 40%.[1,14] When treating *S. aureus* IE, one must consider whether the isolate displays methicillin-resistance, the location of infection (right or left side), presence of prosthetic valves, and history of IVDU. Despite significantly decreased activity of penicillinase-resistant penicillins (eg, methicillin and nafcillin), most isolates remain susceptible to vancomycin. However, there is an increasing incidence of *S. aureus* with an elevated vancomycin MIC of 2 mcg/mL (2 mg/L) which may require use of an alternative agent, such as daptomycin.[3,15] Additionally, strains with intermediate or fully resistant MICs to vancomycin have been rarely reported.[16,17] Fortunately, these strains are not widespread enough to affect empirical antibiotic selection. Susceptibility reports along with clinical response should be assessed to ensure appropriate antimicrobial coverage.

The predominant coagulase-negative organism causing IE has been *S. epidermidis*. However, there has been an increase in isolation of another coagulase-negative species, *S. lugdunensis*.[18] Typically, coagulase-negative staphylococcal IE has a subacute course with numerous complications. Treatment (with or without surgical intervention) is usually successful. On the other hand, *S. lugdunensis* produces a more virulent infection which is more comparable to that of *S. aureus* and, despite similar antibiotic susceptibilities to other CoNS, has a much higher mortality rate.[18]

▶ *Enterococci*

Enterococci are normal flora of the human GI tract and sometimes found in the anterior urethra. Affected patients are typically older males who have undergone genitourinary manipulations or younger females who have had obstetric procedures. Although enterococci are a less common cause of IE, there are two predominant species: *Enterococcus faecium* and *Enterococcus faecalis*. *E. faecalis* is the most common and more susceptible of the strains. However, enterococcal IE represents one of the most problematic gram-positive bacterial infections to treat and cure. Enterococci, especially *E. faecium*, frequently display intrinsic and acquired resistance to multiple antibiotics, including penicillins, vancomycin, aminoglycosides, linezolid, and daptomycin.[19]

▶ *Gram-Negative Bacteria*

Gram-negative bacterial IE is much less common (~2%), but is typically much more difficult to treat than gram-positive bacterial infections.[1,20] Fastidious organisms, such as the HACEK group, tend to predominate, causing approximately 3% of all native valve IE.[1,21,22] HACEK organisms consist of *Haemophilus* spp. (primarily *H. paraphrophilus, H. parainfluenzae*, and *H. aphrophilus*), *Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*. The clinical presentation of IE by these organisms is subacute, with approximately 50% of patients developing complications. These complications are primarily due to the presence of large, friable vegetations and numerous emboli along with development of acute congestive heart failure often requiring valve replacement.[21,23] Traditionally, it was important to allow cultures sufficient incubation time (often 2–3 weeks) in order to isolate these organisms. Newer media and current automated incubation systems are now favored for recovery. Despite improvement in isolating these organisms, they may still not be isolated on culture and, thus, may present as culture-negative IE.

Other gram-negative organisms, such as *Pseudomonas* spp., can cause IE, especially in IVDUs, health care exposure, and in

patients with prosthetic valves. Additionally, IE may be caused by *Salmonella* spp., *Escherichia coli, Citrobacter* spp., *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens, Proteus* spp., and *Providencia* spp.[1,20]

Historically, gram-negative IE typically had a poor prognosis with high mortality rates. However, as nondrug therapy advances to include cardiac surgery in more than half of patients, in-hospital mortality has improved to 24%.[1,20] Treatment usually consists of high-dose combination antimicrobial therapy, with valve replacement often necessary in many patients.

▶ *Culture-Negative IE*

Negative blood cultures are reported in approximately 5% of confirmed IE cases, often resulting in delayed diagnosis and treatment.[1,4,24] Cultures that do not grow bacteria may be the result of previous antibiotic use, subacute right-sided disease, slow growth of fastidious organisms, nonbacterial endocarditis (eg, fungal or intracellular parasitic infections), noninfective endocarditis, or improper collection of blood cultures. If nonbacterial or fastidious organisms are suspected, additional testing is essential. The choice of treatment regimen depends on patient history and risk factors.

▶ *Other Organisms*

Numerous other bacteria, including gram-positive bacilli, unusual gram-negative bacteria, atypical bacteria, and anaerobes, as well as spirochetes, are rare causes of IE.[25] Some of the more common organisms include *Legionella, Coxiella burnetii* (Q fever), and *Brucella*. These rare organisms occur primarily in at-risk patients such as those with prosthetic valves or IVDUs. A comprehensive discussion of these organisms is not feasible for this chapter; for further information, other references (particularly references 1–4 and 8 at the end of this chapter) should be examined. Identification and treatment of these organisms is difficult, and cure rates are low. Therefore, consulting an infectious diseases specialist is warranted.

▶ *Fungi*

Fungal endocarditis is quite uncommon, but has significant mortality and typically affects patients with a history of cardiovascular surgery, total parenteral nutrition (TPN), prolonged courses of broad-spectrum antibiotics, long-term catheter placement, immunocompromised, or IVDU.[4,26] Survival rates were historically poor at approximately 15%, but improved survival rates of ~40% have been reported owing to advances in diagnosis and treatment.[26] Poor prognosis has been attributed to large vegetations, propensity for organism invasion into the myocardium, extensive septic emboli, poor antifungal penetration into vegetations, and low toxic-to-therapeutic ratio and lack of cidal activity of certain antifungals.[21,26] The two most commonly associated organisms are *Candida* spp. and *Aspergillus* spp. Lack of clinical studies makes treatment decisions difficult. Typically, combination and/or high-dose therapy in conjunction with surgery is required.

TREATMENT

General Approaches/Therapeutic Considerations

Treatment of IE often is complicated and difficult. Numerous factors involving vegetations influence the effectiveness of antimicrobial agents. The fibrin matrix of vegetations provides an environment where organisms are relatively free to replicate unimpeded, allowing the microbial density to reach very high concentrations (10^9–10^{10} CFU/g). Once organism density has reached this level, the majority of organisms are in a static growth phase. These factors hinder host defenses, as well as the ability of antimicrobials to produce sufficient kill. This is often seen with β-lactams and glycopeptides as their effectiveness can be significantly diminished with increased bacterial inoculum and stationary growth phase of the bacteria.

KEY CONCEPT Selection of an appropriate antimicrobial agent must combine characteristics such as the ability to penetrate into the vegetation, the ability to achieve adequate drug concentrations, and the ability to be minimally affected by high bacterial inoculum in order to achieve adequate kill rates.

KEY CONCEPT To accomplish this, antimicrobials typically have to be given parenterally at high doses, with an extended treatment course of 4 to 6 weeks (in most cases). Other desirable drug characteristics include bactericidal and synergistic activity.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Crohn disease, breast cancer, CHF and HTN, perforated colon

Surgical History: Bilateral mastectomy (age 35), colon resection (age 48)

FH: Mother had diabetes and kidney disease, died at age 62; father had a history of HTN, dyslipidemia, and BPH, died at age 75

SH: Currently at a rehab facility, but prior to previous admission lived at home. She denied alcohol or tobacco usage.

Meds: Lisinopril 20 mg daily, furosemide 80 mg twice daily, carvedilol 12.5 mg twice daily, infliximab 400 mg every 8 weeks

Allergies: Clindamycin

ROS: Weakness, recent weight loss ~10 pounds (4.55 kg), nausea, vomiting, chills, shortness of breath

PE:

VS: BP 110/60 mm Hg, P 115 beats/min, RR 22 breaths/min, T 38.8°C

Cardiovascular: Tachycardia, worsening murmur than on previous admission

Abd: Obese, soft, tender, guarded, nondistended; (–) bowel sounds

Labs: Within normal limits, except WBC = 16.2 × 10^3/μL (16.2 × 10^9/L), Neutrophils = 72%, Bands = 21%, SCr = 2.9 mg/dL (256.4 μmol/L), BUN 68 mg/dL (24.3 mmol/L urea), BNP 680 pg/mL (196.5 pmol/L), ALT 124 U/L (2.1 μKat/L)

Given this additional information, what is your assessment of the patient's condition?

Do you have any other concerns based on the patient's presenting signs/symptoms?

What do you recommend for empiric treatment for this patient?

What other information would be beneficial?

Empiric Pharmacological Therapy

KEY CONCEPT The overall goal of therapy is to eradicate the infection and minimize/prevent any complications. Patients with suspected IE should be evaluated for risk factors that may provide some indication of the most likely causative organism. If no risk factors can be determined, empirical therapy should primarily cover gram-positive bacterial organisms, specifically *S. aureus*, viridans group streptococci, and enterococci. Thus, vancomycin is a reasonable empiric therapy unless decreased local susceptibilities (mainly for enterococci) or patient concerns in which daptomycin would be more appropriate. If risk factors for other organisms are present, broaden coverage based on suspected pathogens. It is important to monitor the patient's response to therapy closely until cultures and susceptibilities are determined to ensure treatment is appropriately tailored to maximize patient outcome.

Specific Therapy

LO 5

The American Heart Association (AHA) has published guidelines for the management of IE, including specific treatment recommendations.[3] A summary of recommended treatment regimens for the most common organisms (streptococci, staphylococci, and enterococci) is provided in Tables 74–3

Table 74–3

Therapy of Native-Valve Endocarditis Caused by Highly Penicillin-Susceptible Viridans Group Streptococci and *S. gallolyticus (bovis)*

Regimen	Dosage[a] and Route	Duration (weeks)	Strength of Recommendation[b]	Comments
Aqueous crystalline penicillin G sodium[c] *OR*	12–18 million units/24 hour IV either continuously or in four or six equally divided doses	4	Class IIa, Level of Evidence B	Preferred in most patients ≥ 65 years of age or patients with impairment of eighth cranial nerve function or renal function
Ceftriaxone sodium	2 g/24 hour IV/IM in one dose	4	Class IIa, Level of Evidence B	
Aqueous crystalline penicillin G sodium *OR*	12–18 million units/24 hour IV either continuously or in six equally divided doses	2	Class IIa, Level of Evidence B	2-week regimen not intended for patients with cardiac or extracardiac abscess or for those with creatinine clearance of < 20 mL/min/1.73m^2 (0.19 mL/s/m^2), impaired eighth cranial nerve function, or *Abiotrophia, Granulicatella, or Gemella* spp. infection; gentamicin dosage should be adjusted to achieve peak serum concentration of 3–4 mcg/mL (3–4 mg/L; 6.3–8.4 µmol/L) and trough serum concentration of < 1 mcg/mL (1 mg/L; 2.1 µmol/L) when three divided doses are used; there is no optimal drug concentrations for single daily dosing[e]
Ceftriaxone plus	2 g/24 hour IV/IM in one dose	2	Class IIa, Level of Evidence B	
gentamicin sulfate[d] *OR*	3 mg/kg/24 hour IV/IM in one dose	2		
Vancomycin hydrochloride[f]	30 mg/kg/24 hour IV in two equally divided doses	4	Class IIa, Level of Evidence B	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dose should be adjusted to a trough concentration range of 10–15 mcg/mL (10–15 mg/L; 6.9–10.4 µmol/L)

[a]Doses recommended are for patients with normal renal function.

[b]Class IIA—benefit > > risk, level of evidence B—limited populations evaluated; recommendations in favor of treatment or procedure being useful/effective, although some conflicting evidence from single randomized trial or nonrandomized studies.

[c]Ampicillin 2 g IV every 4 hours is a reasonable alternative to penicillin if a penicillin shortage exists.

[d]Other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in three equally divided doses.

[e]Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.

[f]Vancomycin dosages should be infused during course of at least 1 hour to reduce risk of histamine-release "red man" syndrome.

IM, intramuscular; IV, intravenous; highly penicillin-susceptible is defined as an MIC is less than or equal to 0.12 mcg/mL (0.12 mg/L).

Table 74–4

Therapy for Native-Valve Endocarditis Caused by Staphylococci

Regimen	Dosage[a] and Route	Duration (weeks)	Strength of Recommendation[b]	Comments
Oxacillin-Susceptible Strains				
Nafcillin or oxacillin	12 g/24 hour IV in four to six equally divided doses	6	Class I, level of evidence C	For complicated right-sided IE and for left-sided IE, 6-week treatment; for uncomplicated right-sided IE, 2-week treatment
For penicillin-allergic (nonanaphylactoid type) patients			Class I, level of evidence B	Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin
Cefazolin	6 g/24 hour IV in three equally divided doses	6		Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases
Oxacillin-Resistant Strains				
Vancomycin hydrochloride[c]	30 mg/kg/24 hour IV in two equally divided doses	6	Class I, level of evidence C	Adjust vancomycin dosage to achieve trough concentration of 10–20 mcg/mL (10–20 mg/L; 6.9–13.8 μmol/L) (see text for vancomycin alternatives)
Daptomycin	≥ 8 mg/kg/dose	6	Class IIb, level of evidence B	Await additional study data to define optimal dosing

[a]Doses recommended are for patients with normal renal function.

[b]Class I—benefit > > > risk, Class IIb—benefit > or equal to risk; level of evidence B—limited populations evaluated, recommendations that treatment or procedure is useful/effective, evidence from single randomized trial or nonrandomized studies, level of evidence C—limited populations evaluated, recommendations that treatment or procedure is useful/effective, only expert opinion, case series or standard of care.

[c]For specific dosing adjustment and issues concerning vancomycin, see Table 74–3 footnotes.

IV, intravenous.

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through 74–6. However, for more detailed information, refer to the complete guidelines.[3]

▶ *Streptococci*

Most isolates are highly susceptible to penicillin; therefore, penicillin G or ceftriaxone remain the preferred agents unless patients are unable to tolerate β-lactams or penicillin resistance is suspected. Typically, length of treatment is 4 weeks and remains the most common duration. However, a shorter course (ie, 2 weeks) may be employed for a patient with uncomplicated IE due to highly penicillin-susceptible strains with no extracardiac infection or whose creatinine clearance is greater than 20 mL/min/1.73 m^2 (0.19 mL/s/m^2). If the shorter length of therapy is chosen, gentamicin should be added to the previous regimens for the entire course (ie, 2 weeks). Recommended therapies for highly penicillin-susceptible viridans streptococci are summarized in Table 74–3.

When penicillin MICs for viridans group streptococci are greater than 0.12 mcg/mL (0.12 mg/L) but less than or equal to 0.5 mcg/mL [0.5 mg/L], antimicrobial duration should be increased to 4 weeks of penicillin G (ceftriaxone or ampicillin remain alternatives). In addition, combination therapy with gentamicin is recommended during the first 2 weeks if utilizing penicillin G or ampicillin. In patients who are allergic or intolerant to β-lactams, vancomycin monotherapy is an alternative treatment option. In patients with resistant strains of viridans group streptococci (MIC > 0.5 mcg/mL [0.5 mg/L]), treatment should include antimicrobial agents utilized for enterococcal IE (precise agents determined by the susceptibility report) such as high-dose penicillin G, or ampicillin combined with gentamicin. If susceptible, ceftriaxone plus gentamicin may be an alternative.

Table 74–5

Therapy for PVE or Other Prosthetic Material Caused by Staphylococci

Regimen	Dosage[a] and Route	Duration (weeks)	Strength of Recommendation[b]	Comments
Oxacillin-Susceptible Strains				
Nafcillin or oxacillin *plus* Rifampin *plus* Gentamicin sulfate[c]	12 g/24 hour IV in six equally divided doses 900 mg/24 hour IV/orally in three equally divided doses 3 mg/kg/24 hour IV/IM in two or three equally divided doses	6 weeks or longer 6 weeks or longer 2	Class I, level of evidence B	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 74–3 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins.
Oxacillin-Resistant Strains				
Vancomycin hydrochloride *plus* Rifampin *plus* Gentamicin sulfate[c]	30 mg/kg/24 hour IV in two equally divided doses 900 mg/24 hour IV/oral in three equally divided doses 3 mg/kg/24 hour IV/IM in two or three equally divided doses	6 weeks or longer 6 weeks or longer 2	Class I, level of evidence B	Adjust vancomycin to a trough concentration of 10–20 mcg/mL (10–20 mg/L; 6.9–13.8 μmol/L)

[a]Dosages recommended are for patients with normal renal function.

[b]Class I—benefit > > > risk; level of evidence B—limited populations evaluated, recommendations that treatment or procedure is useful/effective, evidence from single randomized trial or nonrandomized studies.

[c]Gentamicin should be administered in close proximity to vancomycin, nafcillin, or oxacillin dosing. See Table 74–3 for appropriate dose of gentamicin.

IM, intramuscular; IV, intravenous

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Vancomycin alone may be used for patients unable to tolerate β-lactams.

Patients with PVE caused by penicillin-susceptible strains of viridans streptococci require treatment for 6 weeks with penicillin G or ceftriaxone with or without gentamicin during the initial 2 weeks of therapy. However, if the organism demonstrates less susceptibility to penicillin (MIC > 0.12 mcg/mL [0.12 mg/L]), combination therapy with penicillin G or ceftriaxone plus gentamicin should be given for the entire 6 weeks. Vancomycin remains the primary alternative for β-lactam (eg, penicillins, cephalosporins) allergic patients.

▶ *Staphylococci*

It is important to determine (a) whether the isolate is methicillin-susceptible versus methicillin-resistant and (b) whether the patient has a native versus prosthetic valve. For patients with native-valve IE, methicillin-susceptible staphylococcal treatment should consist of a penicillinase-resistant penicillin (eg, nafcillin or oxacillin) or cefazolin, and for methicillin-resistant strains, therapy should consist of vancomycin or daptomycin (see Table 74–4). Duration for all therapies should be for 6 weeks. In patients with central nervous system (CNS) involvement (ie, brain abscess), use of penicillinase-resistant penicillin or vancomycin is recommended. If use of daptomycin is needed, consult with infectious diseases is recommended to assist in optimal dosing.

For staphylococcal PVE, treatment length increases significantly, typically requiring a minimum of 6 weeks (see Table 74–5). For methicillin-sensitive staphylococci, a

Patient Encounter, Part 3: Additional Laboratory and Diagnostic Tests

Blood Cultures: 2 out of 3 sets taken on admission are positive for gram-positive cocci in pairs and chains; presumptive report enterococcal species

Labs: CBC with differential and BMP obtained on day 3, all within normal limits excluding WBC 17.1 × 10^3/μL (17.1 × 10^9/L), Neutrophils 78%, Bands = 18%, SCr = 2.3 mg/dL (203.3 μmol/L), BUN 35 mg/dL (12.5 mmol/L urea)

Echo: TTE was inconclusive secondary to difficulty in visualizing the valves.

Given this additional information, would you make any changes in the assessment of your patient?

Would you adjust therapy at this time based on these new data?

Are you now able to determine treatment goals, including length of treatment?

What other information would you like to obtain?

Table 74–6

Therapy for Endocarditis Involving a Native-Valve or Prosthetic-Valve or Other Prosthetic Material Resulting from Enterococcus Species Caused by Strains Susceptible to Penicillin (in patients who can tolerate β-lactam therapy), Gentamicin, and Vancomycin (in patients unable to tolerate β-lactam therapy)

Regimen	Dosage[a] and Route	Duration (weeks)	Strength of Recommendation[b]	Comments
Able to Tolerate β-lactam Therapy				
EITHER				
Ampicillin sodium	12 g/24 hour IV in six divided doses	4–6	Class IIa, level of evidence B	Native valve: 4-week therapy recommended for patients with symptoms of illness ≤ 3 months; 6-week therapy recommended for patients with symptoms > 3 months and for patients with prosthetic valve or prosthetic material. Recommended for patients with creatinine clearance > 50 mL/min/1.73m^2 (0.48 mL/s/m^2).
OR				
Aqueous crystalline penicillin G sodium	18–30 million units/24 hour IV either continuously or in six equally divided doses	4–6	Class IIa, level of evidence B	
plus				
Gentamicin sulfate[c]	3 mg/kg ideal body weight IV in two to three equally divided doses	4–6		
OR				
Combination *β-lactam* Ampicillin	2 g IV every 4 hours	6	Class IIa, level of evidence B	Recommended for patients with initial creatinine clearance < 50 mL/min/1.73m^2 (0.48 mL/s/m^2) or who develop creatinine clearance < 50 mL/min/1.73m^2 (0.48 mL/s/m^2) during therapy with gentamicin-containing regimen.
plus				
Ceftriaxone	2 g IV every 12 hours	6		
Penicillin Resistance or Unable to Tolerate β-lactams				
Vancomycin hydrochloride[d]	30 mg/kg/24 hour IV in two equally divided doses	6	Class IIa, level of evidence B	For patients unable to tolerate β-lactams.
plus			Class IIb; level of evidence C	For patients with penicillin resistance; intrinsic or β-lactamase producer.
Gentamicin sulfate[c]	3 mg/kg/24 hour IV/IM in three equally divided doses	6		For β-lactamase-producing strains, if able to tolerate a β-lactam antibiotic, ampicillin-sulbactam[e] plus aminoglycoside therapy may be used.

[a]Dosages recommended are for patients with normal renal function.

[b]Class IIA—benefit > > risk, level of evidence B—limited populations evaluated; recommendations in favor of treatment or procedure being useful/effective, although some conflicting evidence from single randomized trial or nonrandomized studies; Class IIb—benefit > or equal to risk, Level of evidence C—limited populations evaluated, recommendations that treatment or procedure is useful/effective, only expert opinion, case series or standard of care.

[c]Dosage of gentamicin should be adjusted to achieve a peak serum concentration of 3 to 4 mcg/mL (3–4 mg/L; 6.3–8.4 µmol/L) and a trough concentration of less than 1 mcg/mL (1 mg/L; 2.1 µmol/L).

[d]Dose of vancomycin should be adjusted to obtain a serum trough concentration of 10 to 20 mcg/mL (10–20 mg/L; 6.9–13.8 µmol/L)

[e]Ampicillin-sulbactam dosing is 3 g IV every 6 hours.

IV, intravenous.

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penicillinase-resistant penicillin (ie, nafcillin or oxacillin) should still be used, as well as vancomycin for methicillin-resistant staphylococci. Duration of therapy should be at least 6 weeks. However, with either regimen, addition of gentamicin for first 2 weeks and rifampin for the entire length of treatment is recommended. Infectious diseases consultation is recommended for all patients with *S. aureus* IE, irrespective of methicillin-susceptibility, due to an observed reduction in mortality associated with expert consultation in this patient population.

Increasing resistance of staphylococci necessitates the expanded use of alternative therapies. Secondary to studies in patients with staphylococcal IE in which daptomycin demonstrated similar efficacy when compared to standard

therapy (ie, penicillinase-resistant penicillin for methicillin-sensitive *S. aureus* [MSSA] or vancomycin for methicillin-resistant *S. aureus* [MRSA]), the Food and Drug Administration (FDA) approved the agent for treatment of right-sided IE or bacteremia caused by *S. aureus*.[27] The recommended daptomycin dosing for these indications is 6 mg/kg/day (unless renal adjustments are necessary); however, several studies and current AHA IE guidelines recommend higher dosages of greater than or equal to 8 mg/kg in IE.[3,15,29] Daptomycin, even at higher dosages, has been shown to be safe and well tolerated.[27–29] Additionally, other antibiotics, such as ceftaroline, linezolid, tedizolid, quinupristin/dalfopristin, telavancin, long-acting lipoglycopeptides, and tigecycline alone or in combination, have been used in patients with variable response rates.[30–35] These therapies often are reserved for patients who have been unresponsive to traditional therapy or for multidrug-resistant organisms.

▶ *Enterococci*

For enterococci, it is imperative to determine the specific species given significant differences in antibiotic susceptibility patterns between the two most common organisms (*E. faecalis* vs *E. faecium*). If the organism is susceptible to penicillin, ampicillin, and vancomycin, treatment may consist of high-dose penicillin G, ampicillin, or vancomycin (for β-lactam allergy) plus an aminoglycoside (gentamicin [see Table 74–6] or streptomycin for gentamicin-resistant strains). Treatment length is usually 4 to 6 weeks, with the aminoglycoside used over the entire course if the patient does not develop toxicities. However, 6 weeks of combination β-lactam therapy is recommended as an alternative for patients unable to tolerate aminoglycoside therapy or aminoglycoside resistance, particularly for *E. faecalis*.[3] As resistance develops to penicillin and ampicillin, vancomycin remains a viable treatment option. If the isolate becomes resistant to vancomycin, daptomycin or linezolid are currently the most appropriate/viable treatment options.

Treatment options for vancomycin-resistant enterococci (VRE) have not been well established. However, current recommendations for treating vancomycin-resistant enterococcal isolates include linezolid or daptomycin for a minimum of 6 weeks. The most likely species to develop vancomycin resistance is *E. faecium*, as *E. faecalis* infrequently develops multidrug resistance and ampicillin susceptibility is typically retained in this latter species. Per AHA IE guidelines, dosing for the recommended therapy is daptomycin 10 to 12 mg/kg per dose and linezolid 600 mg IV or orally every 12 hours. However, use of either agent has concerns. Linezolid is a bacteriostatic agent with potential for resistance development and/or increased likelihood of significant hematological side effects over a prolonged treatment course. Daptomycin is considered a bacteriocidal agent, but development of resistance is increasing; thus combination therapy with a beta-lactam (eg, ampicillin or ceftaroline) has been shown to enhanced activity even for daptomycin nonsusceptible organisms. Synergistic combinations with gentamicin, rifampin, or tigecycline have also been utilized with variable results. Other potential agents include long-acting lipoglycopeptides (insufficient data at this point) or quinupristin/dalfopristin (rarely used secondary to side effects and intrinsic resistance to *E. faecalis*).[36] Even with agents displaying susceptibility, combination therapy is often warranted; therefore, consultation with an infectious diseases specialist is recommended if VRE is identified.

Patient Encounter Part 4: Additional Laboratory

Susceptibility Report: *Enterococcus faecium*

Drug	MIC (mg/L)
Ampicillin	≥ 16
Vancomycin	≥ 32
Linezolid	≤ 2
Daptomycin	≤ 2
Gentamicin synergy	> 500

Repeat blood cultures: Preliminary blood cultures from day 3—presumed enterococci

Echo: TEE shows 0.5 × 0.8 cm vegetation on the aortic valve

VS Day 5: BP 118/68 mm Hg, P 108 beats/min, RR 20 breaths/min, T 38.5°C

Labs: CBC with differential and BMP obtained on day 5, all within normal limits excluding WBC 16.1 × 10^3/μL (16.1 × 10^9/L), Neutrophils 76%, Bands = 15%, SCr = 2.1mg/dL (185.6 μmol/L), BUN 32 mg/dL (11.4 mmol/L urea)

Given this additional information, are there any changes in your assessment of the patient?

Do you need to adjust your treatment regimen based on these data?

What are your treatment goals, including nonpharmacologic therapy and length of treatment?

▶ *Gram-Negative Bacteria*

Identification of the exact pathogen is crucial in gram-negative bacterial IE as treatment decisions depend on which organism is isolated. Therapy is usually targeted to the most susceptible antibiotics. Combination therapy is commonly used, usually with the addition of an aminoglycoside or fluoroquinolone. For example, *Pseudomonas* spp. are treated with an antipseudomonal β-lactam (eg, piperacillin/tazobactam, cefepime, imipenem/cilastatin) plus high-dose aminoglycoside (typically tobramycin 8 mg/kg/day).[1] However, exact dosing of antibiotics depends on the organism isolated. Length of treatment is usually a minimum of 6 to 8 weeks and often includes surgical intervention. Consultation with an infectious diseases specialist is recommended.

▶ *HACEK Group*

The HACEK group bacteria are difficult to isolate, often leading to culture-negative IE. If one of these organisms is suspected, it is important to initiate appropriate empirical treatment. The preferred regimen is ceftriaxone (or another third- or fourth-generation cephalosporin), followed by ampicillin-sulbactam due to the increased occurrence of β-lactamase–producing strains. However, for patients who are intolerant of these treatments, fluoroquinolones may be used. The length of treatment for these organisms is typically 4 weeks (native-valve) or 6 weeks (prosthetic-valve).

▶ *Culture-Negative IE*

Treatment for culture-negative IE presents a significant dilemma. As outlined above, therapeutic regimens are usually guided

by isolated organisms. When cultures fail to identify a specific organism, decisions regarding empiric treatment should cover the most common causative pathogens. Patient characteristics and risk factors aid in defining additional organisms requiring coverage (refer to AHA guidelines for specific etiologic features).[3] If the patient is unresponsive to initial treatment, additional coverage for less common organisms becomes warranted. An infectious diseases specialist should be consulted for the management of culture-negative IE.

▶ *Fungi*

Treatment of fungal IE is exceptionally difficult. There is a significant lack of evidence to identify the most appropriate therapy. Currently, amphotericin B is the most common treatment. However, valve replacement surgery is often considered a necessary adjunctive therapy in the majority of cases. Intravenous antifungal therapy requires high doses for a minimum of 6 weeks of treatment, often followed by life-long oral suppression therapy (ie, oral triazoles). Newer antifungals may be effective options, including echinocandins (eg, caspofungin) and voriconazole, depending on the organism and susceptibilities.[26]

Surgery

Surgical intervention has become an integral therapy in combination with pharmacologic management of IE. Valve replacement is the predominant intervention, and is used in almost one-half of all cases of IE.[1] Surgery may be indicated if the patient has unresolved infection, ineffective antimicrobial therapy, more than one episode of serious emboli, refractory congestive heart failure, significant valvular dysfunction, mycotic aneurysm requiring resection, local complications (perivalvular or myocardial abscesses), or prosthetic-valve infection associated with a pathogen demonstrating higher antimicrobial resistance.[37,38] Often a patient's hemodynamic status (eg, blood pressure, heart rate, pulmonary artery pressure) is used to determine when surgical intervention is warranted.[1] Despite appropriate medical management and cure, a significant number of people who develop native-valve endocarditis require valve replacement surgery. Involvement of the aorta or development of IE complications is considered an indication for surgery in the majority of patients with PVE.[39,40]

Antimicrobial Dosing Considerations

The majority of antibiotic and antifungal agents used for the treatment of IE require dosing modifications based on renal or hepatic function. However, the most closely monitored are vancomycin and aminoglycosides. This is due in part because (a) therapeutic drug monitoring of serum concentrations is normally utilized to guide therapy, and (b) there is an increased likelihood of toxicity (ie, nephrotoxicity, ototoxicity) if the drug concentration is too high or adverse outcomes (ie, clinical failure or resistance development) if level is too low. General dosing considerations are included in Table 74–7 for the most common drugs used in the treatment of IE. However, specific dosing adjustments for individual patients should be determined by referring to an appropriate drug dosing reference.

Prophylaxis

KEY CONCEPT Certain conditions have been associated more commonly with IE due to preexisting cardiac disease in the presence of a transient bacteremia. In an effort to prevent the development of IE, prophylactic treatment is generally considered appropriate for these at-risk patients. Although there are no well-controlled clinical studies of these recommendations, it is thought that if antibiotics are given just prior to a procedure, the number of bacteria may be decreased in the bloodstream and prevent the bacteria from adhering to the valves.

Cardiac conditions in which prophylaxis is reasonable include presence of prosthetic valves or material, prior IE, select forms of congenital heart disease, and cardiac transplant patients with cardiac valvulopathy (Table 74–8).[6] Although many patients have other cardiac dysfunction, only patients with these conditions are considered to be at a high risk of developing IE. No prophylaxis is advised in other patients.

Transient bacteremia may occur due to many types of dental and surgical procedures. However, the AHA guidelines significantly limit the types of procedures where prophylaxis is appropriate. Only dental procedures involving manipulation of gingival tissue or periapical region of teeth or perforation of the oral mucosa are considered to increase the likelihood that high-risk patients will develop IE.[6] Viridans group streptococci are the primary bacteria targeted for prophylaxis in this circumstance. On the other hand, prophylaxis for GI or genitourinary surgeries primarily targets enterococci.

LO 6

The AHA guidelines include suggested antibiotic regimens for dental procedures for which prophylaxis is warranted.[6] Recommended regimens are summarized in Table 74–9. Therapy consists of a penicillin for most patients, a cephalosporin for penicillin-allergic patients who have not had an anaphylactic reaction, and clindamycin or a macrolide for penicillin-allergic patients. These guidelines recommend a single oral or intramuscular/intravenous dose initiated shortly before the procedure. A second prophylactic dose is not recommended. However, if an infection develops at the procedure site, additional antibiotics (ie, a therapeutic course) may be required.

Antimicrobial Stewardship in IE

Antimicrobial stewardship efforts in relation to IE should focus on recommendations which optimize antimicrobial management, including but not limited to: appropriate selection of empiric and definitive antimicrobial regimens, suggestion for infectious diseases consultation, and ensuring adequate dosages for selected therapy. Once culture and susceptibility data is (if) available, the stewardship team can work with clinicians to tailor and maximize treatment of the patient. Patients with IE will require a prolonged treatment course (often 4 weeks or more); the stewardship team can

Patient Encounter Part 5: Create a Care Plan

Based on this patient's information, create a care plan for the management of her IE. Be sure to include:

(a) A statement regarding treatment requirements and/or possible problems

(b) Goals of therapy

(c) A patient-specific plan, including preventive plans

(d) A follow-up plan to assess whether the goals have been met and to determine whether the patient experienced any adverse effects

Table 74–7

Dosage Considerations for Common Antibiotics for Treatment of IE[a]

Drug	Renal Adjustment	Hepatic Adjustment	Comments
Penicillin G	Required	None	Extension of dosing interval primarily used for adjustment
Ampicillin	Required	None	Seizures most common AE if dosing not adjusted
Nafcillin	None	If severe (see comment)	Adjustments necessary ONLY in patients with severe hepatic AND renal impairment
Oxacillin	If severe (see comment)	None	For CrCl < 10 mL/min/1.73m^2 (0.1 mL/s/m^2), adjust to lower range of normal dose
Cefazolin	Required	None	Dose and/or dosing interval require adjustment. Based on patient's CrCl
Ceftriaxone	If severe (see comment)	None	Do not exceed 2 g/day if patient has BOTH severe renal AND hepatic impairment
Vancomycin	Required	None	Monitor therapeutic concentrations to guide dosage adjustments (see treatment guidelines for target ranges)
Daptomycin	Required	None	Adjust dosing interval for CrCl < 30 mL/min/1.73m^2 (0.48 mL/s/m^2) CPK should be monitored prior to and during therapy (at least weekly, and more frequently if increasing or on concomitant medications associated with muscle toxicity, particularly statins)
Linezolid	None	None	Metabolites may accumulate in severe renal impairment Monitor for hematologic AE, particularly severe thrombocytopenia Use in severe hepatic impairment not established
Gentamicin	Required	None	Dosing should be based on ideal body weight; however, if significantly obese, use of adjusted body weight may be required to achieve target levels (listed below). Monitor therapeutic concentrations to guide dosage adjustments, and target concentrations vary based on indication Only used as synergy (combination therapy) for gram-positive bacteria. Target concentrations for synergy: peak 3–4 mcg/mL (3–4 mg/L; 6.3–8.4 µmol/L) and trough < 1 mcg/mL (1 mg/L; 2.1 µmol/L) Gentamicin (or tobramycin or amikacin) can be used as treatment for non-HACEK gram-negative bacteria (target concentrations not shown but dependent upon selected aminoglycoside and organism susceptibility)
Rifampin	None	Required	Adjustment based on hepatic dysfunction
Newer and Salvage Drugs			
Ceftaroline	Required	None	Adjustments in dose (33%–67% reduction) are based on patient's CrCl. Suggested dosages for off-label use in IE are higher than standard dosing (ie, 600 mg every 8 hours)
Quinupristin/dalfopristin	None	Possibly	Rarely used secondary to side effects. Adjustments suggested based on pharmacokinetic data. However, no specific recommendations are described
Telavancin	Required	None	Decrease daily dose by 25% if CrCl 30–50 mL/min/1.73 m^2 (0.29–0.48 mL/s/m^2) or if CrCl < 30 mL/min (0.29 mL/s/m^2)—extend interval to every 48 hours
Tigecycline	None	If severe (see comment)	In severe hepatic impairment (Child-Pugh class C)—decrease maintenance dose 50%
Streptomycin	Required	None	Only used as synergy (combination therapy) for gram-positive bacteria. Therapeutic concentrations vary for gram-negative bacteria Monitor therapeutic concentrations to guide dosage adjustments Target concentrations for synergy: peak 20–35 mcg/mL (20–35 mg/L; 34–60 µmol/L) and trough < 10 mcg/mL (10 mg/L; 17 µmol/L)

[a]Gram-negative bacteria, fungal, or atypical treatments are not listed. It is suggested that an infectious diseases consult be obtained if a patient has IE caused by one of these organisms due to the complexity and difficulty in managing these patients.

AE, adverse event; CPK, creatinine phosphokinase; CrCl, creatinine clearance.

Table 74–8

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable[a]

- Prosthetic cardiac valve or prosthetic material used for cardiac-valve repair
- Previous IE
- Congenital heart disease (CHD)[b]
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure[c]
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients who develop cardiac valvulopathy

[a]*All dental procedures* involving manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa are reasonable indications for prophylaxis in patients with the conditions listed above.

[b]Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

[c]Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

Data from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation. 2007;116:1736–1754. ©2007, American Heart Association, Inc.

provide or assist in monitoring serum antibiotic concentrations (if patient is receiving vancomycin or an aminoglycoside) and pertinent laboratory values associated with side effects (such as creatine kinase increase with daptomycin, decreased platelets with linezolid, etc). Additionally, the stewardship team should be aware of potential patients requiring prophylaxis and provide guidance/recommendations for antimicrobial coverage prior to procedures as indicated in the IE prevention guidelines.

OUTCOME EVALUATION

KEY CONCEPT Monitoring for successful therapy is critical for this serious infection to prevent complications, prevent development of resistance, and decrease mortality. Routine assessment of clinical signs and symptoms, as well as laboratory tests (ie, repeat blood cultures), microbiologic testing, and serum drug concentrations (if appropriate), must be performed.

Resolution of signs and symptoms typically occurs within a few days to a week in most cases. Monitor the patient's temperature daily for febrile episodes, as well as other vital signs, with expected normalization of values within 2 to 3 days of antimicrobial therapy initiation.[1] Persistent signs or symptoms could be indicative of inadequate treatment and/or development of resistance.

Blood cultures are the primary laboratory evaluation to assess response to therapy. Collect and monitor blood cultures every 24 to 48 hours until bacteremia is cleared; with appropriate treatment, they should become negative within 3 to 7 days. Perform additional blood cultures if the patient appears unresponsive to current therapy or upon treatment completion to confirm eradication of infection. Evaluate all susceptibility testing reports to assess appropriateness of antimicrobial therapy.

Monitor the patient for potential development of side effects based on selected therapy. For patients receiving vancomycin, collect and assess serum concentrations based on the causative organism, adjusting the dosage regimen if necessary. For patients receiving an aminoglycoside, collect and assess serum concentrations. Refer to treatment Tables 74–3 through 74–6 for target concentrations.

Educate patients on the necessity of prophylactic antibiotics prior to major dental treatments in order to prevent recurrent infections. This is critical in patients with risk factors that predispose them to developing IE, such as prosthetic heart valves, other valvular defects, or previous IE.

Develop a follow-up plan to determine whether the patient has achieved a cure, which includes a clinical evaluation of signs/symptoms, repeat blood cultures, and possibly a repeat echocardiogram. Assess the patient for any adverse events throughout treatment course and at follow-up. Perform follow-up visit within a few weeks after the completion of therapy.

Table 74–9

Prophylactic Regimens for Dental Procedure

		Regimen: Single Dose 30–60 Minutes Before Procedure	
Situation	**Agent**	**Adults**	**Children**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medications	Ampicillin or Cefazolin or Ceftriaxone	2 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[a,b] or Clindamycin or	2 g	50 mg/kg
	Azithromycin or Clarithromycin	600 mg	20 mg/kg
		500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medications	Cefazolin or Ceftriaxone[b] or Clindamycin	1 g IM or IV	50 mg/kg IM or IV
		600 mg IM or IV	20 mg/kg IM or IV

[a]Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

IM, intramuscular.

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Patient Care Process

Collect Information:

- Perform a medication history review for prescription and nonprescription medications and herbal or dietary supplements.
- Determine allergies, including reaction, to medications, food, or material.
- Review past medical and surgical history and findings of physical assessment.
- Review medical records and communicate with the patient to ascertain lifestyle habits, preferences and beliefs, goals for health and function, and socioeconomic factors affecting access to medication or other components of therapy.

Assess the Information:

- Determine whether patient has any risk factors for the development of IE utilizing modified Duke criteria (see Table 74–2).
- Review and document pertinent patient social, medical, and surgical history associated with development or identification of causative organisms of IE.
- Review physical examination and vital signs, relevant laboratory tests (eg, white blood cell count, differential, blood cultures), and diagnostic imaging (echocardiogram) as indicators of diagnosis and severity of the IE infection.
- Assess the empirical pharmacologic regimen for appropriate coverage of likely causative organisms, patient allergies, and potential adverse effects (eg, nephrotoxicity).
- Determine whether selected regimen is on institution's formulary. If not, is there a formulary alternative? If no alternative, is there anything specific to institution to utilize nonformulary agent?
- Determine appropriate duration of therapy based on first negative blood culture.

Develop a Care Plan:

- Once blood culture identification/susceptibility is reported, determine if patient is on appropriate antimicrobial therapy.
- Recommend change in therapy if pathogen is not susceptible to current antimicrobial(s) or if patient is not improving on current therapy (ie, persistent bacteremia, persistent fevers, increasing white blood cell count, etc).
- Determine whether drug doses are optimal for treatment but minimize development of adverse effects.
- Determine appropriate duration of treatment.
- Determine if lifestyle modifications are appropriate.

Implement the Care Plan:

- Educate the patients about the selected antimicrobial therapy and dosing, expected duration, possible adverse effects, and how to self-monitor for worsening of infection and adverse effects.
- Address any patient concerns about IE and its management.
- Discuss importance of lifestyle modifications if applicable.
- Determine if outpatient therapy is required and choose appropriate alternative if in-patient therapy is not feasible based on frequency of dosages, lack of monitoring, or cost/insurance limitations.

Follow-up: Monitor and Evaluate:

- Review medication efficacy and safety. Is the infection resolving? Is patient experiencing any adverse effects from their antimicrobial(s)? Are there any potential drug–drug interactions from this medication?
- Follow up with blood cultures and physical examination. Review medical history and any other pertinent laboratory tests and results of other diagnostic tests.
- Monitor vital signs/symptoms for return to baseline during each clinic follow-up over the duration of therapy. If continued to be abnormal, reassessment of therapy/other diagnostic testing is necessary.
- Once the infection has resolved, educate the patient on importance of preventative antibiotics prior to future invasive dental procedures and to inform all health care providers including dentists of history of having IE.

Abbreviations Introduced in This Chapter

AHA	American Heart Association
CFU	Colony-forming units
CoNS	Coagulase-negative staphylococci
CNS	Central Nervous System
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
IE	Infective endocarditis
IVDUs	Intravenous drug users
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-sensitive *S. aureus*
NBTE	Nonbacterial thrombotic endocarditis
PVE	Prosthetic-valve endocarditis
TEE	Transesophageal echocardiogram
TPN	Total parenteral nutrition
TTE	Transthoracic echocardiogram
VRE	Vancomycin-resistant enterococci
WBC	White blood cell

REFERENCES

1. Fowler VG Jr, Scheld WM, Bayer AS. Endocarditis and intravascular infections. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 8th ed. Philadelphia, PA: Elsevier; 2015:990–1028.e11.
2. Slipczuk L, Codolosa JN, Davila CD, et al. Infective endocarditis epidemiology over five decades: a systematic review. PLoS ONE. 2013;8:e82665.
3. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435–1486.

4. Karchmer AW. Infective endocarditis. In: Bonow Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine, 10th ed. Philadelphia, PA: Saunders; 2014:1524–1550.
5. Bor DH, Woolhandler S, Nardin R, et al. Infective endocarditis in the U.S., 1998–2009: a nationwide study. PLoS ONE. 2013;8: e60033.
6. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. Circulation. 2007;116:1736–1754.
7. Que Y, Moreillon P. Infective endocarditis. Nat Rev Cardiol. 2011;8:322–336.
8. Palraj R, Knoll BM, Baddour LM, Wilson WR. Prosthetic valve endocarditis. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 8th ed. Philadelphia, PA: Elsevier; 2015:1029–1040.e5.
9. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century. Arch Intern Med. 2009;169:463–473.
10. Mestres CA, Fita G, Azqueta M, Miro JM. Role of echocardiogram in decision making for surgery in endocarditis. Curr Infect Dis Rep. 2010;12:321–328.
11. Habib G, Badano L, Tribouilloy C, Vilacosta I, Zamorano JL. Recommendations for the practice of echocardiography in infective endocarditis. Eur J Echocardiogr. 2010;11:202–219.
12. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633–638.
13. Baltimore RS, Gewitz M, Baddour LM, et al. Infective endocarditis in childhood: 2015 update: a scientific statement from the American Heart Association. Circulation. 2015;132:1487–1515.
14. Khan O, Shafi AMA, Timmis A. International guideline changes and the incidence of infective endocarditis: a systematic review. Open Heart. 2016;3:e000498.
15. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis. 2011;52: 285–292.
16. Huang YT, Hsiao CH, Liao CH, Lee CW, Hsueh PR. Bacteremia and infective endocarditis caused by a non-daptomycin-susceptible, vancomycin-intermediate, and methicillin-resistant *Staphylococcus aureus* strain in Taiwan. J Clin Microbiol. 2008;46:1132–1136.
17. Jacqueline C, Caillon J, Boutoille D. Management of MRSA/ GISA, VISA endocarditis. Curr Infect Dis Rep. 2013;15:329–334.
18. Sabe MA, Shrestha NK, Gordon S, Menon V. Staphylococcus lugdunensis: a rare but destructive cause of coagulase-negative staphylococcus infective endocarditis. Eur Heart J Acute Cardiovasc Care. 2014;3:275–280.
19. Aris CA, Contreras GA, Murray BE, et al. Management of multidrug-resistant enterococcal infections. Clin Microbiol Infect. 2010;16:555–562.
20. Morpeth S, Murdoch D, Cabell CH, et al. Non-HACEK gram-negative bacillus endocarditis. Ann Intern Med. 2007; 147:829–835.
21. Durante-Mangoni E, Tripodi MF, Albisinni R, Utili R. Management of gram-negative and fungal endocarditis. Int J Antimicrob Agents. 2010;36S:s40–s45.
22. Chambers ST, Murdoch D, Morris A, et al. HACEK infective endocarditis: characteristics and outcomes from a large, multi-national cohort. PLoS ONE. 2013;8:e63181.
23. Raza SS, Sultan OW, Sohail MR. Gram-negative bacterial endocarditis in adults: state-of-the-heart. Expert Rev Anti Infect Ther. 2010;8:879–885.
24. Katsouli A, Massad MG. Current issues in the diagnosis and management of blood culture-negative infective and non-infective endocarditis. Ann Thorac Surg. 2013;95:1467–1474.
25. Fournier PE, Thuny F, Richet H, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. Clin Infect Dis. 2010;51:131–140.
26. Tattevin P, Revest M, Lefort A, et al. Fungal endocarditis: current challenges. Int J Infect Dis. 2014;44:290–294.
27. Fowler V, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and infective endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006;355:653–665.
28. Guleri A, Utili R, Dohmen P, et al. Daptomycin for the treatment of infective endocarditis: results from European Cubicin outcomes registry and experience (EU-CORE). Infect Dis Ther. 2015;4:283–296.
29. Kaya S, Yilmaz G, Kalkan A, Ertunc B, Koksal I. Treatment of Gram-positive left-sided infective endocarditis with daptomycin. J Infect Chemother. 2013;19:698–702.
30. Tascini C, Bongiorni MG, Doria R, et al. Linezolid for endocarditis: a case series of 14 patients. J Antimicrob Chemother. 2011;66:679–682.
31. Ho TT, Cadena J, Childs LM, et al. Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. J Antimicrob Chemother. 2012;67:1267–1270.
32. Marcos LA, Camins BC. Successful treatment of vancomycin-intermediate *Staphylococcus aureus* pacemaker lead infective endocarditis with telavancin. Antimicrob Agents Chemother. 2010;54:5376–5378.
33. Steele JM, Seabury RW, Hale CM, Mogle BT. Unsuccessful treatment of methicillin-resistant *Staphylococcus aureus* endocarditis with dalbavancin. J Clin Pharm Ther. 2017;00:1–3.
34. Falcone M, Russo A, Venditt M. Optimizing antibiotic therapy of bacteremia and endocarditis due to staphylococci and enterococci: new insights and evidence from the literature. J Infect Chemother. 2015;21:330–339.
35. Sakoulas G, Geriak M. Oral tedizolid phosphate stepdown therapy in two cases of *Staphylococcus areus* endocarditis in intravenous drug abusers. J Pharm Sci Therap. 2016;1:50–55.
36. Johnson JA, Feeney ER, Kubiak DW, Corey GR. Prolonged use of oritavancin for vancomycin-resistant Enterococcus faecium prosthetic valve endocarditis. Open Forum Infect Dis. 2015;2:ofv156.
37. Lalani T, Cabell CH, Benjamin DK, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis: use of propensity score and instrumental variable methods to adjust for treatment-selection bias. Circulation. 2010;121:1005–1013.
38. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012;366:2466–2473.
39. Head SJ, Mokhles MM, Osnabrugge RLJ, et al. Surgery in current therapy for infective endocarditis. Vascular Health and Risk Management 2011;7:255–263.
40. Leontyev S, Borger MA, Modi P, et al. Surgical management of aortic root abscess: a 13 year experience in 172 patients with 100% follow-up. J Thorac Cardiovasc Surg. 2012;143:332–337.

75 Tuberculosis

Rocsanna Namdar and Charles Peloquin

LEARNING OBJECTIVES

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

1. Compare the risk for active tuberculosis (TB) disease among patients based on their age, immune status, place of birth, and time since exposure to an active case.
2. Design an appropriate therapeutic plan for a patient with active TB disease.
3. Distinguish among the diagnostic tests used for patients potentially infected with TB.
4. Assess the effectiveness of therapy in TB patients.
5. Describe the common and important adverse drug effects caused by TB drugs.
6. Select patients for whom therapeutic drug monitoring (TDM) may be valuable and identify the necessary laboratory monitoring parameters for patients on antituberculosis medications.
7. Design appropriate antimicrobial regimens for the treatment of latent TB infection.

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of death worldwide. In 2015, there were about 10.4 million new cases of TB worldwide and an estimated 1.4 million people died from the disease.[1] Most deaths are preventable if access to health care for diagnosis and correct treatment are provided.

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Roughly one-third of the world's population is infected and drug resistance is increasing in many areas.[1] The majority of cases worldwide are found in South-East Asia and Africa. In the United States, about 13 million people have latent TB infection (LTBI), evidenced by a positive skin test (**purified protein derivative** [PPD]) but no signs or symptoms of disease. The PPD is the antigen derived from *Mycobacterium tuberculosis* used to determine the presence of an immune response in patients with previous exposure. Patients testing positive have roughly a 1 in 10 chance of active disease during their lives, with the greatest risk in the first 2 years after infection. In 2016, 9287 new TB cases were reported in the United States; a 2.7% decline from 2015.[2]

The most recent data from the Centers for Disease Control and Prevention (CDC) indicate that TB deaths in the United States have decreased from 2013 by 11.2% to 493 in 2014.[3] (For details, visit the CDC website at www.cdc.gov/nchstp/tb.)

Risk Factors for Infection

LO 1

▶ *Location and Place of Birth*

California, New York, Florida, and Texas accounted for approximately 50% of all TB cases in 2015.[2] These higher numbers may reflect the high-immigration rates into these states.[2] Mexico, the Philippines, Vietnam, India, and China account for the largest numbers of these immigrants.[2] TB is most prevalent in large urban areas and is exacerbated by crowded living conditions.[2] Those in close contact with patients with active pulmonary TB are most likely to become infected.[2,3]

▶ *Race, Ethnicity, Age, and Gender*

In 2016, Asians accounted for approximately 27% of new foreign born TB cases, followed by non-Hispanic blacks (22%), Hispanics (10%), whereas foreign born non-Hispanic whites accounted for 4% of new TB cases in the United States.[3] Among the US born populations in 2016, the highest incidence of TB occurred in Native Hawaiin/Pacific Islander (9.2%) followed by American Indian/Alaska Native (5%).[3] TB is most common among people 25 to 44 years of age, and those 45 to 64 years of age.[3]

Risk Factors for Disease

Once infected, a person's lifetime risk of active TB is about 10%, with about half this risk during the first 2 years.[2–4] Young children, the elderly, and immunocompromised patients have greater risks. KEY CONCEPT HIV is the most important risk factor for active TB because the immune deficit prevents patients from containing the initial infection.[1–4] HIV-infected patients with *M. tuberculosis* infection are roughly 100 times more likely to develop active TB than normal hosts.[1,3,4]

TB is caused by *M. tuberculosis*, a rod-shaped thin aerobic bacterium. It presents either as LTBI or as progressive active disease.[4] The latter typically causes progressive destruction of the lungs, leading to death in most patients who do not receive treatment. *M. tuberculosis* are acid-fast bacilli (AFB). Acid-fast organisms are characterized by wax-like nearly impermeable cells walls which often do not stain with Gram stain and cannot be decolorized by acid alcohol. The cell wall contains a high amount of mycolic acids, long-chain fatty acids, and cell wall lipids which make the wall difficult to attack with conventional antibiotics. The acid-fast stain is a differential stain used to identify acid-fast organisms.

Culture and Susceptibility Testing

KEY CONCEPT Microscopic examination of infected material ("sputum smear" of material on a glass slide) is the most rapid and readily available test to detect AFB in clinical specimens. Three sputum specimens should be collected in patients suspected of pulmonary TB to increase the likelihood of finding AFB. *The sensitivity of the sputum smear is only about 40%, so culture-based TB diagnosis is the current gold standard.*[4–6] Unfortunately, culture is much slower due to the roughly 20-hour doubling time of the bacilli. Furthermore, microscopic examination for AFB through sputum smear alone cannot determine which of over 100 mycobacterial species is present. Depending on the presence of epidemiological risk factors, the usual practice is to isolate the patient and treat empirically until presence of *M. tuberculosis* is confirmed by genetic probe or positive culture.

Antimicrobial susceptibility testing is essential for directing proper treatment. The most common method utilizing solid growth media, known as the *proportion method*, takes 3 to 8 weeks to produce results. Growth in liquid media is faster and can detect live mycobacteria in about 2 weeks.[5,6] Rapid-identification tests include nucleic acid amplification tests utilizing the polymerase chain reaction (PCR).[7–9] Three nucleic acid amplification tests have been approved for use in the United States to detect *M. tuberculosis* in respiratory secretions. These tests are highly sensitive and specific for smear positive patients and somewhat less sensitive in smear negative patients, but only need as few as 1 to 10 organisms/mL (10^3–10^4/L) to give a positive result.[8–10] The Cepheid MTB/RIF Assay performed on the Xpert System is a qualitative test designed for rapid detection of *M. tuberculosis* and rifampin resistance.[11]

Patient Encounter Part 1

HPI: CG is a 46-year-old man who presents to the medical clinic complaining of a 2-month history of a persistent cough that has become productive over the past 3 weeks. He also complains of fever, malaise, and a 6-kg (13-lb) weight loss over the past 2 months.

PMH: Type 2 diabetes mellitus (noninsulin-dependent diabetes mellitus, NIDDM)—not well controlled; hypertension (HTN) × 5 years—not controlled.

FH: Mother, age 82, alive and well, lives with CG. Father died of alcoholic liver disease10 years ago. One brother, age 53, lives with the patient, currently undergoing chemotherapy treatment for lung cancer.

SH: Born and raised in India until the age of 19 when he moved to Los Angeles, California. Single, one daughter. He had a 20-year history of alcohol abuse but has been sober for 5 years. He owns his own import/export business and travels internationally to India and parts of China.

Meds: Lisinopril 20 mg daily; amlodipine 5 mg daily; metformin 500 mg twice daily. Patient reports that he tries to be compliant with his therapies and takes them regularly except when he travels he often forgets; over the past 2 months, he has only gone 3 to 4 days without medication.

What information is suggestive of TB?

What factors place this patient at increased risk for acquiring TB?

New tests looking for specific mutations such as the katG gene associated with isoniazid resistance may facilitate rapid drug therapy decisions in the future. Nitrate reductase assays and porous ceramic support systems are among other rapid drug susceptibility testing techniques currently being investigated.[12] DNA fingerprinting is performed to assist surveillance programs and contact investigations. Various techniques are employed including restriction fragment length polymorphism (RFLP) analysis, spoligotyping, and mycobacterial interspersed repeat units. These techniques exploit conserved fragments in the TB genome that change gradually over time and allow investigators to determine if strains are related to one another. Strains that are related to one another are referred to as clusters. Clusters generally indicate recent transmission and are then targeted for interventions by TB programs.[13]

PATHOPHYSIOLOGY

Primary Infection

KEY CONCEPT *M. tuberculosis* is transmitted from person to person by coughing or any other aerosol producing activities such as sneezing.[4,14] This produces small particles known as droplet nuclei that float in the air for long periods of time. Primary infection usually results from inhaling droplet nuclei that contain *M. tuberculosis*.[4,14] The progression to clinical disease depends on three factors: (1) the number of *M. tuberculosis* organisms inhaled (infecting dose), (2) the virulence of these organisms, and (3) the host's cell-mediated immune response.[4,14] If pulmonary macrophages inhibit or kill the bacilli, the infection is aborted.[14] If not, *M. tuberculosis* eventually spreads throughout the body through the bloodstream.[4,14] *M. tuberculosis* most commonly infects the posterior apical region of the lungs, where conditions are most favorable for its survival.

T lymphocytes become activated over the course of 3 to 4 weeks, producing interferon-γ (IFN-γ) and other cytokines. These stimulate microbicidal macrophages to surround the tuberculous foci and form granulomas to prevent further extension.[14] A granuloma is a nodular aggregation of mononuclear inflammatory cells formed when the immune system attempts to wall off foreign substances. At this point, the infection is largely under control, and bacillary replication falls off dramatically. Any remaining mycobacteria are believed to reside primarily within granulomas or within macrophages that have avoided detection and lysis. Over 1 to 3 months, tissue hypersensitivity occurs, resulting in a positive PPD.[4,14] Approximately 95% of individuals with an intact immune system will enter into this latent phase. KEY CONCEPT Progressive primary disease occurs in roughly 5% of patients, especially children, the elderly, and immunocompromised patients.[15,16] This presents as a progressive pneumonia and frequently spreads, leading to meningitis and other severe forms of TB, often before patients develop positive (PPD) or interferon-γ release assays.[15]

Reactivation Disease

About 10% of infected patients develop reactivation TB, with half occurring in the first 2 years after infection.[4,9] Reactivation TB results when a previously "dormant" focus is reactivated and causes disease. Progression involves the development of caseating granulomas as a result of a vigorous immune response. Liquefaction leads to local spread and a pulmonary cavity results. This provides a portal to the airways and subsequently ambient air that enhances person-to-person spread. Bacterial counts in the cavities can be as high as 10^8/mL (10^{11}/L) of cavitary

fluid.[4,14] Prior to the chemotherapy era, pulmonary TB usually was associated with hypoxia, respiratory acidosis, and eventually death related to asphyxia; a fate that remains all too common in poor countries where patients do not have access to effective therapy.

Extrapulmonary and Miliary Tuberculosis

Caseating granulomas, regardless of location, can spread tubercle bacilli and cause symptoms.[4] Because of muted or altered symptoms, the diagnosis of TB is difficult and often delayed in immunocompromised hosts.[4,14] HIV-infected patients may present with only extrapulmonary TB, which is uncommon in HIV-negative persons. A widely disseminated form of the disease called *miliary TB* can occur, particularly in children and immunocompromised hosts. It can be rapidly fatal and immediate treatment is required.[14]

Influence of HIV Infection on Pathogenesis

HIV infection is the strongest known risk factor for active TB.[14] As $CD4^+$ lymphocytes multiply in response to the mycobacterial infection, HIV multiplies within these cells and selectively destroys them, gradually eliminating the TB-fighting lymphocytes.[16,17] HIV-positive patients often have negative PPD and fail to produce **cavitary lesions**, and fever may be absent. Cavitary lesions are present in a wide variety of pathological processes involving the lung and are observed radiographically as gas or fluid filled areas of the lung in the center of a nodule. Approximately 5% of HIV-infected patients with pulmonary TB who are not being treated effectively with antiretroviral medications will have positive results on acid-fast staining, yet have a normal chest radiograph. Patients coinfected with HIV and TB have a substantially higher risk of early mortality compared with HIV-negative patients with TB.[18]

CLINICAL PRESENTATION AND DIAGNOSIS

Fever, night sweats, weight loss, fatigue, and a productive cough are the classic symptoms of TB.[4,14] Onset may be gradual, and the diagnosis is easily missed if the symptoms are muted.[4,14] Progressive pulmonary disease leads to cavitary lesions visible on x-ray. Physical examination is nonspecific but may be consistent with pneumonia. Dullness to chest percussion, rales, and increased vocal **fremitus** may be observed on examination. Laboratory data often are uninformative, but a modest increase in the white blood cell (WBC) count with a lymphocytic predominance can be seen. Frequently, however, the physical examination is largely unremarkable.

Atypical presentations are common in patients coinfected with HIV.[4,14,18] Symptoms for these patients range from classic pulmonary to muted and nonspecific. Extrapulmonary TB typically presents either as a slowly progressive decline in the effected organ's function or commonly as a mass lesion. Lymphadenopathy is relatively common.[14,15] Abnormal behavior, headaches, or convulsions suggest tuberculous meningitis, although other acute central nervous system (CNS) infections must be excluded.[4,14]

Multidrug resistant TB remains a public health concern. The WHO estimated 600,000 new cases with resistance to rifampicin, of which 490,000 had multidrug-resistant tuberculosis (MDR-TB). There are a number of laboratory tools available for diagnosis of MDR-TB, including phenotypic culture-based drug susceptibility testing as well as molecular methods.[19] The FDA has not yet approved any molecular test for use in the United States, but several validated tests (line-probe assays, molecular beacons, and DNA sequencing) are being used. Molecular testing may be useful in patients with high risk of having MDR-TB, very ill patients who are not improving with standard first line therapy, and outbreak investigations.[20]

The Elderly

Positive PPD test, fevers, night sweats, sputum production, or hemoptysis may be absent, making TB hard to distinguish from other bacterial or viral infections or chronic lung diseases.[4,19] In contrast, mental status changes are twice as common in the elderly, and CNS disease must be considered when TB is entertained. Mortality is six times higher in the elderly, in part owing to delays in diagnosis.[4,19,21]

Children

TB in children may present as atypical bacterial pneumonia, and often involves the lower and middle lobes.[4,15,22] Extrapulmonary TB is more common in children. The Bacille Calmette-Guérin (BCG) is a vaccine made from strains of tubercle bacilli and is used to produce immunity against human TB. It is administered in countries where TB remains common and appears to stimulate children's immune systems to ward off the most serious forms of the disease. In fact, BCG is most effective in reducing infant mortality from TB meningitis and miliary disease. BCG does not block infection, and these same children often experience reactivation TB as young adults.[22]

Skin Testing

TB skin testing with PPD (commercially available as Tubersol or Aplisol) is one of the oldest diagnostic tests still in clinical use.[4,15,17] Also known as the tuberculin skin test, the product is injected into the skin (not subcutaneously) with a fine (27-gauge) needle, a technique referred to as the Mantoux method, and produces a small, raised, blanched wheal to be read by an experienced professional in 48 to 72 hours. The chance of a false-negative result is increased when the patient is immunosuppressed. The CDC does not recommend the routine use of anergy panels to determine if a patient's T-cell immune system reacts to common antigens.[17,23]

Criteria for interpretation are listed in **Table 75–1**.[15]

The "booster effect" occurs in patients who do not respond to an initial PPD test but show a positive reaction if retested 1 to 3 weeks later.[15,20,23] In order to reduce the likelihood that a boosted reaction is misinterpreted as a new infection, the two-step method is recommended at the time of initial testing for individuals such as health care workers or nursing home residents who may be tested periodically. If the first PPD test is negative, repeat the test in 1 to 3 weeks. If the second test is positive, it is most likely a boosted reaction, and the person should be classified as previously infected.

LO 3 Newer Diagnostic Tests

Newer technology has led to the development of blood tests or interferon-γ release assays (IGRAs) that have replaced the PPD test in the United States for individuals 5 years and older who meet the following criteria: likely to be infected with *M. tuberculosis*; low or intermediate risk of disease progression; testing for LTBI is warranted; and have history of BCG vaccine or unlikely to return to have PPD read.[15,23] These newer methods measure the release of interferon-γ in blood in response to TB antigens. The two TB blood tests approved in the United States are: the QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and

Table 75–1

Criteria for Tuberculin Positivity, by Risk Group

Reaction ≥ 5 mm of Induration	Reaction ≥ 10 mm of Induration	Reaction ≥ 15 mm of Induration
HIV-infected persons	Recent immigrants (ie, within the last 5 years) from high-prevalence countries	Persons with no risk factors for TB
A recent contact of a person with TB disease	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees[a] of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/day or more of prednisone for 1 month or longer, taking TNF-α antagonists)[b]	Mycobacteriology laboratory personnel, persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders, other specific malignancies, gastrectomy, and jejunoileal bypass	
	Children younger than 5 years of age or infants, children, and adolescents exposed to adults at high risk	

Interpretation of IGRA Results

The interpretation of IGRAs is based on the amount of IFN-γ, in T-SPOT®.TB. Laboratories should provide both the qualitative and quantitative results.

- Qualitative results are reported positive, negative, indeterminate, or borderline.
- Quantitative results are reported as numerical values that include a response to the TB antigen and 2 controls, nil and mitogen. Quantitative results may be useful for clinical decision making in individual cases, in combination with risk factors.

[a]For persons who are otherwise at low risk and are tested at the start of employment, a reaction of 15 mm or more of induration is considered positive.

[b]Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

the T-SPOT® TB test (T-Spot).[23] The sensitivity of IGRAs ranges from 80% to 90%, and specificity of 95% for diagnosis of latent TB. Recent evidence suggests that prior placement of PPD can boost an IGRA. The boosting effect may wane after several months.[17,23] The IGRAs do not cause the booster phenomenon and are unaffected by BCG, or infection by most nontuberculosis mycobacteria. Results of the IGRAs are available in less than 24 hours, versus the 3 days required for the traditional PPD test. Data are limited for use of IGRAs in children younger than 5 years of age, persons recently exposed to TB, health care workers, and immunodeficient patients.[23] KEY CONCEPT The CDC has endorsed the use of IGRA tests in all circumstances where the PPD is used. IGRAs are approved for the diagnosis of LTBI in HIV-infected patients, but sensitivity is diminished.[23] Testing with both PPD and IGRA generally is not recommended, but may be useful in certain situations (eg, if the initial PPD test is negative and the risk for infection, clinical suspicion, or the risk for poor outcome is high; or if the initial PPD test is positive and additional evidence of infection is required; or the patient has a low risk of infection or progression).[23,24] IGRAs, and for that matter the PPD, should not be used to rule in or rule out the diagnosis of active TB disease.[24]

TREATMENT

General Approaches to Treatment

The primary treatment approach is the use of antimicrobials active against *M. tuberculosis*. Monotherapy can be used only for patients with LTBI, as evidenced by a positive PPD test or positive IGRA in the absence of signs or symptoms of disease. Once active disease is present, typically *three or four drugs* must be used simultaneously from the outset of treatment.[4,14,17,23] The shortest duration of treatment is 4 months in the unusual case of smear and culture negative clinical cases of pulmonary TB, and up to 2 years of treatment may be necessary for advanced cases of MDR-TB.[23,25] **Directly observed treatment** (DOT) is a method used to ensure adherence in which patients are directly observed by a health care worker while taking their antituberculosis medication.[26] Case management interventions such as patient education, counseling, home visits, integration, and coordination of care with specialists and incentives and enableers during treatment of patients wth TB disease are also encouraged. This also is a cost-effective way to ensure completion of treatment.

Desired Outcomes

Steps should be taken to (a) prevent the spread of TB (respiratory isolation); (b) find where TB has already spread (contact investigation); and (c) return the patient to a state of normal weight and well-being. Items (a) and (b) are performed by public health departments. Clinicians involved in the treatment of TB should verify that the local health department has been notified of all new cases of TB. In rare instances, surgery may be needed.[17]

Pharmacologic Therapy

LO 7

► *Treating LTBI*

KEY CONCEPT Isoniazid is used for treating LTBI. Typically, isoniazid 300 mg daily (5–10 mg/kg of body weight) is given alone for 9 months. Lower doses usually are less effective.[17] In some instances, a 6-month duration of treatment with isoniazid alone is an acceptable alternative. Pyridoxine (25–50 mg/day in adults) can reduce the risk of peripheral neuropathy.[17,27] Treatment of LTBI reduces a person's lifetime risk of active TB from about 10%

to about 1%.[17,24] Rifampin 600 mg daily for 4 months can be used when isoniazid resistance is suspected or when the patient cannot tolerate isoniazid.[17,27] Rifabutin 300 mg daily might be substituted for rifampin in patients at high risk of drug interactions.[28] The combination of pyrazinamide and rifampin is no longer recommended.[28,29] Once-weekly doses of isoniazid 900 mg and rifapentine 900 mg given as DOT for 3 months are as effective as 9 months of self-administered isoniazid 300 mg daily.[30] When resistance to isoniazid and rifampin is suspected, there is no regimen proven to be effective (Table 75–2).[27] Note that patients with LTBI are not infectious and there is no isolate on which to perform susceptibility testing. Susceptibility patterns must be inferred based on the most likely source of infection.

LO 2

▶ *Treating Active Disease*

In the United States, TB patients can receive free treatment through the local health department. Treating active TB disease requires combination chemotherapy. KEY CONCEPT Generally, four drugs are started. In particular, isoniazid and rifampin should be included because they are the best drugs available for preventing drug resistance.[17,27] Drug susceptibility testing should be done on the initial isolate for all patients.[17,27] Susceptibility testing is repeated if the patient remains culture-positive 8 weeks or more into therapy.[25]

The standard TB treatment regimen for susceptible TB is isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months, for a total of

Patient Encounter Part 2

VS: BP 142/82 mm Hg, P 90 beats/min, RR 18 breaths/min, T 38°C (100.4°F), O_2 sat 82% (0.82) on room air, Wt 51 kg (112 lb), Ht 5′8″ (173 cm)

HEENT: PERRLA; EOMI

Neck: Supple; no lymphadenopathy, bruits, or JVD; no thyromegaly

Chest: Diffuse rhonchi, decreased breath sounds on left

CV: RRR; no murmurs, rubs, gallops

Abd: (+) BS; nontender, nondistended

Neuro: A&O × 3

Laboratory Values (US Units)

Lab	Normal	Lab	Normal
Na 139 mEq/L	135–145 mEq/L	Hgb 13.5 g/dL	13.5–17.5 g/dL
K 3.9 mEq/L	3.5–5 mEq/L	Hct 40%	40%–54%
Cl 98 mEq/L	95–105 mEq/L	RBC 4.6×10^6 mm^3	$4.6–6.0 \times 10^6$ mm^3
CO_2 38 mEq/L	22–30 mEq/L	WBC 4.0×10^3 mm^3	$4.0–10 \times 10^3$ mm^3
BUN 20 mg/dL	5–25 mg/dL	PMN 51%	50%–65%
SCr 1.0 mg/dL	0.8–1.3 mg/dL	Lymph 25%	25%–35%
Gluc 150 mg/dL	< 140 mg/dL	Mono 2%	2%–6%
AST 36 IU/L	5–40 IU/L		
ALT 28 IU/L	5–35 IU/L		
Tbili 1 mg/dL	0.1–1.2 mg/dL		
PT 10 seconds	10–12 seconds		

Laboratory Values (SI Units)

Lab	Normal	Lab	Normal
Na 139 mmol/L	135–145 mmol/L	Hgb 135 g/L or 8.38 mmol/L	135–175 g/L or 8.38–10.86 mmol/L
K 3.9 mmol/L	3.5–5 mmol/L	Hct 0.40 vol fraction	0.40–0.54 vol fraction
Cl 98 mmol/L	95–105 mmol/L	RBC 4.6×10^{12}/L	$4.6–6.0 \times 10^{12}$/L
CO_2 38 mmol/L	22–30 mmol/L	WBC 4.0×10^9/L	$4.0–10.0 \times 10^9$/L
BUN 7.1 mmol/L	1.8–8.9 mmol/L	PMN 0.51	0.50–0.65
SCr 88 µmol/L	71–115 µmol/L	Lymph 0.25	0.25–0.35
Gluc 8.3 mmol/L	< 7.8 mmol/L	Mono 0.02	0.02–0.06
AST 0.60 µkat/L	0.08–0.67 µkat/L		
ALT 0.47 µkat/L	0.08–0.58 µkat/L		
Tbili 17.1 µmol/L	1.7–20.5 µmol/L		
PT 10 seconds	10–12 seconds		

CXR: Bilateral upper lobe infiltrates with cavitary lesions on left; small left pneumothorax

Clinical Course: The patient was admitted and placed on respiratory isolation. Three separate sputum AFB stain specimens were reported to contain 3+ AFB. IFN-γ was sent and a PPD tuberculin skin test was placed. Sputum samples were sent for AFB, fungi, and bacterial cultures and sensitivities. After 48 hours, the PPD skin test was read as a 7-mm area of induration

Assessment: Active pulmonary TB; pneumothorax; hypertension; type 2 diabetes mellitus

Which signs, symptoms, and other findings are consistent with active TB infection?

Table 75–2

Choosing the Most Effective LTBI Treatment Regimen

Drug	Duration	Dose	Frequency	Comments
Isoniazid	9 months	Adult: 5 mg/kg Children: 10–20 mg/kg	Daily	In HIV-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-NRTIs (NNRTIs) Preferred regimen in children 2–11 years
	9 months	Adult: 15 mg/kg Children: 20–40 mg/kg	Twice weely	Directly observed treatment (DOT) must be used with twice-weekly dosing
	6 months	Adult: 5 mg/kg Children: Not recommended	Daily	Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients
	6 months	Adult: 15 mg/kg Children: Not recommended	Twice weekly	Directly observed treatment (DOT) must be used with twice-weekly dosing
Isoniazid and Rifapentine	3 months	Adults and Children 12 years of age and over: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg RPT: 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥ 50.0 kg	Once weekly	Equal alternative to 9 months of daily isoniazid for otherwise healthy patients age > 12 years DOT is recommended Not recommended for children < 2 years; HIV-infected patients taking antiretroviral therapy, presumed resistance, pregnant women or women expecting to become pregnant during the treatment period
Rifampin	4 months	Adult: 10 mg/kg[a]	Daily	For persons who are contacts of patients with isoniazid-resistant rifampin-susceptible Can be considered for persons who cannot tolerate INH or who have been exposed to INH-resistant TB RIF should not be used to treate HIV-infected person taking some combinations of ART.

[a]In the United States, the recommended regimen for treatment of LTBI in children is a 9-month course of INH. For the treatment of LTBI in infants, children, and adolescents when INH could not be tolerated or the child has had contact with a case patient infected with an isoniazid-resistant but rifamycin-susceptible organism the American Academy of Pediatrics recommends 6 months of daily rifampin (RIF) (180 doses) at a dosage of 10–20 mg/kg.

Adapted from: Latent tuberculosis infection: a guide for primary health care providers 2013. Atlanta, GA: US Department of Health and Human Services; CDC; 2013.

6 months of treatment.[17,27] Extending treatment to 9 months of isoniazid and rifampin treatment is recommended for patients at greater risk of failure and relapse, including those with cavitary lesions on initial chest radiograph and positive cultures at the completion of the initial 2-month phase of treatment, as well as for patients treated initially without pyrazinamide. Ideally, treatment should be continued for at least 6 months from the time that patients convert to a negative culture.[17,27] When the patients' sputum smears convert to negative, the risk of infecting others is greatly reduced, but it is not zero.[11,27] Such patients can be removed from respiratory isolation if they are responding clinically. The decision to discontinue isolation should be done by medical providers experienced in TB control. Table 75–3 shows the recommended treatment regimens. Daily dosing rather than intermittent dosing is preferred; but intermittent dosing can be considered in patients with low risk of relapse and negative HIV test results. When intermittent therapy is used, DOT is essential. Doses missed during an intermittent TB regimen decrease the efficacy of the regimen and increase the relapse rate.

Adjustments to the regimen should be based on susceptibility data.[9,27] Drug resistance should be suspected in patients who have been treated previously for TB. If adjustments are needed, two or more drugs with in vitro activity against the patient's isolate and that were not used previously should be added to the regimen.[9,27] When isoniazid and rifampin cannot be used, either because of drug resistance or intolerance, treatment durations typically become 2 years or more, regardless of immune status.[9,27,31] TB specialists should be consulted regarding cases of drug-resistant TB, or whenever treatment is uncertain.[9,27] Therapeutic drug monitoring (TDM) can direct dosing for such patients. One of the proven reasons for treatment failure is malabsorption of orally administered drugs.[27,31,32] KEY CONCEPT Due to the risk of further drug resistance, it is critical to avoid adding only a single drug to a failing regimen.[9,27]

Special Populations

Treatment for extrapulmonary TB is the same as for pulmonary disease. Unless drug resistance is suspected, corticosteroid treatment should also be added to the treatment regimen of TB meningitis and pericarditis. Patients with CNS TB usually are treated for 12 months.[9,27] Isoniazid and pyrazinamide cross the blood–brain barrier well, but rifampin, ethambutol, and streptomycin can penetrate inflamed meninges. TB osteomyelitis typically is treated for 9 months, occasionally with surgical débridement.[9,27] TB of the soft

Table 75–3

Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Initial Phase		Continuation Phase		
Regimen	Drugs	Interval and Doses[a] (Minimal Duration)	Drugs[b]	Interval and Doses[b] (Minimal Duration)	Comments[c,d]
1	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days per week for 56 doses (8 weeks) or 5 days per week for 40 doses (8 weeks)[c]	Isoniazid/Rifampin	7 days per week for 126 doses (18 weeks) or 5 days per week for 90 doses (18 weeks)[c]	This is the preferred regimen for patient with newly diagnosed pulmonary tuberculosis
2	Isoniazid Rifampin Pyrazinamide Ethambutol	7 days per week for 56 doses or 5 days per week for 40 doses	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)[d]	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve
3	Isoniazid Rifampin Pyrazinamide Ethambutol	3 times weekly for 24 doses (8 weeks)	Isoniazid/Rifampin	Three times weekly for 54 doses (18 weeks)	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance
4	Isoniazid Rifampin Ethambutol Pyrazinamide	7 days per week for 14 doses then twice weekly for 12 doses[e]	Isoniazid/Rifampin	Twice weekly for 36 doses (18 weeks)	Do not use twice weekly regimens in HIV-infected patients or patients with smear positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which in inferior

[a]Other combinations may be appropriate in certain circumstances; additional details are provided in the section "Recommended Treatment Regimens."

[b]When DOT is used, drugs may be given 5 days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice. DOT should be used when drugs are administered < 7 days per week.

[c]Based on expert opinion, patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (31-week) continuation phase.

[d]Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/day.

[e]Alternatively, some US tuberculosis control programs have administered intensive-phase regimens 5 days per week for 15 doses (3 weeks), then twice weekly for 12 dose.

DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.

Centers for Disease Control and Prevention. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. CID. 2016:63;853–867.

tissues can be treated with conventional regimens.[9,27] Patients with diabetes mellitus have been shown to have low 2-hour peak serum concentrations of antimicrobials. TDM can be considered to optimize treatment response.[33] TB in children may be treated with regimens similar to those used in adults, although some physicians extend treatment to 9 months.[9,15-17,27] Pediatric doses of isoniazid and rifampin on a milligram per kilogram basis are higher than those used in adults (Table 75–4).[27]

Pregnant women receive the usual treatment of isoniazid, rifampin, and ethambutol for 9 months.[24] Pyrazinamide has not been studied in large numbers of pregnant women, but anecdotal data suggest that it may be safe.[27,34] The clinician should always determine risk versus benefit and determine if a drug is safe to administer in pregnancy.

▶ *Human Immunodeficiency Virus*

HIV-infected adults may receive a 6-month total treatment regimen with isoniazid, a rifamycin, pyrazinamide, and ethambutol for the first 2 months followed by isoniazid and a rifamycin for 4 months.[9,27,35] Some clinicians recommend extending treatment to 9 months. Rifabutin is used to reduce drug interactions with protease inhibitors and some nonnucleoside reverse transcriptase inhibitors. Integrated antiretroviral therapy (ART) is superior to sequential ART in the treatment of naïve HIV seropositive patients with TB.[36] The optimal timing of integrated HIV and TB therapy is influenced by the patient's immune status.[36] It is recommended to start integrated ART therapy 2 to 12 weeks after initiating anti-TB therapy in patients with CD4 cell counts less than 50/mm^3.[34] TB-HIV experts should manage such patients. Highly intermittent regimens (twice or once weekly) are not recommended for HIV-positive TB patients.[27,35] Some patients with acquired immunodeficiency syndrome (AIDS) malabsorb their oral medications, and drug interactions are common, so TDM can be useful.[27,31,32]

For complete recommendations on management of TB and HIV visit the CDC website: www.cdc.gov/tb/publications/guidelines/HIV_AIDS.htm.

Table 75–4

Antituberculosis Drugs for Adults and Children

Drug	Daily Doses[a,b,c]	Adverse Effects	Monitoring
Isoniazid	*Adults*: 5 mg/kg (300 mg) *Children*: 10–15 mg/kg (300 mg)	Asymptomatic elevation of aminotransferases, clinical hepatitis, fatal hepatitis, peripheral neurotoxicity, CNS system effects, lupus-like syndrome, hypersensitivity, monoamine poisoning, diarrhea	LFT monthly in patients who have preexisting liver disease or who develop abnormal liver function that does not require discontinuation of drug Dosage adjustments may be necessary in patients receiving anticonvulsants or warfarin
Rifampin[d]	*Adults*: 10 mg/kg (600 mg) *Children*: 10–20 mg/kg (600 mg)	Cutaneous reactions, GI reactions (nausea, anorexia, abdominal pain), flu-like syndrome, hepatotoxicity, severe immunologic reactions, orange discoloration of bodily fluids (sputum, urine, sweat, tears), drug interactions owing to induction of hepatic microsomal enzymes	Rifampin causes many drug interactions. For a complete list of drug interactions and effects, refer to CDC website: www.cdc.gov/nchstp/tb/tb
Rifabutin[d]	*Adults*: 5 mg/kg (300 mg) *Children*: Appropriate dosing unknown	Hematologic toxicity, uveitis, GI symptoms, polyarthralgias, hepatotoxicity, pseudojaundice (skin discoloration with normal bilirubin), rash, flu-like syndrome, orange discoloration of bodily fluids (sputum, urine, sweat, tears)	Drug interactions are less problematic than rifampin
Rifapentine[d]	*Adults*: 10 mg/kg (continuation phase) (600 mg) dosed weekly *Children*: The drug is not approved for use in children	Similar to those associated with rifampin	Drug interactions are being investigated and are likely similar to rifampin
Pyrazinamide	*Adults*: Based on IBW: 40–55 kg: 1000 mg; 56–75 kg: 1500 mg; 76–90 kg: 2000 mg *Children*: 15–30 mg/kg	Hepatotoxicity, GI symptoms (nausea, vomiting), nongouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis, transient morbilliform rash, dermatitis	Serum uric acid can serve as a surrogate marker for compliance LFTs in patients with underlying liver disease
Ethambutol[e]	*Adults*: Based on IBW: 40–55 kg: 800 mg; 56–75 kg: 1200 mg; 76–90 kg: 1600 mg *Children*[c]: 15–20 mg/kg daily	Retrobulbar neuritis, peripheral neuritis, cutaneous reactions	Baseline visual acuity testing and testing of color discrimination Monthly testing of visual acuity and color discrimination in patients taking > 15–20 mg/kg, renal insufficiency, or receiving the drug for > 2 months
Cycloserine[f]	*Adults*: 10–15 mg/kg/day, usually 500–750 mg/day in two doses *Children*: 10–15 mg/kg/day	CNS effects	Monthly assessments of neuropsychiatric status Serum concentration may be necessary until appropriate dose is established
Ethionamide[g]	*Adults*: 15–20 mg/kg/day, usually 500–750 mg/day in a single daily dose or two divided doses *Children*: 15–20 mg/kg/day	GI effects, hepatotoxicity, neurotoxicity, endocrine effects	Baseline LFTs Monthly LFTs if underlying liver disease is present TSH at baseline and monthly intervals
Streptomycin	*Adults*[h] *Children*: 20–40 mg/kg/day	Ototoxicity, neurotoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Amikacin/ kanamycin	*Adults*[h] *Children*: 15–30 mg/kg/day IV or intramuscular as a single daily dose	Ototoxicity, nephrotoxicity	Baseline audiogram, vestibular testing, Romberg testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms
Capreomycin	*Adults*[h] *Children*: 15–30 mg/kg/day as a single daily dose	Nephrotoxicity, ototoxicity	Baseline audiogram, vestibular testing, Romberg testing and SCr Monthly assessments of renal function and auditory or vestibular symptoms Baseline and monthly serum K^+ and Mg^{2+}
p-Aminosalicylic acid (PAS)	*Adults*: 8–12 g/day in two or three doses *Children*: 200–300 mg/kg/day in two to four divided doses	Hepatotoxicity, GI distress, malabsorption syndrome, hypothyroidism, coagulopathy	Baseline LFTs and TSH TSH every 3 months
Levofloxacin	Adults: 500–1000 mg daily *Children*[i]: Not recommended	GI disturbance, neurologic effects	No specific monitoring recommended

(*Continued*)

Table 75–4

Antituberculosis Drugs for Adults and Children (*Continued*)

Drug	Daily Doses[a,b,c]	Adverse Effects	Monitoring
Moxifloxacin	*Adults*: 400 mg daily *Children*[j]: Not recommended		
Bedaquiline	*Adults:* Weeks 1–2: 400 mg daily Weeks 3–24: 200 mg three times weekly *Children:* Not recommended	GI disturbances, dizziness, headache, rash, arthralgia	Serum K, Ca, Mg ECG at baseline, weeks 2, 12, 24 Weekly ECG for persons taking other QTc prolonging drugs, history of arrhythmias, hypothyroidism, uncompensated heart failure, or have serum K, Ca, or Mg below normal limits

[a]Dose per weight is based on ideal body weight. Children weighing more than 40 kg should be dosed as adults.

[b]For purposes of this document adult dosing begins at age 15 years.

[c]The authors of this chapter do not agree with the use of maximum doses, since this arbitrarily caps doses for patients who otherwise might need larger doses. These maximum doses were not based on prospective studies in large or overweight individuals, and do not consider patients with documented malabsorption of their medications. Clinical judgment should be used in such circumstances.

[d]Higher doses of rifampin and rifapentine are being studied. Rifabutin dose may need to be adjusted when there is concomitant use of protease inhibitors or nonnucleoside reverse transcriptase inhibitors.

[e]The drug can likely be used safely in older children but should be used with caution in children less than 5 years of age, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg/day can be used if there is suspected or proven resistance to isoniazid or rifampin.

[f]It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimal dose for a given patient.

[g]The single daily dose can be given at bedtime or with the main meal.

[h]Dose: 15 mg/kg/day (1 g), and 10 mg/kg in persons older than 59 years of age (750 mg). Usual dose: 750–1000 mg administered intramuscularly or intravenously, given as a single dose 5–7 days/week and reduced to two or three times per week after the first 2 to 4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

[i]The long-term (more than several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.

[j]The long-term (more than several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.

Data from Centers for Disease Control and Prevention. Treatment of tuberculosis. MMWR 2003;52(RR-11).

► *Multidrug-Resistant TB*

MDR-TB is caused by *M. tuberculosis* that is resistant to at lease isoniazid and rifampin. If drug-resistant TB is suspected, the empiric regimen should be modified based on patterns of suspected resistance. Once susceptibilities are confirmed, regimens can be modified appropriately. Patients with MDR-TB are at high risk of failure and should be treated by specialists or centers with experience treating drug resistant TB. Effective treatement of MDR-TB requires administration, for 18 to 24 months, of four to six drugs to which the infecting organism is susceptible, including second line drugs.

► *Renal Failure*

Isoniazid and rifampin usually do not require dose modification in renal failure.[30,37] Pyrazinamide and ethambutol typically are reduced to three times weekly to avoid accumulation of the parent drug (ethambutol) or metabolites (pyrazinamide).[31,32] Renally cleared TB drugs include the aminoglycosides, ethambutol, cycloserine, and levofloxacin.[31,32] With renal impairment, dosing intervals need to be extended for these drugs. TB drugs should be administered after hemodialysis; three times weekly regimens may be more convenient. Serum concentration monitoring should be performed for cycloserine and ethambutol to avoid dose-related toxicities in renal failure patients.[32,37,38]

► *Hepatic Failure*

Hepatically cleared TB drugs include isoniazid, rifampin, pyrazinamide, ethionamide, and *p*-aminosalicylic acid.[25] Ciprofloxacin and moxifloxacin are about 50% cleared by the liver. Isoniazid, rifampin, pyrazinamide, and to a lesser degree

Patient Encounter Part 3

Based on the information provided, what are the goals of therapy for this patient?

Select and recommend a therapeutic plan for treatment of this patient's TB infection. What drugs, dose, schedule, and duration of therapy are best for this patient?

Who else should be tested? How should any contacts infected by this patient be evaluated and treated?

ethionamide, *p*-aminosalicylic acid, and rarely ethambutol may cause hepatotoxicity.[29,31] These patients require close monitoring, and serum concentration monitoring may be the most accurate way to dose them.[32]

TB Drugs

Detailed information regarding TB drugs can be accessed at the following references.[25,27,31,32] A summary is provided in Table 75–4.[26] Isoniazid, rifampin, and pyrazinamide are the key drugs. Other drugs are used in selected circumstances. Quinolones eventually may be used as first-line drugs, but currently are not.[39,40] In 2012, the Food and Drug Administration approved bedaquiline for the treatment of MDR-TB.[41] Bedaquiline may be used in adults with confirmed pulmonary MDR-TB when an effective treatment regimen cannot otherwise be provided.[42]

It should be used with three or more drugs that are active against the patient's isolate. Bedaquiline carries a black-box warning due to prolongation of QTc interval. Baseline and follow-up electrocardiograms are recommended. Other new therapies include investigational vaccines, and investigational drugs such as pretomanid, delamanid, and SQ109, which are in clinical trials.[43]

OUTCOME EVALUATION

LO 4

Effectiveness of TB therapy is determined by AFB smears and cultures. Send sputum samples for AFB staining and microscopic examination (sputum smears) every 1 to 2 weeks until two consecutive smears are negative. This provides early evidence of a response to treatment.[27] Once on maintenance therapy, *sputum cultures* can be performed monthly until two consecutive cultures are negative, which generally occurs over 2 to 3 months. If sputum cultures continue to be positive after 2 months, repeat drug susceptibility testing and check serum concentrations of the drugs.

KEY CONCEPT The most serious problem with TB therapy is patient nonadherence.[27,44] There is no reliable way to identify such patients a priori, therefore DOT should be used.[9,27,44] DOT also provides increased opportunities to observe the patient for any apparent toxicities, thus improving overall care.[44]

LO 5

Check serum chemistries, including blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), and alanine transaminase (ALT) and a complete blood count with platelets at baseline and periodically thereafter depending on the presence of other factors that may increase the likelihood of toxicity (eg, advanced age, alcohol abuse, pregnancy).[27] Suspect hepatotoxicity in patients whose transaminases exceed five times the upper limit of normal (ULN) or whose total bilirubin exceeds 3 mg/dL (51 µmol/L), and in patients with symptoms such as nausea, vomiting, and jaundice with liver enzyme elevations of more than three times ULN. At this point, discontinue the offending agents. Typically, all TB drugs are stopped, followed by the sequential reintroduction of the drugs, along with frequent testing of liver enzymes. This usually is successful in identifying the offending agent; other agents may be continued (see Table 75–4).[27]

Patient Encounter Part 4

Based on the information provided, which clinical and laboratory parameters should be monitored in this patient to determine efficacy and avoid toxicity?

Is this patient a candidate for therapeutic drug monitoring? Why or why not?

Therapeutic Drug Monitoring

LO 6

TDM is the use of serum drug concentrations to optimize therapy.[27,31,32] Patients with uncomplicated, drug-susceptible TB generally do well. Pharmacokinetic variability of anti-TB drugs can contribute to poor outcomes despite adherence. TDM can be used to shorten the time to response and to treatment completion. The evidence to support the use of TDM in the treatment of TB is growing.[32] TDM can assist in patients failing appropriate DOT (no clinical improvement after 2–4 weeks or smear-positive after 4–6 weeks). Patients with AIDS, diabetes, and various GI disorders often fail to absorb these drugs properly and also are candidates for TDM. Drug concentrations in patients with hepatic or renal disease should be monitored, given their potential for toxicities. In the treatment of MDR-TB, TDM may be particularly useful.[25] Finally, TDM of the TB and HIV drugs is perhaps the most logical way to untangle the complex drug interactions that take place.

For a complete list of drug interactions, visit the CDC website: www.cdc.gov/tb/publications/guidelines/TB_HIV_DRUGS/default.htm.[45] In particular, interactions between the rifamycins (eg, rifampin, rifapentine, rifabutin) and the HIV protease inhibitors and nonnucleoside reverse transcriptase inhibitors are common and require dose and frequency modifications in many cases. Because these are constantly being updated, the preceding link is an excellent way to keep current.

Patient Care Process

Collect Information:

- Obtain a thorough medical and medication history.
- Obtain necessary laboratory tests, cultures, and radiology to determine active infection. (Collect appropriate samples for smears and cultures.)
- Review physical assessment findings.
- Speak with the patient obtain risk factors for infection and risk factors for developing active TB (travel, living conditions, immune status, etc).

Assess the Information:

- Assess the patient's risk factors and signs and symptoms to determine whether the patient might be infected with TB.
- Based on physical examination, medical history, laboratory tests and cultures, and X-rays, determine whether the patient has an active TB infection.
- Assess the efficacy, safety, and patient adherence of required pharmacotherapy.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- Isolate the patient with active disease to prevent the spread of the disease.
- Select and recommend appropriate antituberculosis treatment. Consider susceptibility, HIV status, drug interations, type of TB infection, etc.
- Choose medication doses that are optimal for the patient. Consider renal function, liver function, etc.

(*Continued*)

Patient Care Process (*Continued*)

- Consider DOT.
- Identify the index case that infected the patient, identify all persons infected by both the index case and the new case of TB, and the complete appropriate treatments for those individuals.

Implement the Care Plan:

- Review drugs, duration, dose, frequency, and side effects of selected medications.
- Educate the patient about the importance of compliance with the regimen and the risks of noncompliance.
- Ensure adherence to the treatment regimen by the patient.

Follow-up: Monitor and Evaluate:

- Follow-up at required intervals to obtain AFB stains to evaluate the effectiveness of treatment.
- Review susceptibilities when available and modify treatment regimen as determined by susceptibility results.
- Continue treatment for at least 6 months from the time that the patient converts to a negative culture.
- Consider TDM if no clinical improvement.

Abbreviations Introduced in This Chapter

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
ART	antiretroviral therapy
AST	Aspartate transaminase
BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
DOT	Directly observed therapy
HIV	Human immunodeficiency virus
HTN	Hypertension
IGRA	Interferon-γ release assay
INF	Interferon
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant tuberculosis
NIDDM	Noninsulin-dependent diabetes mellitus
PCR	Polymerase chain reaction
PPD	Purified protein derivative
RFLP	Restriction fragment length polymorphism
TB	Tuberculosis
TDM	Therapeutic drug monitoring
ULN	Upper limit of normal
WBC	White blood cell

REFERENCES

1. World Health Organization Report on the Global Tuberculosis 2016. Available from: http://www.who.int/tb/publications/global_report/en/. Accessed August 27, 2017.
2. Centers for Disease Control and Prevention. Trends in tuberculosis—United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;66:289–294.
3. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2015. Atlanta, GA: U.S. Department of Health and Human Services. CDC; 2016.
4. Fitzgerald DW, Sterling TR, Haas DW. Mycobacterium tuberculosis. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 8th ed. New York: Elsevier; 2015:3129–3165.
5. Heifets L. Mycobacteriology laboratory. Clin Chest Med. 1997;18:35–53.
6. Heifets LB. Drug susceptibility tests in the management of chemotherapy of tuberculosis. In: Heifets LB, ed. Drug Susceptibility in the Chemotherapy of Mycobacterial Infections. Boca Raton, FL: CRC Press; 1991:89–122.
7. Laylabadlo HE, Kaftl HS, Yousefi M, Aghazadeh M, Asgharzadeh M. Pulmonary tuberculosis: where we are? Tuberc Respir Dis. 2016;79:134–142.
8. Issa R, Mohd Hassan NA, Abdul H, et al. Detection and discrimination of Mycobacterium tuberculosis complex. Diagn Microbiol Infect Dis. 2012;72:62–67.
9. Kiraz N, Sglik I, Kiremitci A, et al. Evaluation of the genotype mycobacteria direct assay for direct detection of the Mycobacterium tuberculosis complex obtained from sputum samples. J Med Microbiol. 2010;59:930–934.
10. Hillemann D, Weizenegger M, Kubica T, et al. Use of the genotype MTBDR assay for rapid detection of rifampin and isoniazid resistance in Mycobacterium tuberculosis complex isolates. J Clin Microbiol. 2005;43:3699–3703.
11. Marlowe EM, Novack-Weekley SM, Cumpio J, et al. Evaluation of the Cepheid Xpert MTB/RIF assay for direct detection of Mycobacterium tuberculosis complex in respiratory specimens. J Clin Microbiol. 2011;49:1621–1623.
12. Martin A, Panaiotov S, Portaels F, et al. The nitrate reductase assay for the rapid detection of isoniazid and rifampicin resistance in Mycobacterium tuberculosis: a systematic review and meta-analysis. J Antimicrob Chemother. 2008;62(1):56–64.
13. Guide to the Application of Genotyping to Tuberculosis Prevention and Control. Centers for Disease Control and Prevention; 2004. Available from: http://www.cdc.gov/tb/programs/genotyping/manual.htm. Accessed September 25, 2014.
14. Woolwine SC, Bishai WR. Pathogenesis of tuberculosis from a cellular and molecular perspective. In: Reichman LB, Hershfield ES, eds. Tuberculosis. A Comprehensive International Approach, 3rd ed. New York: Marcel Dekker; 2006:101–117.
15. Lewinsoh DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of tuberculosis in children and adults. CID. 2017;64(1)111–115.
16. Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. Paediatr Respir Rev. 2007;8:107–117.
17. Latent tuberculosis infection: a guide for primary health care providers 2013. Atlanta, GA: US Department of Health and Human Services. CDC; 2013.
18. Kwan CK, Ernst JD. HIV and tuberculosis: a deadly human syndemic. Clin Microbiol Rev. 2011;24:351–376.
19. Gilpin C, Korobitsyn A, Weyer K. Current tools available for the diagnosis of drug-resistant tuberculosis. Therapeutic Advances in Infectious Disease. 2016;3(6):145–151.
20. Report of Expert Consultations on Rapid Molecular Testing to Detect Drug-Resistant Tuberculosis in the United States. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/tb/topic/laboratory/rapidmoleculartesting/default.htm. Accessed July 25, 2018.
21. Zevallos M, Justman JE. Tuberculosis in elderly. Clin Geriatr Med. 2003;19:121–138.
22. Perez-Velez CM, Marais BJ. Tuberculosis in children. N Engl J Med. 2012;367:348–361.

23. Centers for Disease Control and Prevention. Guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection—United States, 2010. MMWR Recomm Rep. 2010;59(RR-5):1–25.
24. Nienhaus A, Schablon A, Diel R. Interferon-gamma release assay for the diagnosis of latent TB infection—analysis of discordant results, when compared to the tuberculin skin test. PLoS One. 2008;3(7):e2665.
25. Peloquin CA. Antituberculosis drugs: pharmacokinetics. In: Heifets LB, ed. Drug Susceptibility in the Chemotherapy of Mycobacterial Infections. Boca Raton, FL: CRC Press; 1991:59–88.
26. Fujiwara PI, Larkin C, Frieden TR. Directly observed therapy in New York City. Clin Chest Med. 1997;18:135–148.
27. Nahid P, Dorman SE, Alipanah N, et al. Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clinical Infectious Diseases. 2016:63(7):853–867.
28. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2007;17:CD003343.
29. Centers for Disease Control and Prevention. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in the American Thoracic Society/CDC recommendations—United States, 2001. MMWR Morb Mortal Wkly Rep. 2001;50(34):733–735.
30. Centers for Disease Control and Prevention. Recommendations for use of an isoniazid-rifapentine regimen with observation to treat latent Mycobacterium tuberculosis. MMWR Morb Mortal Wkly Rep. 2011;60(48):1650–1653.
31. Davies G. Pharmacologic considerations in use and development of antituberculosis drugs. Cold Spring Harbor Perspectives in Medicine. 2015;5(1):a021170.
32. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2014;74:839–854.
33. Heysell SK, Moore JL, Staley D, et al. Early therapeutic drug monitoring for isoniazid and rifampin among diabetics with newly diagnosed tuberculosis in Virginia, USA. Tuberc Res Treat. 2013;2013:1–6.
34. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. BJOG: An International J Obstet Gynaecol. 2010;118:226–231.
35. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf . Accessed July 25, 2018.
36. Abdool Karim SS, Naidoo K, Padayatchi N, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med. 2010;362:697–706.
37. Malone RS, Fish DN, Spiegel DM, et al. The effect of hemodialysis on isoniazid, rifampin, pyrazinamide, and ethambutol. Am J Respir Crit Care Med. 1999;159:1580–1584.
38. Malone RS, Fish DN, Spiegel DM, et al. The effect of hemodialysis on cycloserine, ethionamide, paraminosalicylate acid, and clofazamine. Chest. 1999;116:984–990.
39. Burman WJ. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. Am J Respir Crit Care Med. 2006;174:331–338.
40. Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomized, controlled phase II trial. Lancet. 2009; 373:1183–1189.
41. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371:723–732.
42. Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR. 2013;62(9):1–12.
43. Zhang Y. Advances in the treatment of tuberculosis. Clin Pharmacol Ther. 2007;82:595–600.
44. Volmink J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2009;4:CD0003343.
45. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. Centers for Disease Control and Prevention. Available from: www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm. Accessed August 29, 2017.

76 Gastrointestinal Infections

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LEARNING OBJECTIVES

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

LO

1. Describe the epidemiology and clinical presentation of commonly encountered gastrointestinal (GI) infections.
2. Summarize common risk factors associated with the development of a GI infection.
3. Given a patient with a GI infection, develop an individualized treatment plan.
4. Outline the impact of widespread antimicrobial resistance on current treatment recommendations for GI infections.
5. Discuss the effect of host immunosuppression on the risk of disease complications and treatment strategies associated with GI infections.
6. Educate patients on appropriate prevention measures of GI infections.
7. Describe the role of antimicrobial prophylaxis and/or vaccination for GI infections.

INTRODUCTION

One of the primary concerns related to gastrointestinal (GI) infection, regardless of the cause, is dehydration, which is the second leading cause of worldwide morbidity and mortality.[1] Dehydration is especially problematic for children younger than age 5; however, the highest rate of death in the United States occurs among the elderly.[1] KEY CONCEPT Rehydration is the foundation of therapy for GI infections, and oral rehydration therapy (ORT) is usually preferred (Table 76–1).[2] Single-dose oral ondansetron should be considered the first-line antiemetic in children who are dehydrated with significant vomiting.[3] In nonimmunocompromised hospitalized pediatric patients, *Lactobacillus* supplementation may reduce the length of hospitalization.[4]

LO 1

In the United States, each year 31 major pathogens cause about 9 million episodes of food-borne illness, almost 56,000 hospitalizations, and 1350 deaths. Most illnesses are caused by norovirus, nontyphoidal *Salmonella* (NTS), *Clostridium perfringens*, and *Campylobacter*.[5] KEY CONCEPT The indiscriminate use of proton-pump inhibitor (PPI) therapy leads to changes in gut microbiome and increased susceptibility to enteric bacterial infections.[6] The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) actively track food-borne illnesses via surveillance systems that offer excellent epidemiological information.

BACTERIAL INFECTIONS

SHIGELLOSIS

Epidemiology

Shigella causes bacillary dysentery, which refers to diarrheal stool containing pus and blood. Shigellosis is endemic in most developing countries and is the most important cause of bloody diarrhea worldwide. It is estimated to cause at least 80 million cases and 700,000 deaths each year, the majority of which occur in children less than 5 years old.[7] There are approximately 500,000 infections each year in the United States; it is a particular problem in daycare centers and in areas with crowded living conditions or poor sanitation. Most cases of shigellosis are transmitted through the fecal–oral route. Activities that may lead to shigellosis include handling diapers, ingesting pool water, or consuming vegetables from a sewage-contaminated field. *Shigella* transmission from contaminated food and water, although less common, is associated with large outbreaks.

Pathogenesis

LO 2

Shigella organisms are nonmotile, nonlactose-fermenting, gram-negative rods and are members of the Enterobacteriaceae family. *S. sonnei* (serogroup D) is responsible for most shigellosis cases in the United States. Infection with Shigella occurs after ingestion of as few as 10 to 100 organisms, which may explain the ease of person-to-person spread. Symptoms develop about 1 to 2 days after contracting the bacteria.[8]

Shigella strains invade intestinal epithelial cells, with subsequent multiplication, inflammation, and destruction. This organism only rarely invades the bloodstream; but, bacteremia can occur in malnourished children and immunocompromised patients and is associated with a mortality rate as high as 20%.[9]

Treatment and Monitoring

In April 2017, the CDC issued a health advisory describing the emergence of *Shigella* strains with elevated MIC values for ciprofloxacin. Within this advisory, the CDC outlined new recommendations for the clinical diagnosis and management of this infection as well as new recommendations for laboratories

Table 76–1

Clinical Assessment of Degree of Dehydration in Children Based on Percentage of Body Weight Loss

Variable	Mild (3%–5%)	Moderate (6%–9%)	Severe (10% or More)
Blood pressure	Normal	Normal	Normal to reduced
Quality of pulses	Normal	Normal to slightly decreased	Moderately decreased
Heart rate	Normal	Increased	Increased (bradycardia in severe cases)
Skin turgor	Normal	Decreased	Decreased
Fontanelle	Normal	Sunken	Sunken
Mucous membranes	Slightly dry	Dry	Dry
Eyes	Normal	Sunken orbits/decreased tears	Deeply sunken orbits/decreased tears
Extremities	Warm, normal capillary refill	Delayed capillary refill	Cool, mottled
Mental status	Normal	Normal to listless	Normal to lethargic to comatose
Urine output	Slightly decreased	< 1 mL/kg/hour	< 1 mL/kg/hour
Thirst	Slightly increased	Moderately increased	Very thirsty
Fluid replacement	ORT 50 mL/kg over 2–4 hours	ORT 100 mL/kg over 2–4 hours	Lactated Ringer 40 mL/kg in 15–30 minutes, then 20–40 mL/kg if skin turgor, alertness, and pulse have not returned to normal *or* Lactated Ringer or normal saline 20 mL/kg, repeat if necessary, and then replace water and electrolyte deficits over 1–2 days, followed by ORT 100 mL/kg over 4 hours

From Martin S, Jung R. Gastrointestinal infections and enterotoxigenic poisonings. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York: McGraw-Hill; 2014:1951–1967.

and public health officials. It is now recommended that stool cultures and antimicrobial susceptibility testing be obtained in patients suspected of having a *Shigella* infection. The CDC now recommends that antibiotics not be routinely prescribed for Shigella infections. Antibiotic therapy should be reserved for patients who are immunocompromised or who develop severe illness or when public health officials advise treatment in an outbreak situation.[10] Although treatment can shorten the duration of symptoms by 1 to 2 days, shigellosis is generally a self-limited infection and unnecessary treatment with antibiotics promotes further resistance. Fluoroquinolones, which have generally been considered the first-line drug for the treatment of shigellosis in adults, should not be prescribed if the ciprofloxacin MIC is 0.12 mcg/mL or higher, even if identified by the laboratory as susceptible. In these cases, an infectious disease specialist should be consulted to identify an appropriate antibiotic. In children, oral azithromycin or parenteral ceftriaxone is considered preferable to fluoroquinolones for first-line therapy. All shigellosis cases should be reported to the local health department.[10]

SALMONELLOSIS

Epidemiology

Salmonella are gram-negative facultative rods that cause a wide variety of disease manifestations. *Salmonella enterica* (serotypes Typhi and Paratyphi A and B) cause typhoid (or enteric) fever. Although typhoid fever is now a rare disease in the United States with approximately 400 clinical cases reported per year, these infections cause an estimated 30 million cases and 215,000 deaths annually worldwide.[11] Typhoid fever is most commonly acquired from water or food contaminated by feces from an infected person. The incubation period is 6 to 30 days; illness onset is insidious with gradually increasing fatigue and fever. Nontyphoidal *Salmonella* (NTS) are important causes of reportable food-borne infection. There are an estimated 1.4 million cases of NTS illness annually in the United States, and almost 94 million worldwide.[12] The highest incidence is in those younger than 1 year of age, older than 65 years of age, or in those with HIV/AIDS. Foods commonly associated with infection include raw meat, poultry, eggs, tuna,

Clinical Presentation and Diagnosis of Shigellosis

- Biphasic illness
  - Early—high fever, watery diarrhea without blood
  - Later—after approximately 48 hours, colitis develops with urgency, tenesmus, and dysentery
  - Low-grade fever
  - More frequent small-volume stools ("fractional stools")
  - Vomiting (35%)
- Complications of shigellosis
  - Proctitis or rectal prolapse—more common in infants and young children
  - Intestinal obstruction
  - Colonic perforation
  - Bacteremia—more common in children
  - Metabolic disturbances
  - Neurologic disease—most commonly seizures (approximately 10% of patients)
  - Hemolytic-uremic syndrome (HUS)
- Microscopic examination of stool is extremely useful and reveals multiple polymorphonuclear leukocytes and red blood cells (RBCs). Diagnosis is usually confirmed by stool culture

Patient Encounter 1

A mother carrying a 1-year-old infant comes to you with a prescription for Augmentin® suspension 200 mg/5 mL, 1 teaspoonful q12h for an ear infection. You check the child's prescription record and note that this is the second course of antibiotics over the last 2 months (previously, ampicillin 250 mg po q6h). In addition, the child is on omeprazole suspension 5 mg once daily for GE reflux.

This child is at high risk for what type of gastrointestinal infection?

What risk factors are present to develop this disease in this child?

What are the symptoms of this infection that you could counsel this mother to watch for? How is this different from the normal side effects of Augmentin®?

What antibiotics are less likely to result in an overgrowth of C. difficile *than those listed above, which could still treat the child's otitis media in some circumstances?*

and unwashed food and vegetables. Exotic pets, especially reptiles, are an increasing source of human salmonellosis. NTS strains may also result in bacteremia and focal disease, such as endovascular infections, osteomyelitis, meningitis, and septic arthritis. Antimicrobial-resistant strains are associated with excess bloodstream infections and hospitalizations.[13] Recurrent *Salmonella* bacteremia is an AIDS-defining illness.

LO 2

Risk factors for salmonellosis include extremes of age; alteration of endogenous GI flora due to antimicrobial therapy, surgery, or acid-suppressive therapy[6]; diabetes; malignancy; rheumatologic disorders; HIV infection; and therapeutic immunosuppression. Proper food handling and storage can help prevent *Salmonella* gastroenteritis. Effective handwashing is important, especially when handling eggs and poultry.

Treatment and Monitoring

▶ *Gastroenteritis*

LO 3

Salmonella gastroenteritis is usually self-limited, and antibiotics have no proven value. Patients respond well to ORT. Symptoms typically diminish in 3 to 7 days without sequelae. Antibiotic use may result in a higher rate of chronic carriage and relapse. Antimicrobial use should be limited to preemptive therapy among patients at higher risk for extraintestinal spread or invasive disease (Table 76–2). Antimotility agents should not be used.

Table 76–2

Antimicrobial Indications for Nontyphoidal Salmonellosis (NTS)

Age 3 months or less or 65 years or more
Fever and systemic toxicity
HIV/AIDS
Other immunodeficiency (eg, steroid use, organ transplantation)
Uremia or hemodialysis or renal transplant
Malignancy
Sickle cell anemia or hemoglobinopathy
Inflammatory bowel disease
Aortic aneurysm, prosthetic heart valve, vascular or orthopedic prosthesis

Clinical Presentation and Diagnosis of Salmonellosis

Gastroenteritis

- Onset 8 to 48 hours after ingestion of contaminated food.
- Fever, diarrhea, and cramping.
- Stools are loose, of moderate volume, and without blood.
- Headache, myalgias, and other systemic symptoms can occur.
- Certain underlying conditions (eg, AIDS, inflammatory bowel disease, and prior gastric surgery) predispose the patient to more severe disease.

Enteric Fever

- Febrile illness 5 to 21 days after ingestion of contaminated food or water, which may be persistent and high-grade. A relative bradycardia may be noted at the fever peak.
- Chills, diaphoresis, headache, anorexia, cough, weakness, sore throat, dizziness, muscle pain, and diarrhea may be present before onset of fever.
- Rose spots, a coated tongue, and/or hepatosplenomegaly may be noted.
- Intestinal hemorrhage or perforation, leukopenia, anemia, and subclinical disseminated intravascular coagulopathy may occur.
- Culture of stool, blood, or bone marrow for *Salmonella* species is helpful.

▶ *Enteric Fever*

The current drug of choice for typhoid fever in adults is a fluoroquinolone, such as ciprofloxacin. Azithromycin or ceftriaxone are preferred in children. The recommended adult dose of ciprofloxacin for uncomplicated typhoid fever is 500 mg orally twice daily for 5 to 7 days; however, decreased susceptibility to ciprofloxacin is a significant problem in many parts of the world. In the United States, *Salmonella* spp. with decreased ciprofloxacin susceptibility are associated with travel to the Indian subcontinent.[14] If ciprofloxacin resistance is present, ceftriaxone may be used; however, this agent may be less suitable in some low- and middle-income countries due to cost and route of administration. Azithromycin is an effective alternative for uncomplicated typhoid fever.[15]

Two typhoid vaccines are available for use in the United States; however, neither is licensed by the FDA for the prevention of paratyphoid fever. Immunization is recommended for travelers going to endemic areas such as Latin America, Asia, and Africa; household contacts of chronic carriers; and laboratory personnel who frequently work with *Salmonella* serotype Typhi.[16] Vaccination is increasingly important for travelers to consider since the growth of multidrug-resistant strains of *Salmonella* serotype Typhi have become common in many regions.

▶ *Bacteremia and Focal Infections*

Treatment of *Salmonella* bacteremia should be initiated with either a fluoroquinolone (eg, levofloxacin, ciprofloxacin) or a third-generation cephalosporin (eg, ceftriaxone). Given increasing antimicrobial resistance, life-threatening infections should be treated with both agents until susceptibilities are

available.[12] If there is no evidence of an endovascular infection, therapy for bacteremia should continue for 10 to 14 days. For patients with suspected meningitis, high-dose ceftriaxone is preferred because of its optimal penetration of the blood–CSF barrier. Osteomyelitis and joint infections, often associated with sickle-cell anemia, are difficult to eradicate and require longer durations of antimicrobial therapy (at least 4–6 weeks), as do patients who are infected with HIV.[12]

▶ *Chronic Carrier State*

A chronic carrier state, defined as positive stool or urine cultures for more than 12 months, develops in 1% to 4% of adults with typhoid fever. Effective agents for eradication of chronic carriage include amoxicillin (3 g orally divided three times a day in adults for 3 months), trimethoprim-sulfamethoxazole (one double-strength tablet orally twice a day for 3 months), or ciprofloxacin (750 mg orally twice daily for 4 weeks). Surgery in combination with antibiotic therapy is indicated in patients with biliary tract abnormalities.

CAMPYLOBACTERIOSIS

Epidemiology

Campylobacter jejuni is the most commonly identified cause of bacterial gastroenteritis worldwide. In the United States, this organism accounts for an estimated 1.4 million infections, 13,000 hospitalizations, and 100 deaths annually.[17] Risk factors for *Campylobacter* infection include consumption of contaminated foods of animal origin, especially undercooked poultry or other foods that are cross-contaminated by raw poultry meat during food preparation; unpasteurized milk; contaminated water; foreign travel; contact with farm animals and pets; and the use of antimicrobial therapy.[18] People should be instructed to wash their hands after contact with raw meats and animals.

In developed countries, there are two distinct age peaks for Campylobacter infection: younger than 1 year of age and 15 to 44 years of age, with a mild male predominance. In developing countries, *Campylobacter*–associated diarrhea is primarily a pediatric disease.

Patient Encounter 2

A 55-year-old male, who was diagnosed with nonsmall cell lung cancer (NSCLC) about 6 months, has now completed three courses of cytotoxic chemotherapy, completing the third course about 10 days ago. He now presents to his local emergency department (ED) with a 3-day history of nausea, several episodes of vomiting, abdominal pain, and non-bloody diarrhea. He also complains of episodes of chills and nightsweats over the past 2 days. The patient states that he first noticed these symptoms following a church picnic that took place on a hot summer day. He and his wife had arrived at the picnic a bit late after the others had started eating. The patient states that he did wonder how long some of the food had been sitting out in the sun. STAT blood cultures are positive for nontyphoidal *Salmonella* (NTS).

What risk factors are present in this patient that may have predisposed him to developing Salmonella *bacteremia?*

What treatment strategy would you recommend? Are there any special considerations given this patient's immunosuppression?

Clinical Presentation and Diagnosis of Campylobacteriosis

- Incubation period of 1 to 7 days.
- A brief prodrome of fever, headache, and myalgias is followed by crampy abdominal pain, a high fever, and several bowel movements per day, which may be watery or bloody.
- The abdominal pain and tenderness may be localized, and pain in the right lower quadrant may mimic acute appendicitis. Abdominal pain is more prevalent in *Campylobacter* infection than in either *Shigella* or *Salmonella* infections.
- Tenesmus occurs in approximately 25% of patients.
- Fecal leukocytes and red blood cells (RBCs) are detected in the stools of 75% of infected individuals. Diagnosis of *Campylobacter* is established by stool culture.

Pathophysiology

Campylobacter spp. are gram-negative bacilli that have a curved or spiral shape. *Campylobacter* are sensitive to stomach acidity; as a result, diseases or medications that buffer gastric acidity may increase the risk of infection. The infectious inoculum for *C. jejuni* is low, similar to that for *Salmonella* spp. After an incubation period, infection is established in the jejunum, ileum, colon, and rectum.

Treatment

LO 3 Effective fluid and electrolyte replacement is the cornerstone of therapy for patients with *Campylobacter* infection. In most cases, this can be accomplished with the use of oral glucose–electrolyte solutions. Antibiotic therapy should be considered in patients with high fevers, bloody stools, symptoms lasting longer than 1 week, pregnancy, infection with HIV, and other immunocompromising conditions.

LO 4 Azithromycin is the recommended first-line drug (500 mg orally daily for 1–3 days) for the treatment of *Campylobacter* infections.[19] A fluoroquinolone or a tetracycline are alternatives; however, the widespread use of these agents in food animals has resulted in fluoroquinolone resistant *Campylobacter* strains worldwide.[18] *Campylobacter fetus* is the most commonly identified species in patients with bacteremia, which primarily occurs in patients who are elderly or immunocompromised. In addition, focal infections such as cellulitis, vascular infections, meningitis, and abscesses may be present. *C. fetus* has a predilection for the vascular endothelium and implanted medical devices.[20] For these serious infections, treatment with a third-generation cephalosporin, gentamicin, ampicillin, or a carbapenem is recommended.[19] LO 6 Antimotility agents should be avoided because they may prolong the duration of symptoms and have been associated with worse outcomes. Postinfectious complications associated with *Campylobacter* infection include reactive arthritis (1%) and Guillain-Barré syndrome (0.1%).

ENTEROHEMORRHAGIC *ESCHERICHIA COLI*

Epidemiology

KEY CONCEPT Blood in the stool indicates the possibility of inflammatory mucosal disease of the colon such as enterohemorrhagic Escherchia coli (EHEC), a pathogenic subgroup of shiga toxin-producing E. coli (STEC) and an

LO 1

Clinical Presentation and Diagnosis of EHEC

- Incubation period of 3 to 5 days.
- Bloody stools.
- Leukocytosis is often present; fever is frequently absent.
- Abdominal tenderness.
- HUS in 2% to 10% of patients (especially children 1–5 years of age and the elderly in nursing homes); develops on average 1 week after the onset of diarrhea.
- EHEC belonging to serotype 0157:H7 characteristically do not ferment sorbitol, whereas more than 70% of intestinal microbiome *E. coli* do. To properly screen EHEC strains in cases of diarrhea, stool should be placed on special sorbitol-MacConkey agar. In addition, stool should be tested directly for the presence of Stx I and II by enzyme immunoassay (EIA).

important cause of bloody diarrhea in the United States. Acute hemorrhagic colitis has been primarily associated with the O157:H7 serotype. This serotype is responsible for large outbreaks of infection, has higher rates of complications, and appears to be more pathogenic than non-EHEC STEC strains. The spectrum of disease associated with *E. coli* O157:H7 includes bloody diarrhea, which is seen in up to 95% of patients; nonbloody diarrhea; hemolytic-uremic syndrome (HUS); and thrombotic thrombocytopenic purpura (TTP).[21]

An estimated 265,000 STEC infections occur each year in the United States. Serotype O157:H7 causes about one-third of these infections. Very young children and the elderly are more likely to develop severe illness and HUS; however, healthy older children and young adults can also become seriously ill.[22] Outbreaks of diarrhea due to *E. coli* O157:H7 and other STECs have occurred following ingestion of contaminated beef, unpasteurized milk, vegetables (eg, alfalfa sprouts, coleslaw, and lettuce), and apple juice. The most important reservoir for *E. coli* O157:H7 is the GI tract of cattle. Person-to-person transmission also occurs, and swimming in infant pools or contaminated lakes or drinking contaminated municipal water are additional risk factors. The incidence of diagnosed *E. coli* O157:H7 infections in the United States is greater among rural populations and usually occur in summer and autumn months.

Pathophysiology

The infectious inoculum of EHEC is very low, between 1 and 100 colony-forming units (CFUs). The major virulence factor for EHEC is the production of two Shiga-like cytotoxins (Shiga toxin [Stx] I and II), which are responsible for vascular damage and systemic effects such as HUS. Adhesion mediates initial attachment of EHEC to intestinal epithelial cells. Following attachment, these organisms produce lesions on individual intestinal epithelial cells in the small or large intestine resulting in diarrhea.

Treatment

The only recommended treatment of EHEC infection is supportive, including fluid and electrolyte replacement, usually in the form of ORT. Most illnesses resolve in 5 to 7 days. Patients should be monitored for the development of HUS.[21] Antibiotics are currently contraindicated because they can induce the expression and release of toxin. Antimotility agents should be avoided because they delay clearance of the pathogen and toxin, which increases the risk of systemic complications. The incidence of HUS has declined in recent years and nonsteroidal anti-inflammatory drugs (NSAIDs) are increasingly recognized as an important contributor to acute kidney injury in infected children, especially if volume depleted.[23]

LO 6

Prevention of EHEC infection is especially important because no therapeutic interventions are available to lessen the risk of the development of HUS. Hamburgers should be cooked thoroughly until the temperature of the thickest part of the patty is 72°C. All surfaces and utensils that contact raw meat should be washed thoroughly before reuse. Fruits and vegetables should be washed thoroughly, especially those that will not be cooked. Handwashing is also very important and should include the supervision of handwashing by children in daycare centers.

CHOLERA

Epidemiology

Cholera is an intestinal infection that is caused by the bacterium *Vibrio cholerae* that leads to a massive loss of fluid through the GI tract and often results in life-threatening dehydration and shock. The biotypes of *V. cholerae* responsible for pandemics are serogroups O1 (El Tor) and O139. Worldwide this infection affects 3 to 5 million people and causes about 100,000 deaths per year, almost entirely in developing countries. Cholera can be transmitted by water or by food tainted with contaminated water, particularly undercooked seafood. Infants and young toddlers who are not breastfed at the time of exposure are at increased risk of infection.[24]

Pathophysiology

V. cholerae are gram-negative bacilli that pass through the stomach to colonize the upper small intestine. They possess filamentous protein extensions that attach to receptors on the intestinal mucosa, and their motility assists with penetration of the mucus layer. The cholera enterotoxin consists of two subunits, one of which (subunit A) is transported into the cells and causes an increase in cyclic adenosine monophosphate (cAMP), which leads to the secretion of fluid into the small intestine. This large volume of GI fluid results in the watery diarrhea that is characteristic of cholera and leads to stools made up of an electrolyte-rich isotonic fluid that is highly infectious. Low gastric acid levels have been associated with more severe disease.

Patient Encounter 3

A 26-year-old man is travelling to Mexico with his new bride for a 2-week honeymoon. On the fifth day of their trip, he notices an acute onset of very watery diarrhea following a buffet-style meal at his hotel. He also states that he enjoyed several mixed alcoholic drinks during the evening. He denies noting blood or pus in his stools, nor does he complain of any abdominal cramping. He is also noted to be afebrile.

What is the most likely organism infecting this patient?

Would loperamide be appropriate for the treatment of this patient?

If this patient had been prescribed an antibiotic before departing on this trip for empiric use, if needed, should he begin taking them at this time?

Is this patient at increased risk of developing hemolytic uremic syndrome (HUS)?

Clinical Presentation and Diagnosis of Cholera

- Incubation period of 18 hours to 5 days.
- Abrupt, painless onset of watery diarrhea and vomiting. The diarrheal fluid is usually clear and may be as much as 10 to 20 liters per day.
- Large volumes of rice-water stools, which may have fishy odor.
- Dehydration is often severe and puts patients at risk for death within hours of disease onset. Symptoms of severe dehydration include low blood pressure, poor skin turgor, sunken eyes, and rapid pulse.
- Severe muscle cramps in extremities are due to electrolyte imbalances caused by fluid loss. These cramps should resolve with treatment.
- Metabolic acidosis.

Treatment

LO4 LO5

The cornerstone of cholera treatment is fluid replacement. Without treatment, the case-fatality rate for severe cholera is approximately 50%. For cholera, rice-based ORT is better than glucose-based ORT because it reduces the number of stools. Antibiotic prophylaxis is not warranted. The current WHO treatment protocol recommends antibiotics for only "severe" symptoms; however, this is controversial and some expert groups argue that antibiotics should be used more liberally in significant outbreaks.[25] With effective antibiotic therapy, the illness is shortened by about 50%, and the duration of excretion of *V. cholerae* in the stool is shortened to 1 or 2 days.[26] Antibiotic treatment should be dictated by local antimicrobial susceptibility profiles. Azithromycin and ciprofloxacin are commonly used; doxycycline may be recommended in areas of low tetracycline resistance. Azithromycin may be more effective than ciprofloxacin in terms of shortened duration of diarrhea, reduced stool volume, and cessation of fecal excretion of cholera vibrios.[24] Azithromycin is preferred in children younger than 8 years old and pregnant women.

Primary preventive strategies include ensuring a safe water supply and safe food preparation, improving sanitation, and patient education. In 2016, the FDA approved the first and only vaccine in the United States for the prevention of cholera (Vaxchora®) due to serogroup 01. It is indicated for adults (age 18–64) travelling to an area of active *V. cholerae* 01 transmission who have risk factors for poor outcomes if infected. This is a live vaccine that is administered as a single dose a minimum of 10 days before potential exposure.

TRAVELER DIARRHEA

Epidemiology

Traveler's diarrhea (TD) commonly occurs when visitors from developed countries travel to developing countries. More than 50 million people are at risk for TD each year; the incidence of one episode of TD during a 2-week trip is 10% to 40%. These infections arise following the consumption of food or water contaminated with bacteria, viruses, or parasites. KEY CONCEPT Bacteria such as *Shigella*, *Salmonella*, *Campylobacter*, and enterotoxigenic *E. coli* (ETEC) are responsible for 60% to 85% of TD cases. Noroviruses are increasingly recognized as a significant cause of TD as well. Most of these illnesses occur during the first 2 weeks of travel and last about 4 days without therapy. Protozoans are an uncommon cause but should be suspected if diarrhea lasts for more than 2 weeks.[27]

Food and water contaminated with fecal matter are the main sources of pathogens that lead to TD. Particularly problematic foods and beverages include salads, unpeeled fruits, raw or poorly cooked meats and seafood, unpasteurized dairy products, and tap water (including ice). Food from street vendors and buffet-style meals are particularly risky. The consumption of more than five alcoholic drinks per day is a risk factor for TD, especially in males.

Clinical Presentation and Diagnosis of Traveler Diarrhea

- Frequent, loose stools
- Nausea and vomiting
- Abdominal pain
- Fecal urgency
- Dysentery
- Signs and symptoms related to specific causative pathogen

Pathophysiology

Enterotoxigenic *E. coli*, which is responsible for up to 70% of TD cases in Mexico, produces both heat-labile enterotoxins (LT) and heat-stable enterotoxins (ST). Both toxins demonstrate cellular mechanisms similar to those of cholera toxins and lead to a great increase in both fluid and electrolyte secretion. These *E. coli* strains are not invasive, as are the Shiga-toxin–producing EHEC strains. These organisms lead to a profuse, watery diarrhea without blood, leukocytes, or abdominal cramping.

Treatment

The goal of treatment is to maintain hydration and functional status and to prevent disruption of travel plans. For travelers with mild cases of diarrhea, oral rehydration salts can prevent and treat dehydration and may be particularly important for children and the elderly. Loperamide (to a maximum dose of 16 mg/day) may be used for milder diarrhea; however, this agent is not recommended for use alone if bloody diarrhea or fever is present. Antibiotics are effective at reducing the duration of illness to 1 or 2 days. Providing the traveler with a means for empiric self-treatment is an effective method of treating this illness without promoting the inappropriate use of antibiotics. Therapy should be initiated after the first episode of diarrhea that is uncomfortable or interferes with activities.[27] In general, levofloxacin or ciprofloxacin are recommended as first-line agents for travel to most parts of the world.[19,28] Azithromycin is an alternative and is preferred in areas where quinolone-resistant *Campylobacter* is prevalent (eg, Thailand, India). Azithromycin can also be used in pregnant women and children (10 mg/kg/day orally for 3 days).[28] Rifaximin, a nonabsorbed oral antibiotic, is approved for treatment of TD caused by ETEC in persons at least 12 years old and has been used off-label in younger children at a dose of 20 to 40 mg/kg/day for 4 days. This agent may be a good choice for persons traveling to destinations where ETEC is the predominant pathogen, such as Mexico. Many clinicians will recommend the use of loperamide in dysentery if it is combined with an antibiotic.[27]

KEY CONCEPT The education of travelers about high-risk food and beverages is an important component for travelers to at-risk regions. Slogans such as "peel it, boil it, cook it, or forget it" can help to remind travelers of the foods that may be contaminated; however, reduction in the incidence of TD is often more related to the level of santitation at the destination than specific interventions made by the traveler.[27] Antibiotic prophylaxis is not recommended by the CDC because it can lead to drug-resistant organisms, including extended-spectrum beta-lactamase (ESBL)-producing strains,[29] and may give travelers a false sense of security. However, some health care professionals do prescribe prophylactic antibiotics for those who are at high risk of developing TD (eg, immunocompromised persons, patients with impaired gastric acid production) or for those who cannot risk temporary incapacitation (eg, athletes, diplomats, business people). A fluoroquinolone antibiotic, such as levofloxacin or ciprofloxacin, is usually used first line for this purpose at a dose of one tablet daily during travel and for 2 days following return.[28] Although not approved for prophylaxis, rifaximin may be an option for travelers to Mexico because it is not absorbed and should be less likely to select out resistant organisms than are the fluoroquinolones. Bismuth subsalicylate (Pepto-Bismol; 525 mg orally four times daily for up to 3 weeks) provides a rate of protection of about 60% against TD in adults and children 12 years and older. It should be avoided in persons taking anticoagulants or other salicylates. The data supporting the use of synbiotics, prebiotics, and probiotics to minimize TD are not consistently strong and are not recommended for this purpose.[27] No effective vaccines are available for TD.

CLOSTRIDIUM DIFFICILE INFECTION

Epidemiology

C. difficile is the primary cause of hospital-acquired infectious diarrhea in hospitalized patients, including children. Both the incidence and severity of *C. difficile* infection (CDI) have been increasing in the United States.[30] The incidence of CDI has increased from 4.5 per 1000 adult discharges in 2001 to 8.2 per 1000 discharges in 2010. Annual attributable costs associated with CDI exceed $1.5 billion in the United States.[31] In 2011, an estimated 500,000 people suffered from CDI in the United States and 29,000 died within 30 days of CDI diagnosis. An increasing proportion of CDI patients have a community-acquired infection. These patients are often younger, lack traditional risk factors, and generally have less severe disease compared with those with hospital-acquired infections.[30] A primary risk factor in both adults and children for these community-acquired infections appears to be therapeutic gastric acid suppression.[32,33] In February, 2012, the FDA issued a warning that the use of PPIs may be associated with a higher risk for CDI. Common risk factors for hospital-acquired CDI include increasing age, severe underlying illness, intensive care unit admission, gastric acid suppression, and exposure to antimicrobials, especially broad-spectrum, multiple-drug regimens. KEY CONCEPT Nosocomial Clostridium difficile-associated diarrhea (CDAD) is almost always associated with antimicrobial use; therefore, unnecessary and inappropriate antibiotic therapy should be avoided. Clindamycin, fluoroquinolones, cephalosporins, and penicillins are antibiotics most commonly associated with CDAD, but almost all antibiotics except aminoglycosides have been implicated.[31]

Pathophysiology

C. difficile, a gram-positive, spore-forming anaerobe, is spread by the fecal–oral route, and patient-to-patient spread is an important mode of transmission within the hospital. The organism is ingested either as the vegetative form or spores, which can survive for long periods in the environment and can traverse the acidic stomach. In the small intestine, spores germinate into the vegetative form. Once the GI tract is colonized with spores, disruption of the gut flora, which occurs with antibiotic therapy, allows *C. difficile* to proliferate. Toxin production is essential for the disease to occur and is responsible for the inflammation, fluid and mucus secretion, and mucosal damage that lead to diarrhea or colitis.

Treatment

Patients who develop CDI while receiving an antibiotic should have the antibiotic discontinued, if possible. The use of concurrent antibiotics during CDI therapy, or soon thereafter, lowers the chances of a clinical cure and increases the risk of recurrence.[34] If antimicrobial therapy must continue, an attempt should be made to switch the patient to an agent with a lower risk of CDI.[31] Clinical practice guidelines recommend that initial antimicrobial therapy should be based on the severity of illness.[35]

Metronidazole (500 mg orally three times daily for 7–14 days; or, 30 mg/kg/day divided into four daily doses for children) is the recommended first-line drug for initial treatment of mild-to-moderate CDI. Oral vancomycin (125 mg four times daily for 7–14 days; or, 40–50 mg/kg/day divided into four daily doses for children) is the recommended first-line drug therapy for initial treatment of severe CDI,[35] which is usually defined as a serum creatinine increase to more than 1.5 times baseline or a white blood cell count greater than 15,000 cells/mm^3 (15 × 10^9/L). Other risk factors for severe disease include age more than 65 years, hypoalbuminemia, immunosuppression, and severe underlying disease. For the treatment of severe, complicated CDI (refractory hypotension, ileus, and/or toxic megacolon), a higher dose of vancomycin (500 mg orally four times daily) may be combined with IV metronidazole (500 mg every 8 hours). Vancomycin may be given as a retention enema (500 mg in 100 mL of normal saline every 6 hours) if a complete ileus is present.[35] The use of antimotility agents should be avoided because they may precipitate toxic megacolon. Surgical intervention may be lifesaving, particularly in cases complicated by toxic megacolon or colonic perforation. Antimicrobial stewardship programs can decrease the incidence of CDIs and better assure appropriate initial therapy.[36]

Fidaxomicin, a drug that is minimally absorbed, has no activity against organisms other than clostridia, and allows for preservation of normal gut flora, is also approved for the treatment of CDI. The recommended dose is 200 mg orally twice daily for 10 days. In clinical trials, there were fewer recurrences in patients treated with fidaxomicin compared with vancomycin.[37] Fidaxomicin is costly, but may be considered for recurrent CDI or where the risk of recurrence is high. One hospital that used fidaxomicin as first-line therapy for many patients with CDI noted a decreased readmission rate and overall decreased hospital costs versus vancomycin.[38]

The recurrence rate after an initial episode of CDI is approximately 20% to 25%, with the highest risk within the first 2 weeks.[39] This rate is independent of the initial antibiotic choice. Continuous use of acid suppression therapies increases the risk of CDI recurrences.[40] Treatment of the first recurrence of CDI is usually treated with the same regimen used for the initial episode; however, this choice should also depend on the clinical condition of the patient, as recommended for the initial therapy choice. Metronidazole should not be used beyond the first recurrence or for long-term chronic treatment due to the risk of neurotoxicity. The treatment of second or later recurrences of CDI should be undertaken with vancomycin using a tapered

Clinical Presentation and Diagnosis of CDAD

- Symptoms can start as early as the first day of antimicrobial therapy or several weeks after antibiotic therapy is completed.
- Asymptomatic carriage.
- Diarrhea:
  - Acute watery diarrhea with lower abdominal pain, low-grade fever, and mild or absent leukocytosis.
  - Mild, with only three or four loose watery stools per day.
  - *C. difficile* toxins are present in stool, but sigmoidoscopic examination is normal.
- Colitis:
  - Profuse, watery diarrhea with 5 to 15 bowel movements per day, abdominal pain, abdominal distention, nausea, and anorexia.
  - Left or right lower quadrant abdominal pain and cramps that are relieved by passage of diarrhea.
  - Dehydration and low-grade fever.
  - Sigmoidoscopic examination may reveal a nonspecific diffuse or patchy erythematous colitis with or without pseudomembranes.
- Toxic megacolon: Suggested by acute dilation of the colon to a diameter greater than 6 cm, associated systemic toxicity, and the absence of mechanical obstruction. It carries a high mortality rate.
- Fulminant colitis: Acute abdomen and systemic symptoms such as fever, tachycardia, dehydration, and hypotension. Some patients have marked leukocytosis (up to 40×10^3 white blood cells/mm^3 [40×10^9/L]). Diarrhea is usually prominent but may not occur in patients with paralytic ileus and toxic megacolon.
- Recurrent disease:
  - Risk factors include increased age, recent abdominal surgery, increased number of *C. difficile* diarrheal episodes, and leukocytosis.
  - 20% to 25% of patients develop a second episode of CDAD within 2 months of the initial diagnosis.
- In most cases, *C. difficile* toxin testing of a single unformed stool specimen effectively establishes the diagnosis. Stool culture is the most sensitive test, but it is not clinically practical due to slow turnaround time. Enzyme immunoassay (EIA) testing for toxin A and B is rapid, but less sensitive, and repeat testing may be necessary if the initial test is negative. Many labs now use newer tests, such as EIA detection of glutamate dehydrogenase (GDH) and polymerase chain reaction (PCR) technology. Leukocytosis, hypoalbuminemia, and fecal leukocytes are nonspecific but suggestive of *C. difficile* infection.
- In selected patients, sigmoidoscopy, colonoscopy, or abdominal CT scan can provide useful diagnostic information.

and/or pulse regimen.[35] Fidaxomicin may be superior to vancomycin at preventing CDAD recurrences secondary to non-NAP1/B1/027 strains.[37] Rifaximin, administered directly following a course of metronidazole or vancomycin, may be an option for the prevention of recurrent episodes of CDI in some patients. In 2016, the FDA approved bezlotoxumab, a human monoclonal antibody that binds to *C. difficile* toxin B, to reduce recurrence of CDI in patients at high risk for recurrence. This drug is administered as a single infusion (10 mg/kg); but, it is important to note it is not an antibacterial drug and must be used in conjunction with antibacterial drug treatment.[41] Fecal microbiota transplantation (FMT) has a reported efficacy of about 90% in preventing recurrent CDI and this therapy is emerging as a first-line option for patients with multiple recurrent episodes of CDI.[42]

Strict infection control measures, including contact precautions, should be instituted for all patients with CDAD. Environmental

Patient Encounter 4

A 56-year-old woman with a history of stage III COPD presents to her local medical hospital complaining of acute onset shortness-of-breath and a worsening and more productive cough. She is admitted to the general medicine floor of the hospital with a presumed community-acquired pneumonia and COPD exacerbation. Upon admission, this patient also complains of a bothersome case of diarrhea that has been present for about the past week. She thought it may be due to "something she ate," but it has begun to concern her because it does not seem to be going away. Upon chart review, you note that this patient was in the hospital 3 weeks ago, at which time she was treated for pneumonia for 10 days with cefepime and levofloxacin. She also received pantoprazole at that time for SRMD prophylaxis and was continued on it at discharge with an outpatient prescription. Upon this admission, she is noted to be afebrile, her white blood cell count is 11,800/μL (11,800/10^9/L) and her serum creatinine is 1.3 mg/dL (99.2 μmol/L), which is stable upon comparison with her previous hospital admission. A chest x-ray is negative for infiltrates or any acute changes since the last admission. Due to her recent history of antibiotic use and new-onset diarrhea, a stool sample is sent to the microbiology lab for a *C. difficile* toxin determination.

Should this patient be prescribed diphenoxylate/atropine (Lomotil®) to decrease her diarrhea while the C. difficile *toxin lab is pending?*

What antimicrobial therapy should you recommend for this patient? Should an antimicrobial agent be started prior to receiving the C. difficile *toxin lab result?*

The C. difficile *toxin report comes back from the lab and is positive. What should you recommend regarding the antibiotics (ceftriaxone and azithromycin) that were started on admission to treat this patient's presumed pneumonia?*

Assuming this patient is successfully treated for her CDI, what is the risk of the infection recurring? If it does recur, what antimicrobial agent should be recommended to treat the first recurrence?

cleaning with chlorine-containing agents should be used to eliminate *C. difficile* spores. Because alcohol is ineffective in killing spores, it is essential that health care workers wash their hands with soap and water rather than using alcohol-based hand sanitizers. Meticulous handwashing is the single most important strategy to decrease the patient-to-patient transmission of *C. difficile*. Although some systematic reviews have concluded that the use of probiotics may help prevent CDIs,[43] randomized controlled trials (RCTs) have failed to do so.[44] Probiotics should not be recommended for the prevention of CDI in hospitalized patients without additional evidence from RCTs.

CRYPTOSPORIDIOSIS

Epidemiology

Cryptosporidiosis has been recognized as a human disease since the 1970s, with increasing importance in the 1980s and 1990s because of its relationship with HIV/AIDS. *Cryptosporidium* is now recognized as a major cause of diarrhea in children, especially those less than 2 years old,[45] and has been linked with childhood malnutrition and death in low resource settings. Studies using PCR and antigen detection have identified Cryptosporidium in 15% to 25% of children with diarrhea, which is often prolonged (7–14 days) or persistent (> 14 days).[46] Incident rates have also increased in the United States, which is partially attributed to recreational water outbreaks and likely reflects increased use of communal swimming venues (eg, lakes, swimming pools, and water parks) by young children.[47]

Cryptosporidiosis is spread person-to-person, usually via the fecal–oral route; by animals, particularly cattle and sheep; and through the environment, especially water.

Pathophysiology

Cryptosporidium is an intracellular protozoan parasite that is capable of completing its entire life cycle within one host. Humans become infected upon ingestion of the oocysts, and autoinfection and persistent infections are possible owing to repeated life cycles within the GI tract. As few as 10 to 100 oocysts can cause infection.

Treatment

In general, immunocompetent persons and those with asymptomatic infection do not require antimicrobial therapy. In patients with HIV/AIDS, the optimal therapy is restoration of immune function through use of antiretroviral therapy (ART). For persons in whom antimicrobial therapy is deemed necessary or in HIV/AIDS patients in whom ART is ineffective, a combination of an antimicrobial and an antidiarrheal agent is recommended.[46]

Clinical Presentation and Diagnosis of Cryptosporidiosis

General

- 7- to 10-day incubation period.
- Profuse, watery diarrhea with mucus but not blood or leukocytes that lasts for approximately 2 weeks.
- Nausea, vomiting, fever, and abdominal cramps may accompany the diarrhea.
- Simplest method of diagnosis is detection of oocysts by modified acid-fast staining of a stool specimen. Standard ova and parasite test does not include *Cryptosporidium*.

Immunocompetent

- May manifest as asymptomatic disease, acute diarrhea, or persistent diarrhea lasting for several weeks.
- Usually self-limiting.

Immunocompromised

- May manifest as asymptomatic disease, chronic diarrhea lasting at least 2 months, or fulminant infection with at least 2 L of watery stool per day.
- In HIV-infected individuals, asymptomatic disease is more common in those with a $CD4^+$ cell count greater than 200 cells/mm^3 (200 × 10^6/L), and fulminant infection is more common in those with a $CD4^+$ cell count of less than 50 cells/mm^3 (50 × 10^6/L).

Nitazoxanide is the only FDA-approved agent for the treatment of cryptosporidiosis in adults and children 1 year and older. This agent has demonstrated efficacy in cryptosporidiosis in immunocompetent persons, malnourished children, and HIV/AIDS patients. Patients who are infected with both HIV and *Cryptosporidium* usually require longer therapy durations and higher doses than immunocompetent patients. Alternative agents include paromomycin, azithromycin, and clarithromycin.[46]

VIRAL GASTROENTERITIS

KEY CONCEPT Viruses are the most common cause of diarrheal illness in the world and, in the United States, account for 450,000 illnesses and 160,000 hospitalizations for adults and children, respectively, and more than 4000 deaths. Many viruses may cause gastroenteritis, including rotaviruses, noroviruses, astroviruses, enteric adenoviruses, and coronaviruses (Table 76–3). This chapter focuses on rotaviruses.

Table 76–3

Agents Responsible for Acute Viral Gastroenteritis and Diarrhea

Virus	Peak Age	Peak Time	Duration	Transmission	Symptoms
Rotavirus	6 months–2 years	Winter	3–8 days	Fecal–oral, water, food	Diarrhea, vomiting, fever, abdominal pain
Enteric adenovirus	< 2 years	Year-round	7–9 days	Fecal–oral	Diarrhea, respiratory symptoms, vomiting, fever
Astrovirus	< 7 years	Winter	1–4 days	Fecal–oral, water, shellfish	Vomiting, diarrhea, fever, abdominal pain
Noroviruses	> 5 years	Variable	12–24 hours	Fecal–oral, food, aerosol	Nausea, vomiting, diarrhea, abdominal cramps, headache, fever, chills, myalgia

Modified from Martin S, Jung R. Gastrointestinal infections and enterotoxigenic poisonings. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill; 2011:1951–1967.

Clinical Presentation and Diagnosis of Rotavirus Infection

- Incubation period of 2 days.
- 2- to 3-day prodrome of fever and vomiting.
- Profuse diarrhea without blood or leukocytes (up to 10–20 stools per day).
- Severe dehydration.
- Anorexia.
- Fever may be present.
- Presentation in adults may vary from asymptomatic to nonspecific symptoms of headache, malaise, and chills to severe diarrhea, nausea, and vomiting.
- Diagnosis can be made by polymerase chain reaction (PCR) of the stool.

Patient Encounter 5

A young woman comes into your pharmacy to pick up a pediatric oral electrolyte solution recommended by her child's doctor for her 3-year-old child's mild dehydration. Her child has been ill with a gastroenteritis for the last 3 days and she vocalizes that unfortunately her child has contracted some sort of GI bug 3 to 4 times a year since he has been a young infant. He had not been able to receive the preventative vaccine the child's doctor had recommended because it contains cow proteins and she and her husband are devout Hindus. She is also concerned about the mercury content in vaccines and has been very careful about what vaccines she has allowed herself and her family to receive. She has also heard that the rotavirus vaccine can cause an intestinal blockage in infants. You note she looks about ready to deliver and when you ask her, she indicates that her due date is in 2 weeks.

What scientific findings could you discuss with this mother to persuade her to get her soon-to-be newborn immunized for rotavirus?

ROTAVIRUS

Rotavirus causes between 600,000 and 875,000 deaths each year, with the highest rates in the very young and in developing countries. Rotavirus is the leading cause of childhood gastroenteritis and death worldwide. Most infections occur in children between 6 months and 2 years of age, typically during the winter season, but adults may be infected as well. Worldwide, rotavirus causes more than 2 million hospitalizations and 600,000 deaths per year in children younger than 5 years of age and approximately 60,000 hospitalizations in the United States each year. Almost all children will experience at least one episode of rotavirus infection before 5 years of age. Person-to-person transmission occurs through the fecal–oral route.

The mechanism of diarrhea has not been clearly elucidated, but theories include a reduction in the absorptive surface along with impaired absorption owing to cellular damage, enterotoxigenic effects of a rotavirus protein, and stimulation of the enteric nervous system.

The cornerstone of rotavirus treatment is supportive care and rehydration with ORT or IV fluids. Antimotility and antisecretory agents should not be used owing to their potential side effects in children and the self-limited nature of the disease. KEY CONCEPT Two oral rotavirus vaccines are currently approved by the FDA and, since their introduction, these vaccines have reduced diarrhea-related health care use in children by as much as 94% and have conferred protection on unvaccinated children (herd immunity). This reduction in health care usage has saved an estimated $1 billion over a 4-year period.[48,49] The CDC Advisory Committee on Immunization Practices recommends vaccination at 2, 4, and 6 months for *RotaTeq* and 2 and 4 months for *Rotarix*. There is a small risk of intussusception from rotavirus vaccination within a week or two of the first 2 doses. This risk is estimated to be between 1 in 20,000 and 1 in 100,000 infants who receive the vaccine.[50]

LO 7

FOOD POISONING

Each year in the United States, approximately 76 million food-borne illnesses occur, leading to 325,000 hospitalizations and more than 5000 deaths. Many bacterial and viral pathogens that have been discussed previously in this chapter (eg, *Salmonella, Shigella, Campylobacter, E. coli*, and noroviruses) can cause food poisoning. Other bacteria that can cause food-borne illness include *Staphylococcus aureus, C. perfringens, Clostridium botulinum,* and *Bacillus cereus* (Table 76–4). Food poisoning should be suspected if at least two individuals present with similar symptoms after the ingestion of a common food in the prior 72 hours.

Table 76–4

Food Poisonings

Organism	Onset (Hours)	Associated Foods	Duration	Symptoms	Treatment
Staphylococcus aureus	1–6	Salad, pastries, ham, poultry	12 hours	Nausea, vomiting	Supportive
Bacillus cereus—emetic	0.5–6	Rice, noodles, pasta, pastries	24 hours	Vomiting	Supportive
Bacillus cereus—diarrheal	8–16	Meats, vegetables, soups, sauces, milk products	24 hours	Diarrhea, abdominal pain	Supportive
Clostridium perfringens (type A)	8–12	Meats, poultry	24 hours	Nausea; abdominal cramps; profuse, watery diarrhea	Supportive
Clostridium botulinum	18–24	Canned fruits, vegetables, meats, honey, salsa, relish	Weeks	Acute GI symptoms followed by symmetric, descending, flaccid paralysis; death is possible	Supportive (including mechanical ventilation); trivalent antitoxin

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Identify allergies or rashes to medications and other substances.
- Review the medical history and physical assessment findings. In a child the growth curves and immunization records are especially important.
- Speak with the patient's parents to identify feeding and food preferences, any cultural beliefs, health goals, or socioeconomic factors that affect medication access, vaccination compliance, and other aspects of care.

Assess the Information:

- Determine if the patient is taking any substance that could interact with prescription medications (eg, vitamins, iron drops, probiotics).
- Based on medical history, determine if the patient has risk factors for GI disorders, such as diarrhea, *C. difficile* colitis, etc.
- Based on physical examination and review of systems, identify signs or symptoms associated with diarrhea or possible *C. difficile* infection.
- Determine the child's growth history from growth curve or parents and determine if weight loss has occurred.
- Determine the cause of any weight loss (eg, anorexia, dehydration, insufficient calories).
- Determine adherence to current medication regimen.
- Identify potential adverse drug events or drug interactions with medication regimen.

Develop a Care Plan:

- Determine if the child is currently showing symptoms of reflux (spitting up, regurgitation of feedings, vomiting) and whether omeprazole is still needed.
- Determine whether treatment of otitis meets current guidelines.
- Determine whether immunizations are needed in the near future.

Implement the Care Plan:

- Determine if the patient has insurance coverage and if recommended agents are included in the health system's formulary.
- Educate the patient's parents about changes in drug therapy, the administration of liquid medications, potential adverse effects associated with the new antibiotic, and how to manage and report adverse effects that may occur.
- Dialogue with parents about concerns or past problems administering liquid medications; suggest possible solutions.
- Indicate what actions to take if the child vomits the dose or the parents forget to administer a dose.
- Counsel parents on recognition of symptoms of *C. difficile* infection, serious diarrhea, and dehydration and actions to take if these occur, including notification of the child's primary care physician.
- Discuss importance of completing the full antibiotic course and routine vaccinations.

Follow-up: Monitor and Evaluate:

- Offer assistance for follow-up for parents who have problems administering medications or who need help with choosing an oral rehydration solution.
- Follow-up assessing for symptoms of chronic diarrhea.
- Follow-up the child's weight gain using a child-specific growth curve.

Abbreviations Introduced in This Chapter

CDAD	*Clostridium difficile*-associated diarrhea
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CFUs	Colony-forming units
EHEC	Enterohemorrhagic *Escherichia coli*
ESBL	Extended-spectrum beta-lactamase
FMT	Fecal microbiota transplantation
HUS	Hemolytic-uremic syndrome
ORT	Oral rehydration therapy
MIC	Minimum inhibitory concentration
NSAID	Nonsteroidal anti-inflammatory drug
NTS	Nontyphoidal *Salmonella*
PPI	Proton-pump inhibitor
STEC	Shiga toxin-producing *E. coli*
TTP	Thrombotic thrombocytopenic purpura
WHO	World Health Organization

REFERENCES

1. Martin S, Jung R. Gastrointestinal infections and enterotoxigenic poisonings. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharma Cotherapy: A Pathophysiologic Approach, 9th ed. New York: McGraw-Hill; 2014:1807–1820.
2. Hartling L, Bellemare S, Wiebe N, et al. Oral versus intravenous rehydration for treating dehydration due to gastronenteritis in children. Cochrane Database Syst Rev. 2006:CD004390.
3. Freedman SB, Ali S, Oleszczuk M, et al. Treatment of acute gastronenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries. Evid Based Child Health. 2013;8:1123–1137.
4. Salari P, Nikfar S, Abdollahi M. A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. Inflamm Allergy Drug Targets. 2012;11:3–14.
5. Scallan E, Hoekstra RM, Angulo FJ, et al. Foodborne illness acquired in the United States—major pathogens. Emerg Infect Dis. 2011;17:7–15.
6. Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther. 2011;34:1269–1281.

7. World Health Organization. Guidelines for the control of shigellosis, including epidemics due to Shigella dysenteriae type 1. 2005.
8. Dupont HL. *Shigella* species (bacillary dysentery). In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 7th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2009, Chap. 224.
9. Moralez EI, Lofland D. Shigellosis with resultant septic shock and renal failure. Clin Lab Sci Summer. 2011;24(3):147–152.
10. CDC. Recommendations for diagnosing and managing *Shigella* strains with possible reduced susceptibility to ciprofloxacin. Health Alert Network. April 18, 2017.
11. Date KA, Newton AE, Medalla F, et al. Changing patterns in enteric fever incidence and increasing antibiotic resistance of enteric fever isolates in the United States, 2008–2012. Clin Infect Dis. 2016;63:322–329.
12. Hohmann EL. Nontyphoidal salmonellosis. Clin Infect Dis. 2001;32:263–269.
13. Crump JA, Medalla FM, Joyce KW, et al. Antimicrobial resistance among invasive nontyphoidal *Salmonella enterica* isolates in the United States: National Antimicrobial Resistance Monitoring System, 1996 to 2007. Antimicrob Agents Chemother. 2011;55:1148–1154.
14. Lynch MF, Blanton EM, Bulens S, et al. Typhoid fever in the United States, 1999–2006. JAMA. 2009;302:859–865.
15. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clin Infect Dis. 2010;50:241–246.
16. Jackson BR, Iqbal S, Mahon B. Updated recommendations for the use of typhoid vaccine—Advisory Committee on Immunization Practices, United States, 2015. MMWR Morb Mortal Wkly Rep. 2015;64(11):305–308.
17. Kaakoush NO, Castano-Rodriguez N, Mitchell HM, Man SM. Global epidemiology of *Campylobacter* infection. Clin Microbiol Rev. 2015;28:687–720.
18. Luangtongkum T, Jeon B, Han J, et al. Antibiotic resistance in *Campylobacter*: emergence, transmission, and persistence. Future Microbiol. 2009;4:189–200.
19. John Hopkins Medicine. Antibiotic Guidelines. 2015–2016.
20. Pacanowski J, Lalande V, Lacombe K, et al. *Campylobacter* bacteremia: clinical features and factors associated with fatal outcome. Clin Infect Dis. 2008;47:790–796.
21. Goldwater PN, Bettelheim KA. Treatment of enterohemorrhagic *Escherichia coli* (EHEC) infection and hemolytic uremic syndrome (HUS). BMC Medicine. 2012;10:12.
22. CDC. General information: E. coli. Nov. 6, 2015.
23. Chandramobhan G, Anand SK. Acute kidney injury. In: Berkowitz C, ed. Berkowitz's Pediatrics, 4th ed. Elk Grove, IA: American Academy of Pediatrics; 2012.
24. Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. Lancet. 2017 Mar 13. [Epub ahead of print.]
25. Sack DA, Sack RB, Chaignat CL. Getting serious about cholera. N Engl J Med. 2006;355:649–651.
26. Nelson EJ, Nelson DS, Salam MA, Sack DA. Antibiotics for both moderate and severe cholera. N Engl J Med. 2011;364:5–7.
27. Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. JAMA. 2015;313:71–80.
28. Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. Am J Gastroenterol. 2016;111:602–622.
29. Kantele A, Laaveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing *Enterobacteriaceae.* Clin Infect Dis. 2015;60:837–846.
30. Khanna S, Pardi DS, Aronson SL. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. Am J Gastroenterol. 2012;107:89–95.
31. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults. A systematic review. JAMA. 2015;313:398–408.
32. Lewis PO, Litchfield JM, Tharp JL, et al. Risk and severity of hospital-acquired *Clostridium difficile* infection in patients taking proton pump inhibitors. Pharmacotherapy. 2016;36:986–993.
33. Nylund CM, Eide M, Gorman GH. Association of *Clostridium difficile* infections with acid suppression medications in children. J Pediatr. 2014;165:979–984.
34. Shaughnessy MK, Amundson WH, Kuskowski MA, et al. Unnecessary antimicrobial use in patients with current or recent *Clostridium difficile* infection. Infect Control Hosp Epidemiol. 2013;34:109–116.
35. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431–455.
36. Le F, Arora V, Shah DN, et al. A real-world evaluation of oral vancomycin for severe *Clostridium difficile* infection: implications for antibiotic stewardship programs. Pharmacotherapy. 2012;32:129–134.
37. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med. 2011;364:422–431.
38. Gallagher JC, Reilly JP, Navalkele B, et al. Clinical and economic benefits of fidaxomicin compared to vancomycin for *Clostridium difficile* infection. Antimicrob Agents Chemother. 2015;59:7007–7010.
39. Treatment of *Clostridium difficile* infection. Med Lett Drugs Ther. 2011;53:14–16.
40. McDonald EG, Milligan J, Frenette C, Lee TC. Continuous proton pump inhibitor therapy and the associated risk of recurrent *Clostridium difficile* infection. JAMA Intern Med. 2015;175:784–791.
41. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. N Engl J Med. 2017;376:305–317.
42. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile.* N Engl J Med. 2013;368:407–415.
43. Shen NT, Maw A, Tmanova LL, et al. Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: a systematic review with meta-regression analysis. Gastroenterology. 2017;152:1889–1900.
44. Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhea and *Clostridium difficile* diarrhea in older patients (PLACIDE): a randomized, double-blind, placebo-controlled, multicenter trial. Lancet. 2013;382:1249–1257.
45. Mmbaga BT, Houpt ER. Cryptosporidium and giardia infections in children: a review. Pediatr Clin North Am. 2017;64:837–850.
46. Checkly W, White AC, Jaganath D, et al. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. Lancet Infect Dis. 2015;15:85–94.
47. Yoder JS, Harral C, Beach MJ. Cryptosporidiosis surveillance—United States, 2006–2008. MMWR Surveill Summ. 2010;59:1–14.
48. Panozzo CA, Becker-Dreps S, Pate V, et al. Direct, indirect, total, and overall effectiveness of the rotavirus vaccines for the prevention of gastroenteritis hospitalizations in privately insured US children, 2007–2010. Am J Epidemiol. 2014;179:895–909.
49. Leshem E, Moritz RE, Curns AT, et al. Rotavirus vaccines and health care utilization for diarrhea in the United States (2007–2011). Pediatrics. 2014;134:15–23.
50. Haber P, Parashar UD, Haber M, DeStefano F. Intussusception after monovalent rotavirus vaccine—United States, Vaccine Adverse Event Reporting System (VAERS), 2008–2014. Vaccine. 2015;33:4873–4877.

77 Intraabdominal Infections

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LEARNING OBJECTIVES

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

1. Define and differentiate between primary and secondary intraabdominal infections (IAIs).
2. Describe the microbiology typically seen with primary and secondary IAIs.
3. Describe the clinical presentation typically seen with primary and secondary IAIs.
4. Describe the role of culture and susceptibility information for diagnosis and treatment of IAIs.
5. Recommend the most appropriate drug and nondrug measures to treat IAIs.
6. Recommend an appropriate antimicrobial regimen for treatment of primary and secondary IAIs.
7. Describe the patient-assessment process during the treatment of IAIs.
8. Introduce the concepts of antimicrobial stewardship programs (ASPs) and antimicrobial de-escalation as it pertains to the treatment of IAIs.

INTRODUCTION

Intraabdominal infections (IAIs) are those contained within the peritoneal cavity or retroperitoneal space. The peritoneal cavity extends from the undersurface of the diaphragm to the floor of the pelvis and contains the stomach, small bowel, large bowel, liver, gallbladder, and spleen. The duodenum, pancreas, kidneys, adrenal glands, great vessels (aorta and vena cava), and most mesenteric vascular structures reside in the retroperitoneum, which is the anatomical space in the abdominal cavity behind the peritoneum. IAIs may be generalized or localized. They may be contained within visceral structures, such as the liver, gallbladder, spleen, pancreas, kidney, or female reproductive organs. Two general types of IAI are discussed throughout this chapter: peritonitis and abscess. **Peritonitis** is defined as the acute inflammatory response of the peritoneal lining to microorganisms, chemicals, irradiation, or foreign-body injury.

An **abscess** is a purulent collection of fluid separated from surrounding tissue by a wall consisting of inflammatory cells and adjacent organs. It usually contains necrotic debris, bacteria, and inflammatory cells. Peritonitis and abscess differ considerably in presentation and approach to treatment.

EPIDEMIOLOGY AND ETIOLOGY

LO 1

Peritonitis may be classified as primary, secondary, or tertiary. Primary peritonitis, also called spontaneous bacterial peritonitis, is an infection of the peritoneal cavity without an evident source of bacteria from the abdomen.[1,2] In secondary peritonitis, a focal disease process is evident within the abdomen. Secondary peritonitis may involve perforation of the gastrointestinal (GI) tract (possibly because of ulceration, ischemia, or obstruction), postoperative peritonitis, or posttraumatic peritonitis (eg, blunt or penetrating trauma). Tertiary peritonitis occurs in critically ill patients, and it is an infection that persists or recurs at least 48 hours after apparently adequate management of primary or secondary peritonitis. Factors related to the development of tertiary peritonitis are not well described although it is more often associated with opportunistic and nosocomial pathogens.

KEY CONCEPT Most IAIs are secondary infections that are caused by a defect in the GI tract that must be treated by surgical drainage, resection, and/or repair. The prevalence of primary peritonitis is 10% to 30% in hospitalized patients with alcoholic cirrhosis.[3] Patients undergoing continuous ambulatory peritoneal dialysis (CAPD) average one episode of peritonitis every 2 years.[4] The majority of these are related directly to the peritoneal dialysis (PD) rather than nondialysis-related intraabdominal or systemic processes. Secondary peritonitis may be caused by perforation of a peptic ulcer; traumatic perforation of the stomach, small or large bowel, uterus, or urinary bladder; appendicitis; pancreatitis; diverticulitis; bowel infarction; inflammatory bowel disease; cholecystitis; operative contamination of the peritoneum; or diseases of the female genital tract such as septic abortion, postoperative uterine infection, endometritis, or salpingitis. Appendicitis is one of the most common causes of IAI.[5]

Primary peritonitis in adults occurs most commonly in association with alcoholic cirrhosis, especially in the end stage, or with ascites caused by postnecrotic cirrhosis, chronic active hepatitis, acute viral hepatitis, congestive heart failure, malignancy, systemic lupus erythematosus, and nephrotic syndrome. It also may result from the use of a peritoneal catheter for dialysis with renal failure or central nervous system (CNS) ventriculoperitoneal shunting for hydrocephalus. Abscesses are the result of chronic inflammation and may occur without preceding generalized peritonitis. They may be located within the peritoneal cavity or in a visceral organ and may vary in size, taking a few weeks to years to form.

Patient Encounter 1, Part 1

A 56-year-old woman with a history of epilepsy presents to the surgery clinic with chief complaints of abdominal pain. She had a cholecystectomy 2 weeks ago and had an uneventful course. Her current medications are oxycodone 10 mg orally every 6 hours, acetaminophen 500 mg orally every 6 hours as needed, and divalproex sodium ER 250 mg orally every day. On the previous hospital course, she was treated with a 2-day course of ceftriaxone.

PMH: Epilepsy and CKD, stage 3

Meds: Oxycodone 10 mg orally every 6 hours, acetaminophen 500 mg orally every 6 hours as needed, divalproex sodium ER 250 mg daily

SOC: Single, no alcohol, smoking, or illicit drugs

PE:

Tender, hard, distended abdomen, negative bowel sounds. Rest of the physical examination is noncontributory.

VS: T 100.4°F (38.0°C), BP 100/70 mm Hg, P 124 beats/min, RR 22 breaths/min, Wt 140 lb (63.6 kg), Ht 5′5″ (165 cm)

Labs: Hct 15.0% (0.150), Hgb 5.1 g/dL (51 g/L; 3.17 mmol/L), WBC 14 × 10^3/mm^3 (14 × 10^9/L), serum creatinine 3.2 mg/dL (283 µmol/L), BUN 30 mg/dL (10.7 mmol/L), Na 140 mEq/L (140 mmol/L), K 4.9 mEq/L (4.9 mmol/L), Cl 95 mEq/L (95 mmol/L), CO_2 20 mEq/L (20 mmol/L), total bilirubin 1.8 mg/dL (30.8 µmol/L), aPTT 32.0 seconds

Comment on the diagnostic approach which should be taken in this patient in order to determine a diagnosis.

What are the top two diagnoses that could be made for this patient?

Based on your assessment of her medication history, are there any of her medications that could be potentiating her clinical condition?

What pharmacotherapeutic treatments should the pharmacy clinician focus on?

Patient Encounter 2, Part 1

A 65-year-old man with a history of hypertension, diabetes, and ESRD on CAPD presents to the emergency room with a 3-day history of fevers and abdominal pain. His surgical history comprises an appendectomy (3 years ago) and PD catheter placement (2 years ago). He has had three cases of bacterial peritonitis in the past 2 years with the last case being polymicrobial including *Pseudomonas aeruginosa* with increasing patterns of resistance. His lab values are as follows:

PMH: Hypertension, diabetes, and ESRD with residual renal function of 50 mL/day

Meds: Lisinopril 20 mg orally daily, metformin 1000 mg orally twice daily, aspirin 81 mg daily

SOC: Single, no alcohol, smoking, or illicit drugs

PE:

The patient is tender to palpation and winces in pain.

VS: T 101°F (38.3°C), BP 110/75 mm Hg, P 99 beats/min, RR 12 breaths/min, Wt 250 lb (dry weight on admission [114 kg]), Ht 6′2″ (188 cm)

Labs: Na 142 mEq/L (142 mmol/L), K 4.5 mEq/L (4.5 mmol/L), Cl 95 mEq/L (95 mmol/L), CO_2 22 mEq/L (22 mmol/L), glucose 250 mg/dL (13.9 mmol/L), BUN 42 mg/dL (15.0 mmol/L), serum creatinine 4.2 mg/dL (371 µmol/L), total bilirubin 1.2 mg/dL (20.5 µmol/L), lactate 4.0 mg/dL (0.44 mmol/L), Hct 30% (0.30), Hgb 10 g/dL (100 g/L; 6.21 mmol/L), WBC 14.5 × 10^3/mm^3 (14.5 × 10^9/L).

What test(s) or lab(s) should be done to ascertain the cause of his continued fevers and abdominal pain?

Which monitoring parameters should be monitored in the next 24 to 48 hours?

What pharmacological treatment (fluids, antibiotics, and doses)? What potential toxicities exist?

List the most likely organisms and resistance patterns that can result from overuse of antimicrobials for intraabdominal processes.

PATHOPHYSIOLOGY

IAI results from bacterial entry into the peritoneal or retroperitoneal spaces or from bacterial collections within intraabdominal organs. In primary peritonitis, bacteria may enter the abdomen via the bloodstream or the lymphatic system by transmigration through the bowel wall, through an indwelling PD catheter, a ventriculoperitoneal catheter, or via the fallopian tubes in females. Hematogenous bacterial spread (through the bloodstream) occurs more frequently with tuberculosis peritonitis or peritonitis associated with cirrhotic ascites. When peritonitis results from PD, skin-surface flora are introduced via the peritoneal catheter. In secondary peritonitis, bacteria most often enter the peritoneum or retroperitoneum as a result of perforation of the GI or female genital tracts caused by diseases or traumatic injuries.

If bacteria that enter the abdomen are not contained by cellular and humoral defense mechanisms, bacterial dissemination occurs throughout the peritoneal cavity, resulting in peritonitis. This is more likely to occur in the presence of a foreign body, hematoma, necrotic tissue, large bacterial inoculum, continuing bacterial contamination, and contamination involving a mixture of synergistic organisms.

The fluid and protein shift into the abdomen (called **third spacing**) may be so dramatic that circulating blood volume is decreased, which causes decreased cardiac output and hypovolemic shock. Fluid shifts into the peritoneum occur secondary to inflammatory processes and leaky capillaries, as well as sepsis. Accompanying fever, vomiting, or diarrhea may worsen the fluid imbalance. A reflex sympathetic response, manifested by sweating, tachycardia, and vasoconstriction, may be evident. With an inflamed peritoneum, bacteria and endotoxins are absorbed easily into the bloodstream (**translocation**), and this may result in septic shock.[1] Other foreign substances present in the peritoneal cavity potentiate peritonitis, notably feces, dead tissue, barium from medical imaging procedures, mucus, bile, and blood.

Many of the manifestations of IAIs, particularly peritonitis, result from cytokine activity. Inflammatory cytokines are produced by macrophages and neutrophils in response to

bacteria and bacterial products or to tissue injury, resulting from the surgical incision.[1] The outer membrane components of gram-negative and gram-positive organisms contribute to the cascade of proinflammatory cytokines, ultimately leading to end-organ dysfunction (lungs, heart, kidneys) and septic shock.[6] Peritonitis may result in death because of the effects on major organ systems.

An abscess occurs if peritoneal contamination is localized but bacterial elimination is incomplete. The location of the abscess often is related to the site of primary disease. For example, abscesses resulting from appendicitis tend to appear in the right lower quadrant or the pelvis; those resulting from diverticulitis tend to appear in the left lower quadrant or pelvis. A mature abscess may have a fibrinous capsule that isolates bacteria and the liquid core from antimicrobials and immunologic defenses. In such cases, surgical drainage is the only effective therapy.

Microbiology of Intraabdominal Infection

LO 2

KEY CONCEPT Primary bacterial peritonitis is often caused by a single organism. In children, the pathogen is usually *Streptococcus pneumoniae* or a group A *Streptococcus*, *Escherichia coli*, or *Bacteroides* species.[4,7] When peritonitis occurs in association with cirrhotic ascites, *E. coli* and *Klebsiella* are isolated most frequently.[8] Other potential pathogens are *Haemophilus pneumoniae*, *Pseudomonas*, anaerobes, and *S. pneumoniae*.[9] Occasionally, primary peritonitis may be caused by *Mycobacterium tuberculosis*. Peritonitis in patients undergoing PD is caused most often by common skin organisms ranging from *Staphylococcus aureus* to *Staphylococcus epidermidis*.[10]

KEY CONCEPT Because of the diverse bacteria present in the GI tract, secondary intraabdominal infections are often polymicrobial.[2,11]

Bacterial Synergism and Other Factors

A combination of aerobic and anaerobic organisms appears to increase the severity of infection (synergism). Facultative bacteria (eg, *E. coli*) may provide an environment conducive to the growth of anaerobic bacteria.[2] Although many bacteria isolated in mixed infections are nonpathogenic by themselves, their presence may be essential for the pathogenicity of the bacterial mixture.[3]

Complicating the clinical picture for treatment are polymicrobial IAIs with certain bacterial species being isolated such as enterococci or *P. aeruginosa*. Depending on the patient's immune system (immunocompromised host), targeting these organisms may be necessary to avoid treatment failure or mortality.[12]

CLINICAL PRESENTATION AND DIAGNOSIS

IAIs have a wide spectrum of clinical features. Peritonitis usually is easily recognized, but intraabdominal abscess often may continue unrecognized for long periods of time. Patients with primary and secondary peritonitis present quite differently.

Clinical Presentation of Primary Peritonitis

LO 3

General

Patients may not be in acute distress, particularly with peritoneal dialysis (PD)-related peritonitis.

Symptoms

Patients may complain of nausea, vomiting (sometimes with diarrhea), and abdominal tenderness.

Signs

- Temperature may range from only mildly elevated to significantly elevated. In patients undergoing PD, temperature may not be elevated.
- Bowel sounds may be hypoactive.
- Cirrhotic patients may have worsening encephalopathy.
- There may be cloudy dialysate fluid with PD.

Laboratory Tests

- The WBC may range from mildly elevated to significantly elevated.
- Ascitic fluid usually contains more than $0.25 \times 10^3/mm^3$ ($0.25 \times 10^9/L$) leukocytes, and bacteria may be evident on gram stain of a centrifuged specimen.

Other Diagnostic Tests

Culture of peritoneal dialysate or ascitic fluid should be positive.

TREATMENT

The primary goals of treatment are correction of the intraabdominal disease processes or injuries that have caused infection and drainage of collections (source control) of purulent material (abscess). A secondary objective is to resolve the infection without major organ system complications (eg, pulmonary, hepatic, cardiovascular, or renal failure) or adverse drug effects. Ideally, the patient should be discharged from the hospital with full function for self-care and routine daily activities.

General Approach to Treatment

The treatment of IAI most often requires the coordinated use of four major modalities: (a) prompt drainage, (b) support of vital functions, (c) appropriate antimicrobial therapy to treatinfection not eradicated by surgery,[13] and (d) antimicrobial stewardship principles.[14,15] Antimicrobials are an important adjunct to drainage procedures in the treatment of secondary IAIs; however, the use of antimicrobial agents without surgical intervention, especially in secondary peritonitis, usually is inadequate. For most cases of primary peritonitis, drainage procedures may not be required, and antimicrobial agents become the mainstay of therapy.

KEY CONCEPT In the early phase of serious IAIs, attention should be given to preserving major organ system function. With generalized peritonitis, large volumes of intravenous (IV) fluids are required to maintain intravascular volume, to improve cardiovascular function, and to ensure adequate tissue perfusion and oxygenation. Adequate urine output should be maintained to ensure appropriate fluid resuscitation and to preserve renal function. A common cause of early death is hypovolemic shock caused by inadequate intravascular volume expansion and tissue perfusion.

An additional important component of therapy is nutrition. IAIs often involve the GI tract directly or disrupt its function (paralytic ileus). The return of GI motility may take days, weeks, and occasionally, months. In the interim, enteral or parenteral

LO 3

Clinical Presentation of Secondary Peritonitis

General

Patients may be in acute distress.

Symptoms

- Patients may complain of nausea, vomiting, and generalized abdominal pain.
- Patients may demonstrate abdominal guarding and rigidity.

Signs

- Sweating, tachypnea, and tachycardia are present.
- Temperature is normal initially, then may increase to 100°F to 102°F (37.8–38.9°C) within the first few hours, and may continue to rise for the next several hours.
- Hypotension and shock may develop if intravascular volume is not restored.
- Decreased urine output may develop secondary to dehydration or intravascular volume depletion.
- Bowel sounds are faint initially and eventually cease.

Laboratory Tests

- The WBC count is typically high (WBCs 15–20 × 10^3/mm^3 [15–20 × 10^9/L]), with neutrophils predominating and an elevated percentage of immature neutrophils (bands).
- The hematocrit and blood urea nitrogen increase because of dehydration.
- Hyperventilation and vomiting result in early alkalosis, which changes to acidosis and lactic academia due to reduced intravascular volume and diminished tissue perfusion.

Other Diagnostic Tests

Abdominal radiographs may be useful because free air in the abdomen (indicating intestinal perforation) or distension of the small or large bowel is often evident.

nutrition as indicated facilitates improved immune function and wound healing to ensure recovery.

Nonpharmacologic Therapy

▶ *Drainage Procedures*

Primary peritonitis is treated with antimicrobials and rarely requires drainage. Secondary peritonitis requires surgical removal of the inflamed or gangrenous tissue to prevent further bacterial contamination. If the surgical procedure is suboptimal, attempts are made to provide drainage of the infected or gangrenous structures.

The drainage of purulent material is the critical component of management of an intraabdominal abscess. This may be performed surgically or with percutaneous image-guided techniques.[16] Without adequate drainage of the abscess, antimicrobial therapy and fluid resuscitation can be expected to fail. In addition, the most valuable microbiologic information may be obtained at the time of percutaneous or operative abscess drainage.

LO 4

▶ *Fluid Therapy*

LO 5

In patients with peritonitis, hypovolemia is often accompanied by acidosis, and large volumes of an IV solution such as lactated Ringer's may be required initially to restore intravascular volume. Maintenance fluids should be instituted (after intravascular volume is restored) with 0.9% sodium chloride and potassium chloride (20 mEq/L [20 mmol/L]) or 5% dextrose and 0.45% sodium chloride with potassium chloride (20 mEq/L [20 mmol/L]). The administration rate should be based on estimated daily fluid loss through urine and nasogastric suction, including 0.5 to 1.0 L for insensible fluid loss. Aggressive fluid therapy often must be continued in the postoperative period because fluid will continue to sequester in the peritoneal cavity, bowel wall, and lumen.

Pharmacologic Therapy

▶ *Antimicrobial Therapy*

The goals of antimicrobial therapy are as follows:

- To control bacteremia and prevent the establishment of metastatic foci of infection
- To reduce suppurative complications after bacterial contamination
- To prevent local spread of existing infection
- To de-escalate antimicrobials as soon as pathogens are identified and culture and sensitivity data are reported

KEY CONCEPT An empirical antimicrobial regimen should be started as soon as the presence of IAI is suspected and before identification of the infecting organisms is complete. Therapy must be initiated based on the likely pathogens, which vary

Patient Encounter 1, Part 2: Physical Examination and Diagnostic Tests

PE:

The patient is experiencing more pain (8/10 pain scale) and the attending physician decides to perform an invasive test.

Ascitic fluid analysis is reported as following: hazy yellow color with 3225/mm^3 (3.225 × 10^9/L) WBC, (40% [0.40] neutrophils, 5% [0.05] lymphocytes, 55% [0.55] macrophages). Urinalysis is not significant because the patient is oliguric. Other physical examination findings are nonsignificant.

VS: As noted previously

Labs: As noted previously

Serum: As noted previously

KUB: Negative findings

DPL (diagnostic peritoneal lavage): 3225/mm^3 (3225 × 10^9/L)

Microbiological cultures: 2/2 bottles from the blood positive for gram-positive pairs in chains and gram-negative bacilli.

Discuss the most appropriate pharmacologic course of treatment, outlining medications, dosing, and monitoring parameters.

List the goals of treatment and follow-up plan that should be developed by the clinician to ensure positive patient outcomes.

Patient Encounter 2, Part 2

The patient's clinical status grows worse over the next couple of hours despite the efforts of the team. He is now placed on vasopressor therapy combined with fluids, and antibiotics are begun emergently. He is intubated for respiratory failure and he is now anuric.

What are your next steps in terms of a care plan as well as monitoring parameters for this patient?

If the patient's cultures reveal carbapenem resistant Klebsiella pneumoniae, *what are two new agents that could be used and what treatment duration should you use?*

What is the overall goal of treatment in patients with intraabdominal infections?

How do the pharmacologic and nonpharmacologic goals compare in this patient?

depending on the site of IAI, the underlying disease process, and individual history of previous organisms. Cultures of metastatic IAI sites generally are not useful for directing antimicrobial therapy. Table 77–1 lists the likely pathogens against which antimicrobial agents should be directed.

Table 77–1

Likely Intraabdominal Pathogens

Type of Infection	Aerobes	Anaerobes
Primary (Spontaneous) Bacterial Peritonitis		
Children	Group A *Streptococcus*, *E. coli*, pneumococci	—
Cirrhosis	*E. coli*, *Klebsiella*, pneumococci (many others)	—
Peritoneal dialysis	*Staphylococcus*, *Streptococcus*, *E. coli*, *Klebsiella*, *Pseudomonas*	—
Secondary Bacterial Peritonitis		
Gastroduodenal	*Streptococcus*, *E. coli*	—
Biliary tract	*E. coli*, *Klebsiella*, enterococci	*Clostridium* or *Bacteroides* (infrequent)
Small or large bowel	*E. coli*, *Klebsiella*, *Proteus*	*B. fragilis* and other *Bacteroides*, *Clostridium*
Appendicitis	*E. coli*, *Pseudomonas*	*Bacteroides*
Abscesses	*E. coli*, *Klebsiella*, *Streptococcus*, enterococci	*B. fragilis* and other *Bacteroides*, *Clostridium*, anaerobic cocci
Liver	*E. coli*, *Klebsiella*, *Streptococcus*, enterococci, *Staphylococcus*, amoeba	*Bacteroides* (infrequent)
Spleen	*Staphylococcus*, *Streptococcus*, *E. coli*, *Salmonella*	

▶ *Antimicrobial Experience*

Important findings from clinical trials regarding selection of antimicrobials for IAIs are as follows:

- Antimicrobial regimens for secondary IAIs should cover a broad spectrum of aerobic and anaerobic bacteria from the GI tract. It is believed that the overuse of antimicrobials has contributed to the development of IAIs with carbapenem-resistant *Enterobacteriaceae* (CRE), *Pseudomonas* and *Acinetobacter* spp., as well as greater prevalence of methicillin-resistant *S. aureus* (MRSA), *Candida* spp., and *Enterococcus* IAIs. This has made drug selection a challenge.[17,18]
- Single-agent regimens (such as antianaerobic cephalosporins, extended-spectrum penicillins with β-lactamase inhibitors, or carbapenems) are as effective with fewer adverse effects as combinations of aminoglycosides (more adverse reactions) or fluoroquinolones (more incidences of *Clostridium difficile*) with antianaerobic agents. This is also true for antimicrobial treatment of acute bacterial contamination from penetrating abdominal trauma.
- LO 8 Antimicrobial stewardship efforts in the treatment of IAIs show promise to curb antimicrobial overuse that contributes to multidrug-resistant (MDR) organisms, without affecting positive outcomes.[19] Strategies utilized by antimicrobial stewardship programs (ASPs) are impactful on antimicrobial use when they incorporate institution-specific antibiograms, utilize national guidelines for treatment, and routinely proactively target adherence with prescribers for IAIs.[17]
- Metronidazole in combination with either certain cephalosporins for mild-moderate infections, and high-risk or high-severity infections or ciprofloxacin/levofloxacin (for the aforementioned infections) is considered effective empiric antimicrobial regimens.
- Oral alternatives such as moxifloxacin; the combination of levofloxacin or ciprofloxacin plus metronidazole; or amoxicillin-clavulanate can be considered if patients can be transitioned (after susceptibility results and clinical improvements are noted).
- Results from recent trials suggest that a 4-day duration of therapy is acceptable for most patients with IAIs with adequate source control.[20,21]
- New agents for the treatment of MDR gram-negative bacilli for complicated IAIs have recently been approved. Ceftolazone is a novel cephalosporin with the β-lactamase inhibitor tazobactam which both confers enhanced activity against *Pseudomonas aeruginosa* and MDR gram-negative bacilli. Ceftazidime-avibactam is another combination antibiotic (β-lactam/β-lactamase inhibitor) and treatment option in complicated IAIs (*Klebsiella pneumonia* CRE). Both new antibiotics have been studied in combination with metronidazole. ASPs will need to ensure proper use of these agents to limit resistance as much as possible.[22–26]
- IAIs present in many different ways and with a wide spectrum of severity. The antibiotic regimen employed and duration of treatment depend on the specific clinical circumstances (ie, the nature of the underlying disease process and the condition of the patient).

Recommendations

LO 6 KEY CONCEPT For most IAIs, the antimicrobial regimen should be effective against both aerobic and anaerobic bacteria.[15] Although

Table 77–2

Recommended Agents for the Treatment of Community-Acquired Complicated Intraabdominal Infections in Adults

Agents Recommended for Mild-to-Moderate Infections	Agents Recommended for High-Risk or High-Severity Infections
Single Agent	
Cefoxitin[a]	Piperacillin–tazobactam
Moxifloxacin[b]	Imipenem–cilastatin,[c]
Ertapenem[c]	Meropenem,[c] doripenem[c]
Combination Regimens	
Cefazolin,[a] cefuroxime,[a] ceftriaxone, cefotaxime each in combination with metronidazole	Cefepime or ceftazidime each in combination with metronidazole
Ciprofloxacin[b] or levofloxacin[b] each in combination with metronidazole	Ciprofloxacin[b] or levofloxacin[b] each in combination with metronidazole

[a]Empiric first- and second-generation cephalosporin use should be avoided unless local antibiograms show > 80%–90% susceptibility of *E. coli* to these agents.

[b]Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show > 80%–90% susceptibility of *E. coli* to quinolones.

[c]Carbapenems should typically be reserved for settings where there is a high risk of resistance to other agents.

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it is impossible to provide antimicrobial activity against every possible pathogen, agents with activity against enteric gram-negative bacilli, such as *E. coli* and *Klebsiella*, and anaerobes, such as *B. fragilis* and *Clostridia* spp., should be administered.

Table 77–2 presents the recommended agents for treatment of community-acquired and complicated IAIs from the Infectious Diseases Society of America and the Surgical Infection Society.[27] These recommendations were formulated using an evidence-based approach. Most community-acquired infections are "mild to moderate," whereas health care–associated infections tend to be more severe and difficult to treat. Table 77–3 presents guidelines for treatment and alternative regimens for specific situations. These are general guidelines; there are many factors that cannot be incorporated into such a table.

Aminoglycosides (with nephrotoxicity being a concern) and clindamycin have been relegated to secondary or tertiary options for the treatment of IAIs. Metronidazole is the agent of first choice for *B. fragilis*; but others, such as antianaerobic cephalosporins (eg, cefoxitin, cefotetan, or ceftizoxime), and combinations of extended-spectrum penicillins with β-lactamase inhibitors would be suitable alternatives. Preemptive antifungal therapy may be indicated with either an azole antifungal (fluconazole) or an echinocandin (caspofungin or micafungin) in patients who are immunocompromised or postsurgical with recurrent infection. These patients are more likely to develop a fungus secondary to risk factors such as being on broad-spectrum antimicrobials, having central lines, and being on parenteral nutrition.

In immunocompromised patients or patients with valvular heart disease or a prosthetic heart valve, there is justification to provide specific antimicrobial activity against enterococci. Ampicillin or other penicillins are active against enterococci (eg, penicillin and piperacillin) and should be used in patients at high-risk, patients with persistent or recurrent IAI, or patients who are immunosuppressed, such as after organ transplantation. Ampicillin remains the drug of choice for this indication because it is most active in vitro against enterococci and is relatively inexpensive. Vancomycin is active against most enterococci; however, resistance is increasing.

Intraperitoneal (IP) administration of antibiotics is preferred over IV therapy in the treatment of peritonitis that occurs in patients undergoing CAPD.[29] The International Society of Peritoneal Dialysis guidelines for the diagnosis and pharmacotherapy of PD-associated infections provide dosing recommendations for intermittent and continuous therapy based on the modality of dialysis (CAPD or automated peritoneal dialysis [APD]) and the extent of the patient's residual renal function.[10]

KEY CONCEPT Antimicrobial agents effective against both gram-positive and gram-negative organisms should be used for initial IP empirical therapy for peritonitis in PD patients. The most important factors to take into consideration for initial antimicrobial selection are the dialysis center's and the patient's history of infecting organisms and their susceptibilities. The use of cefazolin (loading dose [LD] 500 mg/L, maintenance dose [MD] 125 mg/L) plus ceftazidime (LD 500 mg/L, MD 125 mg/L) or cefepime (LD 250–500 mg/L, MD 100–125 mg/L) or gentamicin (LD 8 mg/L, MD 4 mg/L) or tobramycin (LD-3 mg/kg, MD-0.3 mg/kg) is suitable for initial empirical therapy. If patients are allergic to cephalosporin antibiotics, vancomycin (LD 30 mg/kg, MD 1.5 mg/kg/bag) or an aminoglycoside should be substituted. Aztreonam (LD 1000 mg/L, MD 250 mg/L) is an alternative to ceftazidime or cefepime in this patient population. Another option is monotherapy with imipenem-cilastin (LD 250 mg/L, MD 50 mg/L) or cefepime. Antimicrobial doses should be increased empirically by 25% in patients with residual renal function (> 100 mL/day urine output).[10] Repeat dialysis effluent cell counts and cultures should be done after at least 3 to 5 days of antimicrobial therapy, which should continue for at least a 14- to 28-day treatment course dependent on the microorganism identified. The reader is referred to these guidelines for additional information.[10]

After acute bacterial contamination, such as with abdominal trauma where GI contents contaminate the peritoneum, combination antimicrobial regimens are not required. If the patient is seen soon after injury (within 2 hours) and surgical measures are instituted promptly, antianaerobic cephalosporins (eg, cefoxitin or cefotetan) or extended-spectrum penicillins are effective in preventing most infectious complications. Antimicrobials should be administered as soon as possible after injury.[29]

For appendicitis, the antimicrobial regimen used should depend on the appearance of the appendix at the time of operation, which may be normal, inflamed, gangrenous, or perforated. Because the condition of the appendix is unknown preoperatively, it is advisable to begin antimicrobial agents before the appendectomy is performed. Reasonable regimens would be antianaerobic cephalosporins or, if the patient is seriously ill, a carbapenem or β-lactam–β-lactamase-inhibitor combination which are more broad spectrum in their scope. If, at operation, the appendix were normal or inflamed, postoperative antimicrobials would not be required. If the appendix is gangrenous or perforated, a treatment course of 4 days with the agents listed in Table 77–2 is appropriate.

Table 77–3

Guidelines for Empiric Antimicrobial Agents for Intraabdominal Infections[10,27]

	Primary Agents	Alternatives
Primary (Spontaneous) Bacterial Peritonitis		
Cirrhosis	Ceftriaxone, cefotaxime	1. Piperacillin–tazobactam, carbapenems 2. Aztreonam combined with an agent active against *Streptococcus* spp. (eg, vancomycin) or quinolones with significant *Streptococcus* spp. activity (levofloxacin, moxifloxacin)
Peritoneal dialysis	Initial empiric regimens should be active against both gram-positive (including *S. aureus*) and gram-negative pathogens: gram-positive agent (first-generation cephalosporin or vancomycin) plus a gram-negative agent (third-generation cephalosporin or aminoglycoside)	1. Cefepime or carbapenems may be used alone. 2. Aztreonam or an aminoglycoside may be used in place of ceftazidime or cefepime as long as combined with a gram-positive agent. 3. Quinolones may be used in place of gram-negative agents if local susceptibilities allow.
	1. *Staphylococcus* spp.: oxacillin/nafcillin or first-generation cephalosporin	1. Vancomycin should be used if concern for methicillin-resistant *Staphylococcus* spp. 2. Add rifampin for 5–7 days with vancomycin to reduce the risk for relapsing or repeat methicillin-resistant *Staphylococcus aureus* peritonitis.
	2. *Streptococcus* or *Enterococcus*: ampicillin	1. An aminoglycoside may be added for *Enterococcus* spp. 2. Linezolid, daptomycin, or quinupristin/dalfopristin should be used to treat vancomycin-resistant *Enterococcus* spp. not susceptible to ampicillin.
	3. Aerobic gram-negative bacilli: ceftazidime or cefepime	1. The regimen should be based on in vitro sensitivity tests.
	4. *Pseudomonas aeruginosa*: two agents with differing mechanisms of action, such as an oral quinolone plus ceftazidime, cefepime, gentamicin, or a carbapenem	
Secondary Bacterial Peritonitis		
Perforated peptic ulcer	First-generation cephalosporins	1. Ceftriaxone, cefotaxime, or antianaerobic cephalosporins[a]
Other	Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam or carbapenem	1. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin[b] alone 2. Aztreonam with vancomycin and metronidazole 3. Antianaerobic cephalosporins[a]
Abscess		
General	Third- or fourth-generation cephalosporin with metronidazole, piperacillin–tazobactam	1. Imipenem–cilastatin, meropenem, doripenem, or ertapenem 2. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin alone
Liver	As above	Use metronidazole if amoebic liver abscess is suspected
Spleen	Ceftriaxone or cefotaxime	Moxifloxacin[b] or levofloxacin[b]
Other Intraabdominal Infections		
Appendicitis	Same management as for community-acquired complicated intraabdominal infections as listed in Table 77–2	
Community-Acquired Acute Cholecystitis	Ceftriaxone or cefotaxime	Severe infection, piperacillin/tazobactam, antipseudomonal carbapenem, aztreonam with metronidazole
Cholangitis	Ceftriaxone or cefotaxime each with or without metronidazole	Vancomycin with aztreonam with or without metronidazole
Acute Contamination from Abdominal Trauma	Antianaerobic cephalosporins[a] or metronidazole with either ceftriaxone or cefotaxime	1. Piperacillin/tazobactam or a carbapenem 2. Ciprofloxacin[b] or levofloxacin[b] each with metronidazole or moxifloxacin alone

[a]Cefoxitin or cefotetan; these agents should be avoided empirically unless local antibiograms show > 80%–90% susceptibility of *E. coli* to these agents.

[b]Use of quinolones may be associated with treatment failure due to increasing resistance of enteric pathogens including *E. coli*. Empiric quinolone use should be avoided unless local antibiograms show > 80%–90% susceptibility of *E. coli* to quinolones.

KEY CONCEPT Acute intraabdominal contamination, such as after a traumatic injury, may be treated with a short course (24 hours) of antimicrobials if therapy is begun quickly.[29] For established infections (ie, peritonitis or intraabdominal abscess), an antimicrobial course limited to 4 days is justified. Under certain conditions, therapy for longer than 4 days would be justified (eg, poor response, resistant organism identified, or failure to control the source of infection). For some abscesses, such as pyogenic liver abscess, antimicrobials may be required for a month or longer because of resistance increasing after initial antimicrobial treatment.

OUTCOME EVALUATION

LO 7

Whether diagnosed with primary or secondary peritonitis, monitor the patient for relief of symptoms. Once antimicrobials are initiated and the other important therapies described earlier are used, most patients should improve within 2 to 3 days. Successful antimicrobial therapy with resolution of infection will result in decreased pain, manifested as resolution of abdominal guarding and decreased use of pain medications over time. The patient should not appear in distress, with the exception of recognized discomfort and pain from incisions, drains, and a nasogastric tube.

Monitor vital signs and WBC count with differential; each should normalize as the infection resolves. At 24 to 48 hours, aerobic bacterial culture results should be available. If a suspected pathogen is not susceptible to the antimicrobial agents being given, and the patient has not sufficiently improved, the regimen should be adjusted. If the isolated pathogen is susceptible to one antimicrobial and the patient is improving, therapy should be streamlined to a single agent.

With anaerobic culturing techniques and the slow growth of these organisms, anaerobes often are not identified until 4 to 7 days after culture, and sensitivity information is difficult to obtain. For this reason, anaerobic culture information generally is not helpful for selection of the antianaerobic component of the antimicrobial regimen.

Once the patient's temperature is normal for 48 to 72 hours and the patient is eating, consider changing the IV antibiotic to an oral regimen for the duration of antibiotic treatment. Monitor the serum creatinine level to evaluate for renal complications as well as potential drug toxicity. Bowel sounds should return to normal. Evaluate the patient daily for development of rash or other drug-related adverse effects such as antibiotic-associated diarrhea.

For patients with primary peritonitis, if peritoneal dialysate cultures were positive initially, repeat cultures should be negative. For patients with secondary peritonitis, monitor the amount of fluid draining if a drain was placed. The volume of drainage should lessen as the infection resolves. Repeat abdominal radiographs should return to normal.

If symptoms do not improve, the patient should be evaluated for persistent infection. There are many reasons for poor patient outcome with IAI; improper antimicrobial selection is only one. The patient may be immunocompromised, which decreases the likelihood of successful outcome with any regimen. It is impossible for antimicrobials to completely compensate for a nonfunctioning immune system. There may be surgical reasons for poor patient outcome. Failure to identify all intraabdominal foci of infection or leaks from a GI anastomosis may cause continued IAI. Even when IAI is controlled, accompanying organ system failure, most often renal or respiratory, may lead to patient demise.

KEY CONCEPT Health care–associated infections are becoming more commonly seen for IAIs with increasing prevalence of acute care hospital admissions or admissions from chronic care settings. The major pathogens include more resistant gram-negative flora, *Candida* infections causing peritonitis, and *Enterococcus* species.[30]

The outcome from IAI is not determined solely by what transpires in the abdomen. Unsatisfactory outcomes in patients with IAIs may result from complications that arise in other organ systems. Infectious complications commonly associated with mortality after IAI are urinary tract infections and pneumonia.[18] Reasons for antimicrobial failure may not always be apparent. Even when antimicrobial susceptibility tests indicate that an organism is susceptible to the antimicrobial agent, therapeutic failures may occur. There may be poor penetration of the antimicrobial agent into the focus of infection, or bacterial resistance may develop after initiation of antimicrobial therapy. Superinfection—a secondary infection resulting from the preferential killing of the primary pathogen—can be caused

Patient Care Process

Collect Information:

- You should do a thorough patient medication history at the time of admission to document all recent medication use, including nonprescription medications and use of complementary or alternative medicines. You should also document any drug allergies or intolerances for your patient. You should also search for all available patient information in the pertinent patient's medical record.

Assess the Information:

- Be cognizant for the initial antimicrobial regimen conforming to standard guidelines (unless an appropriate justification for an alternative regimen is evident). See Table 77–3.

Develop a Care Plan:

- You should review the dosages of all medications to be sure that they are appropriate for age, weight, and major organ function.
- You should also verify that the drugs selected are not contraindicated in the patient with allergies or drug–drug interactions.

Implement the Care Plan:

- You should select antimicrobials that are appropriate based on the susceptibility information, while reviewing the results of the cultures obtained both preoperatively or during the surgical procedure. Antimicrobials should be de-escalated when clinically appropriate. You should educate other practitioners on proper de-escalation technique.
- On the fifth day of antimicrobial treatment or when GI function returns, determine whether parenteral antimicrobial agents can be switched to oral agents to complete therapy. This again is part of a robust ASP best practice.
- Assess nutritional needs and recommend appropriate supplementation. When the patient is tolerating an oral diet, determine whether any parenteral medications can be switched to the oral route.

Follow-up: Monitor and Evaluate:

- You should monitor the patient for the development of potential complications of treatment such as delayed hypersensitivity reactions, antibiotic-induced diarrhea, pseudomembranous colitis, or fungal superinfections (eg, oral thrush).
- You should also educate the patient on the medications administered in the hospital as well as any new medications prescribed for use at home.
- You should also advise the patient to contact his or her doctor or pharmacist if he or she experiences any adverse effects from medications.

by *Candida*; however, Enterococci or opportunistic gram-negative bacilli such as *Pseudomonas* or ESBL-producing Enterobacteriaceae may also be involved.

Treatment regimens for IAI can be deemed successful if the patient recovers from the infection without recurrent peritonitis or intraabdominal abscess and without the need for additional antimicrobials. A regimen can be considered unsuccessful if a significant adverse drug reaction occurs, reoperation or percutaneous drainage is necessary, or improvement is delayed beyond 1 or 2 weeks.

Abbreviations Introduced in This Chapter

APD	Automated peritoneal dialysis
ASP	Antimicrobial stewardship program
CAPD	Continuous ambulatory peritoneal dialysis
CRE	Carbapenemase-resistant Enterobacteriacae
DPL	Diagnostic peritoneal lavage
ESBL	Extended-spectrum producing β-lactamase Enterobacteriacae
IAIs	Intraabdominal infections
IP	Intraperitoneal
KPC	Klebsiella pneumonia carbapenemase
LD	Loading dose
MD	Maintenance dose
MDR	Multidrug-resistant
MRSA	Methicillin-resistant *S. aureus*
PD	Peritoneal dialysis

REFERENCES

1. Ordonez CA, Puyana JC. Management of peritonitis in the critically ill patient. Surg Clin North Am. 2006;86:1323–1349.
2. Marshall JC. Intra-abdominal infections. Microbes Infect. 2004;6:1015–1025.
3. Mowat C, Stanley AJ. Spontaneous bacterial peritonitis—diagnosis, treatment, and prevention. Aliment Pharmacol Therap. 2001;15:1851–1859.
4. Vas S, Oreopoulos DG. Infections in patients undergoing peritoneal dialysis. Infect Dis Clin North Am. 2001;15:743–774.
5. National Hospital Discharge Survey. CDC/NCHS. Available from: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHDS/NHDS_2010_Documentation.pdf. Accessed August 31, 2017.
6. Sartelli M, Viale P, Abu-Zidan FM, et al. Management of intra-abdominal infections: recommendations by the WES 2016 consensus conference. World J Emerg Surg. 2016;8:1–31.
7. Thompson AE, Marshall JC, Opal SM. Intraabdominal infections in infants and children: Descriptions and definitions. Pediatr Crit Care Med. 2005;6:S30–S35.
8. Căruntu FA, Benea L. Spontaneous bacterial peritonitis: pathogenesis, diagnosis, treatment. J Gastroint Liver Dis. 2006;15:51–56.
9. Johnson DH, Cuhna BA. Infections in cirrhosis. Infect Dis Clin North Am. 2001;15:363–371.
10. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on prevention and treatment. Perit Dial Int. 2016;36:481–508.
11. Brook I. Microbiology and management of abdominal infections. Dig Dis Sci. 2008;53:2585–2591.
12. Ball CG, Hansen G, Harding G, et al. Canadian practice guidelines for surgical intra-abdominal infections. Can J Infect Dis Med Microbiol. 2010;21:11–37.
13. Gauzit R, Pean Y, Barth X, et al. Epidemiology, management, and prognosis of secondary non-postoperative peritonitis: a French prospective observational multicenter study. Surg Infect. 2009;10(2):119–127.
14. Saretelli M, Duane TM, Catena F, et al. Antimicrobial stewardship: a call to action for surgeons. Surg Infect. 2016;17(6):625–632.
15. Hoffman C, Zak M, Avery L, Brown J. Treatment modalities and antimicrobial stewardship initiatives in the management of intra-abdominal infections. Antibiotics. 2016;5:11.
16. Jaffe TA, Nelson RC, Delong DM, Paulson EK. Practice patterns in percutaneous image-guided intraabdominal abscess drainage: survey of academic and private practice centers. Radiology. 2004;233:750–756.
17. MacVane SH. Antimicrobial resistance in the intensive care unit: a focus on gram-negative bacterial infections. J Intensive Care Med. 2017;32(1):25–37.
18. Sartelli M, Catena F, di Saveno S, et al. The challenge of antimicrobial resistance in managing intra-abdominal infections. Surg Infect. 2015;16(3):213–221.
19. Montravers P, Augustin P, Grall N, et al. Characteristics and outcomes of anti-infective de-escalation during health-care associated intra-abdominal infections. Crit Care. 2016;20(83):1–12.
20. Approved: New Antimicrobial Stewardship Standard. Joint Commission. Available from: https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf. Accessed August 31, 2017.
21. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. New Engl J Med. 2015;372;1996–2005.
22. Zhanel GG, Chung P, Adam H, et al. Ceftolozan/tazobactam: a novel cephalosporin/β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative bacilli. Drugs. 2014;74:31–51.
23. Buckman SA, Krekel T, Muller AE, Mazuski JE. Ceftzidime-avibactam for the treatment of complicated intra-abdominal infections. Expert Opin Pharmacother. 2016;17(17):2341–2349.
24. Solomkin J, Hershberger E, Miller B, et al. Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, Phase 3 trial (ASPECT-cIAI). Clin Infect Dis. 2015;60(10):1462–1471.
25. Mazuski JE, Gaskink LB, Broadhurst H, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind Phase 3 program. Clin Infect Dis. 2016;62(11):1380–1389.
26. Syue LS, Chen YH, Ko WC, Hsueh PR. New drugs for the treatment of complicated intra-abdominal infections in the era of increasing antimicrobial resistance. Int J Antimicrobial Agents. 2016;47:250–258.
27. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133–164.
28. Wiggins KJ, Craig JC, Johnson DW, Strippoli GF. Treatment for peritoneal dialysis-associated peritonitis. Cochrane Database Syst Rev. 2008;(1):CD005284.
29. Bozorgzadeh A, Pizzi WF, Barie PS, et al. The duration of antibiotic administration in penetrating abdominal trauma. Am J Surg. 1999;172:125–135.
30. Mazuski JE, Tessier JM, May AK, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. Surg Infect. 2017;18(1):1–76.

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78 Parasitic Diseases

Madeline A. King and Jason C. Gallagher

LEARNING OBJECTIVES

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

LO

1. Identify the primary reasons why some parasitic diseases may be more prevalent in the US population.
2. Describe the treatment algorithm for giardiasis and amebiasis.
3. List one effective therapy for nematodes and select the drugs of choice for strongyloidiasis and tapeworms.
4. List three major reasons why travelers are infected with malaria.
5. Describe the presenting signs and symptoms of malaria.
6. List some specific toxicities of mefloquine.
7. Identify the monitoring parameters for quinidine gluconate in severe malaria.
8. Define the major complications of falciparum malaria.
9. Discuss the cardiovascular complications of chronic South American trypanosomiasis.
10. Describe the steps to take to eradicate lice infestation and scabies.

INTRODUCTION

LO 1

Globalization, including international tourism, has lead to increases in the spread of various infectious diseases from endemic areas to areas new to these pathogens. Population shifts with refugees and new immigrant populations from other parts of the world have brought new parasitic infections to our shores. Migrant farm workers, the large and growing Central and South American immigrant population, and an increasing presence of immunosuppressed patients represent significant sources of parasitic infections in the United States.[1–4]

Parasitism is a relationship between organisms where one organism (the parasite) thrives at the expense of the host. Parasites have made metabolic and other defensive adaptations over time to increase their ability to survive host defenses and allow them to utilize the host's biochemical systems to synthesize necessary cellular components.

Although acquired immunity to some parasitic diseases may lower the level of infection, absolute immunity as seen in viral and some bacterial infections is seldom seen in parasitic diseases. Since parasitic infections produce a wide variety of antigens because of the many life cycle phases, it is more difficult for the immune system to identify a constant antigen against which specific antibodies are protective.[5] However, malaria remains a likely candidate for a vaccine and there are ongoing studies to develop one.[6] Additionally, a vaccine for hookworms may advance to clinical trials based off initial animal studies.[7]

For more detailed discussions of parasites and the human parasites not discussed here, readers are directed to resources on parasites and parasitic diseases.[8,9] Discussion in this chapter includes parasitic diseases more likely seen in the United States and includes gastrointestinal (GI) parasites (primarily giardiasis and amebiasis), protozoan infections (malaria and South American trypanosomiasis), some common helminthic diseases (specifically those caused by nematodes and cestodes), and ectoparasites (lice and scabies).

GIARDIASIS

Epidemiology and Etiology

Giardia lamblia (also called *G. intestinalis* and *G. duodenalis*) is the most common intestinal parasite responsible for diarrheal syndromes throughout the world and is the most frequently identified intestinal parasite in the United States, with over 16,000 reported cases from 2011 to 2012.[10] *G. lamblia* is often encountered in areas with poor sanitation, particularly contaminated water.

Patient Encounter 1: Giardiasis

PB is a 31-year-old US resident who recently traveled to Guatemala to visit a friend. Although the majority of his meals were from his friend's home or from restaurants, he had a craving for "street food" the day he left and tried grilled corn, tacos, and a fresh fruit drink. Two days after his return he developed severe nausea and diarrhea that alternated with constipation. When he is seen at the travel clinic at a local hospital, he reports nausea and crampy, watery diarrhea with foul-smelling, "light-colored" stools for 3 days.

Are his symptoms characteristic of parasite-associated diarrhea?

How would you differentiate giardiasis from an Escherichia coli*–induced diarrhea?*

Do you think he requires treatment? If so, with what agent?

G. lamblia has been identified as the first documented enteric pathogen in children in developing countries. Giardiasis rates in the United States have been decreasing in recent years.[8–10]

G. lamblia is found in the small intestine, the gallbladder, and in biliary drainage.[8,10] The distribution of giardiasis is worldwide, with children or persons living in close quarters being more susceptible.[10]

Pathophysiology

There are two stages in the life cycle of *G. lamblia*: trophozoite and cyst. Giardiasis is caused by ingestion of *G. lamblia* cysts in contaminated water or food, via person-to-person contact, or fecal-oral contact, and has an incubation period of approximately 12–20 days.[8,10] The protozoan excysts in low gastric pH to release the trophozoite. Colonization and multiplication of the trophozoite lead to mucosal invasion, localized edema, and flattening of intestinal villi, resulting in malabsorption states in the host. Achlorhydria, hypogammaglobulinemia, or deficiency in secretory immunoglobulin A (IgA) predispose to giardiasis.[8] Individuals with human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS) may have higher carriage rates than the general population. Some patients may develop irritable bowel syndrome or lactose intolerance after chronic giardiasis.[11]

Pharmacologic Therapy

LO 2

KEY CONCEPT All symptomatic adults and children over the age of 8 years with giardiasis should be treated with metronidazole, tinidazole, or nitazoxanide. See Table 78–1 for treatment regimens.[12] Alternative drugs include furazolidone, paromomycin, quinacrine 100 mg, or albendazole. Paromomycin is preferred for pregnant patients. The pediatric dose of metronidazole is 15 mg/kg/day three times daily for 7 days. Pediatric patients can be treated with metronidazole, furazolidone, or quinacrine.[12] Quinacrine is available from specialized pharmacies.[12,13]

Table 78–1

Treatment Regimens for Giardiasis

	Giardiasis	
Drug	**Adult Dosing and Duration**	**Pediatric Dosing**
Primary:		
Metronidazole	250 mg po 3 times daily × 7 days	15 mg/kg/day divided in 3 doses
Tinidazole	2g po as one dose	
Nitazoxanide	500 mg twice daily × 3 days	
Alternatives:		
Furazolidone	100 mg 4 times daily × 7 days	6 mg/kg/day in 4 doses
Paromomycin	25–35 mg/kg/day in 3 divided doses × 7 days	
Quinacrine	100 mg 3 times daily × 5 days	5 mg/kg/day × 5–7 days
Albendazole	400 mg daily × 5 days	

Clinical Presentation and Diagnosis of Giardiasis[8,9]

Acute Onset

- Diarrhea, cramp-like abdominal pain, bloating, and flatulence
- Malaise, anorexia, nausea, and belching

Chronic Symptoms

- Diarrhea: Foul-smelling, copious, light-colored, and greasy stools
- Weight loss, steatorrhea, and vitamin B_{12} and fat-soluble vitamin deficiencies
- Constipation alternating with diarrhea

Diagnosis

- Diagnosis is made by examination of fresh stool or a preserved specimen during acute diarrheal phase
- Fresh stool may show trophozoites, whereas preserved specimens yield cysts. (*Note:* stool for ova may show the presence of other parasites [eg, *Cryptosporidium parvum, Entamoeba histolytica*, or *Entamoeba hartmanni*]; multiple stool samples may be needed.)
- Stool examination for ova and parasites is the major means of diagnosis; other diagnostic tests include an enzyme-linked immunosorbent assay (ELISA).

Patient Care Process: Giardiasis

Collect Information:

- Evaluate patient medical history, recent travel, signs, and symptoms.
- Conduct a medication history, review laboratory findings, and consider if stool for ova and parasites or other tests may be necessary for diagnosis of giardiasis.

Assess the Information:

- Evaluate available laboratory data in conjunction with symptoms to confirm the diagnosis.
  - Unlike toxigenic *Escherichia coli* or food poisoning, there is no blood, mucus, or cellular exudate in giardiasis.
- Differentiate chronic giardiasis from amebiasis or other intestinal infections.

Develop a Care Plan:

Choose the most appropriate medications based on adherence and cost.

Implement the Care Plan:

- Address patient concerns about the infection and the therapy.
- Counsel patient on proper use of medications and possible adverse effects.
- Recommend fluids and electrolyte replacement.

Follow-up: Monitor and Evaluate:

- Decide if patient should come back for follow-up.
- Inform patient about the need for repeat stool for ova and parasites or for reevaluation at the end of therapy if symptoms persist or worsen.

Metronidazole and tinidazole act by disrupting DNA and inhibiting nucleic acid synthesis. Paromomycin acts by binding to 30S ribosomal subunits, inhibiting protein synthesis. Nitazoxanide interferes with the pyruvate:ferredoxin oxioreductase enzyme-dependent electron transfer reaction which is needed for anaerobic metabolism. Furazolidone interferes with the microbial enzyme system to prevent acetylation of coenzyme A. Paromomycin, quinacrine, nitazoxanide, albendazole, and tinidazole should be taken with food.[13] See Table 78–6 for adverse reactions related to drugs.

Outcome Evaluation

Patients who fail initial therapy with metronidazole should receive a second course of therapy. Long-term infection can result in malnourishment due to malabsorption.[9] Giardiasis can be prevented by good hygiene and by using caution in food and drink consumption in endemic areas.

AMEBIASIS

Epidemiology and Etiology

Amebiasis remains one of the most important parasitic diseases because of its worldwide distribution and serious GI manifestations. The major causative agent in amebiasis is *E. histolytica*, which invades the colon and must be differentiated from *Entamoeba dispar*, which is associated with an asymptomatic carrier state and is considered nonpathogenic.[14,15] Invasive amebiasis is almost exclusively the result of ingesting *E. histolytica* cysts found in fecally contaminated food or water. Approximately 50 million cases of invasive disease result each year worldwide, leading to an excess of 100,000 deaths. In the general population, the highest incidence is found in institutionalized mentally disabled patients, sexually active homosexuals, patients with advanced HIV, Native Americans, and new immigrants from endemic areas (eg, Mexico, South and Southeast Asia, West and South Africa, and portions of Central and South America).[14,15]

Pathophysiology

E. histolytica cysts invade mucosal cells of colonic epithelium, producing the classic flask-shaped ulcer in the submucosa. The trophozoites are released and have a cytocidal effect on cells. If the trophozoite gets into the portal circulation, it will be carried to the liver, where it produces abscess and periportal fibrosis. Liver abscesses are more common in men than women and are rarely seen in children. Amebic ulcerations can affect the perineum and genitalia, and abscesses may occur in the lung and brain.[14,16]

Erosion of liver abscesses can result in peritonitis. Liver abscesses that are located in the right lobe can spread to the lungs and pleura. Pericardial infection, although rare, may be associated with extension of the amebic abscesses from the liver.

Patient Encounter 2: Amebiasis

BK is a 25-year-old student who, on returning from studying abroad Egypt, is seen in the emergency department with complaints of a 3-day history of severe diarrhea, cramps, and postprandial abdominal pain. The abdominal pain is over the right lower quadrant and associated with nausea and flatulence. BK indicates that he had some diarrhea, possibly with blood, the night after he celebrated the end of the semester at a local restaurant in Hurghada. The diarrhea subsided after treatment from a local physician with paromomycin. However, 5 days later after his return to the United States, his symptoms came back.

What specific findings in this patient suggest that he may have giardiasis, amebiasis, or an E. coli*–associated diarrhea?*

What specific laboratory or diagnostic test will confirm a diagnosis of amebiasis?

Describe some of the complications associated with amebiasis.

Clinical Presentation and Diagnosis of Amebiasis[17]

Intestinal Disease

- Vague abdominal discomfort
- Symptoms may range from malaise to severe abdominal cramps, flatulence, and nonbloody or bloody diarrhea (heme-positive in 100% of cases) with mucus
- May have low-grade fever
- Eosinophilia is usually absent, although mild leukocytosis is not unusual

Note: Fecal screening may show other intestinal parasites, including *Cryptosporidium* spp., *Balantidium coli, Dientamoeba fragilis, Isospora belli, G. lamblia,* or *Blastocystis hominis.*

Amebic Liver Abscess

- May present with high fever with significant leukocytosis with left shift, anemia, elevated alanine aminotransferase, and dull abdominal pain on palpation
- *Physical findings:* Right upper quadrant pain, hepatomegaly, and liver tenderness, with referred pain to the left or right shoulder (*Note:* erosion of liver abscesses may present as peritonitis)

KEY CONCEPT Diagnosis

- Three stool specimens should be used and a permanent stained smear should be used.
- Intestinal amebiasis is diagnosed by demonstrating *E. histolytica* cysts or trophozoites from ova and parasite exam.
- Microscopy may not differentiate between the pathogenic *E. histolytica* and the nonpathogenic (commensal) *E. dispar* or *Entamoeba moshkovskii* in stools.
- Sensitive techniques are available to detect *E. histolytica* in stool: antigen detection, antibody test (ELISA) and polymerase chain reaction (PCR).
- Endoscopy with scrapings or biopsy and stained slides (iron hematoxylin or trichrome) may provide more definitive diagnosis of amebiasis.
- Diagnosis for liver abscess includes serology and liver scans (using isotopes by ultrasound or computed tomography [CT]) or magnetic resonance imaging (MRI); however, none of these are specific for liver abcess. In rare instances, needle aspiration of hepatic abscess may be attempted using ultrasound guidance.

Extraintestinal infection can be seen in the liver, lungs, heart, brain, eyes, skin, or genitourinary organs.[14,16] Complications and death result from the ability of *E. histolytica* to lyse host cells and destroy host tissue.[13,14,16,17]

Pharmacologic Therapy

LO 2

For asymptomatic patients, treatment should be given due to the possibility of spreading disease to others or developing disease within the year.[18] Iodoquinol, diloxanide furoate, and paromomycin are nonabsorbed luminal agents that are recommended for asymptomatic or intraluminal infection. Metronidazole, tinidazole, or nitazoxanide are recommended for mild to moderate diarrheal infection, and except for nitazoxanide, are recommended for severe or extrahepatic disease. However, an agent that is effective in the GI lumen may not attain sufficient tissue concentrations to be effective. Paromomycin is the preferred agent in pregnant patients. See Table 78–2 for treatment regimens.[12,13] See Table 78–6 for adverse reactions related to drugs.

Patients with severe intestinal disease or liver abscess should receive metronidazole followed by the luminal agents indicated previously. Tinidazole is an alternative to metronidazole and can be crushed and added to cherry syrup for children if necessary.[12] If there is no prompt response to metronidazole or aspiration of the abscess, an antibiotic regimen should be added due to the potential for a bacterial infection. Patients who cannot tolerate oral metronidazole should receive intravenous (IV) metronidazole.[14,16]

Patient Care Process: Amebiasis

Collect Information:

- Ask the patient about specific symptoms, travel history, food and water intake, and if any other travelers experienced similar symptoms.
- Collect stool samples.
- Conduct a medication history and check for allergies.

Assess the Information:

- Based on physical examination, review of systems, and travel history, determine if these findings are consistent with amebiasis.
- Determine, based on the results of the diagnostic tests, whether this is amebic colitis or colitis with liver abscess.

Develop a Care Plan:

- Verify the availability of the drug or drugs you intend to use.
- Select pharmacotherapy and appropriate regimen and check for any potential drug interactions.

Implement the Care Plan:

- Address any patient concerns and discuss the need for medication adherence and dietary restrictions.

Follow-up: Monitor and Evaluate:

- Follow-up in 10 days and repeat tests to evaluate therapy.
- Monitor for efficacy and toxicity.

Table 78–2

Treatment Regimens for Amebiasis

	Amebiasis	
Drug	**Adult Dosing and Duration**	**Pediatric Dosing**
Paromomycin	25–35 mg/kg/day in 3 doses × 7 days	Same as adult
Iodoquinol		30–40 mg/kg daily in 3 doses (max 2g)
Metronidazole	650 mg 3 times daily × 20 days	50 mg/kg/day in 3 doses
Tinidazole	750 mg 3 times daily × 10 days	50 mg/kg/day
Diloxanide furoate	2 g daily × 3 days	20 mg/kg/day in 3 doses × 10 days

Outcome Evaluation

Follow-up in patients with amebiasis should include repeat stool examinations, serology, colonoscopy (in colitis), or CT scan a month after the end of therapy. Serial liver scans have demonstrated healing of liver abscesses over 4 to 8 months after adequate therapy.[16,19]

HELMINTHIC DISEASES

Helminthic infections include three groups of organisms: roundworms or nematodes, flukes (trematodes), and tapeworms (cestodes). Brief descriptions of some of the helminthic infections most commonly seen in North America and their treatments are provided here. Although helminthic infections may not produce clinical manifestations, they can cause significant pathology. One factor that determines the pathogenicity of helminthic infections is their population density; a high-density population ("worm burden") results in predictable disease presentation. In the United States, these infections are reported most frequently in recent immigrants from Southeast Asia, the Caribbean, Mexico, and Central America.[20–22] Populations at risk include institutionalized patients, preschool children in daycare centers, residents of Native American reservations, and homosexuals.[20,21] Certain conditions and drugs (anesthesia and corticosteroids) can cause atypical localization of worms. Immunocompromised patients can be overwhelmed by some helminthic infections, such as *Strongyloides stercoralis*.[23]

Nematodes

▶ *Hookworm Disease*

Hookworm infection is caused by two species of nematodes, *Ancylostoma duodenale,* which is worldwide, and *Necator americanus,* which is found in the southeastern United States.[20–22] Infective larvae enter the host in contaminated food or water or penetrate the skin and migrate to the small intestine. The adult worm attaches to GI mucosa and causes injury by lytic destruction of the tissue. Over time, the adult worm can cause anemia and hypoproteinemia in the host.[24–26]

▶ *Treatment*

KEY CONCEPT The goals of therpay are to both kill the worms and replace depleted iron. The drugs of choice are albendazole or

mebendazole, which is also active against ascariasis, enterobiasis, trichuriasis, and hookworm.[12,13] Mebendazole inhibits glucose uptake and microtubule assemply, resulting in immobilization and death of the worm. Diagnosis is by detection of eggs or larvae in stool. An alternative agent is pyrantel pamoate, which acts on nicotinic acetylcholine receptors as a neuromuscular blocking agent which causes worm paralysis. Stool examination for eggs and larvae should be repeated in 2 weeks and the patient retreated if necessary.[13]

Ascariasis

The causative agent in ascariasis is the giant roundworm *Ascaris lumbricoides,* which is found worldwide and is responsible for about 4 million infections in the United States annually, primarily affecting residents of the Appalachian mountain range and the Gulf Coast region.[20–22] Migration of the worm into the lungs usually produces pneumonitis, fever, cough, eosinophilia, and pulmonary infiltrates. *Ascaris* infection can also cause abdominal discomfort, intestinal obstruction, and appendicitis. Diagnosis is made by detection of the characteristic eggs in the stool or passed worms.[21]

▶ *Treatment*

In both adults and pediatric patients older than 2 years of age, albendazole or mebendazole is appropriate. Ivermectin or nitazoxanide are alternatives. The stool should be checked within 2 weeks and the patient retreated when warranted. Surgery or endoscopy may be indicated.[12,13]

Enterobiasis

Enterobiasis, or pinworm infection, is caused by *Enterobius vermicularis*. It is the most widely distributed helminthic infection in the world. There are approximately 42 million cases in the United States, primarily affecting children. It is transmitted person-to-person via the fecal to oral route (ie, direct contact with infected feces or handling infected items) or contact with water contaminated with *E. vermicularis* eggs. The most common manifestation of the infection is cutaneous irritation in the perianal region, resulting from the migrating female or the presence of eggs. The intense pruritus may lead to dermatitis and secondary bacterial infections. Diagnosis is made by the use of a perianal swab and cellophane tape sampling, which will aid in egg identification.[22]

▶ *Treatment*

The three agents that are administered for enterobiasis are pyrantel pamoate, mebendazole, and albendazole. Following treatment with one of these agents, all bedding and underclothing should be sterilized by steaming or washing in the hot cycle of the washing machine to eradicate the eggs.[12,13]

Strongyloidiasis

Strongyloidiasis is caused by *Strongyloides stercoralis,* which has a worldwide distribution and is predominantly prevalent in South America (Brazil and Columbia) and in Southeast Asia.[22] Strongyloidiasis is primarily seen among institutionalized populations (those in mental hospitals and children's hospitals) and immunocompromised individuals (those with HIV infection, AIDS, and patients with hematologic malignancies).[23,27,28] The worm is usually found in the upper intestine, where the eggs are deposited and hatch to form the rhabditiform larvae. The rhabditiform larvae (male and female) migrate to the bowel where they may be excreted in the feces. If excreted in the feces, the larva can evolve into either one of two forms after copulation: a free-living noninfectious rhabditiform larva, or parasitic, infectious filariform larva. The filariform larva can penetrate host skin and migrate to the lungs and produce progeny, a process called autoinfection. This can result in hyperinfection (ie, an increased number of larva in the intestine, lungs, and other internal organs), especially in an immunocompromised host.[29]

Patients with acute infection may develop a localized pruritic rash, but heavy infestations can produce eosinophilia (10%–15% eosinophils [0.10–0.15]), diarrhea, abdominal pain, and intestinal obstruction. Administration of corticosteroids or other immunosuppressive drugs to an infected individual can result in hyperinfections and disseminated strongyloidiasis.[23,28] KEY CONCEPT The symptoms appear in cutaneous, pulmonary, and finally intestinal phases. Diagnosis of strongyloidiasis is made by identification of the rhabditiform larva in stool, sputum, or duodenal fluid, or from small bowel biopsy specimens. Even though antigen testing (ELISA essay) remains the most sensitive method, stool examinations and other body fluids should also be utilized in the diagnosis.[23,27]

▶ *Treatment*

LO 3

KEY CONCEPT The drug of choice for strongyloidiasis is oral ivermectin or alternatively, albendazole.[12,13] Ivermectin may also be given with the two doses 2 weeks apart due to the auto-infection cycle taking 2 to 3 weeks.[13] Albendazole may be less effective than ivermectin. With hyperinfection or disseminated strongyloidiasis, immunosuppressive drugs should be discontinued and ivermectin should be given daily until all symptoms are resolved. Patients should be tested periodically to ensure the elimination of the larva. Individuals from an endemic area who are candidates for organ transplantation must be screened for *S. stercoralis*.[23] A veterinary drug, moxidectin, may be effective for *S. stercoralis* in humans as well, although clinical trials are still being conducted for its efficacy and safety.[30] Intravenous ivermectin is used in veterinary medicine also and may be selectively utilized in severely ill patients who cannot tolerate oral medication, if Food and Drug Administration (FDA) approval for the exception is obtained.[12]

Cestodiasis

Cestodiasis (tapeworm infection) is caused by species of the phylum Platyhelminthes (flatworms) and include, among others, the pork tapeworm (*Taenia solium*) and the beef tapeworm (*T. saginata*). *T. saginata* is the most common tapeworm and is endemic in Latin America, Africa, Central Asia, and the Middle East.[13] *T. solium* causes the most common infectious disease of the nervous system in humans and is the most common preventable cause of epilepsy in developing countries.[31]

The cestodes can be acquired by eating undercooked meat. The tapeworm attaches itself to the mucosal wall of the upper jejunum by the scolex (mouth parts) and by two to four cup-shaped suckers. *T. saginata* has a structure called a rostellum, which has hooks to help with its grip.[32] Since the parasite lacks a digestive system, it obtains all nutrients directly from the host. The scolex, proglottids (segments), and eggs are specific for each species and used for identification of tapeworms. Tapeworm infections are caused by ingestion of poorly cooked meat that contains the larva or cysticerci. Cysticerci, when released from the contaminated meat by host digestive juices, mature in the host jejunum. Cystericercosis is the term for systemic disease caused by the larva of *T. solium* (oncosphere or hexacanth), usually acquired by ingestion of eggs in contaminated food or

by autoinfection. During cysticercosis, the larvae penetrate the bowel and migrate through the bloodstream to infect different organs, including the central nervous system (CNS) (neurocysticercosis). Identification of both *T. saginata* and *T. solium* infections is accomplished by recovery of the gravid proglottids and the scolex in the stool. Newer diagnostic tools for neurocysticercosis include serum and cerebrospinal antigen and antibody testing. Spinal fluid may show eosinophilia, pleocytosis, and reactive lymphoid cells.[17,34]

▶ *Treatment*

KEY CONCEPT Pharmacological treatment of tapeworms kills adult worms but not eggs, which presents an issue for individuals with *T. solium*. Tapeworm infections are treated with praziquantel or albendazole.[12,34] Niclosamide is an alternative and may be obtained from a compounding pharmacy.[13] The doses of antihelmintic therapy can be repeated if necessary for both adults and children. The treatment for cysticercosis and neurocysticercosis may include surgery, anticonvulsants (neurocysticercosis can cause seizures), steroids, and anthelmintic therapy. See Table 78–3 for treatment regimens.[31] Steroids are used to treat inflammation caused by the invasion of brain tissue and prevent life-threatening complications of the disease caused by increased intracranial pressure. The inflammatory response as a result of parasite death after administration of anti-helminthics must be mediated. Dexamethasone 0.1 mg/kg per day, prednisolone 1 mg/kg per day, or prednisone 1 mg/kg per day may be used for 5 days up to 2 weeks. Steroids should be tapered rather than abruptly stopped to avoid worsening of symptoms.[13,31,35] See Table 78–6 for adverse reactions related to drugs.

LO 3

Outcome Evaluation

Morbidity and disease due to helminthic infections are related to the intensity of infection. The major adverse effects of helminthic infections are malnutrition, fatigue, and diminished work capacity. Unlike other helminthic infections, strongyloidiasis can cause autoinfection, and in the presence of immunosuppression, it can cause CNS and disseminated infections, which have high mortality.[23,28]

The most serious complication of cysticercosis is neurocysticercosis that can cause strokes and seizures.[31,36] Treatment of neurocysticercosis with anthelmintic treatment remains controversial, but should still be administered or prescribed when available. Patients should receive MRI follow-up to evaluate reduction in number of cysts.[36]

Table 78–3

Treatment Regimens for Helminthic Diseases

	Helminthic Diseases	
Drug	**Adult Dosing and Duration**	**Pediatric Dosing**
Hookworm, Ascariasis		
Primary:		
Albendazole	400 mg × 1 dose	Same as adult
Mebendazole	100 mg twice daily × 2 days	Same as adult
Alternative (Hookworm):		
Pyrantel pamoate	11 mg/kg/daily × 3 days	Same as adult
Alternative (Ascariasis):		
Ivermectin	150–200 mcg/kg × 1 dose	Same as adult
Enterobiasis		
Primary:		
Pyrantel pamoate	11 mg/kg (max 1g) × 1 dose	Same as adult
Mebendazole	100 mg × 1 dose	Same as adult
Albendazole	400 mg × 1 dose (may repeat doses in 2 weeks)	Same as adult
Strongyloidiasis		
Primary:		
Ivermectin	200 mcg/kg/day × 2 doses	Same as adult
Alternative:		
Albendazole	400 mg twice daily × 3–5 days	Same as adult
Cestodiasis		
Primary:		
Praziquantel	5–10 mg/kg × 1 dose	Same as adult
Alternative:		
Albendazole	15 mg/kg/day (max 800 mg) in 2 doses × 8–30 days	Same as adult
Nicolsamide	2g × 1 dose	50 mg/kg × 1 dose
Neurocysticercosis		
Albendazole	15 mg/kg/day (max 800 mg[a]) in 2 doses × 7–28 days	Same as adult
Praziquantel	100 mg/kg/day PO in 3 doses on day 1, then 50 mg/kg/day in 3 doses for 15–30 days	> 4 years, dose as adult

[a]Up to 1200 mg per day can be used for subarachnoid disease.

Patient Encounter 3, Part 1: Malaria

AR is a 52-year-old man who returned recently from building homes in Uganda. He started feeling unwell after returning, and he developed a temperature as high as 39.0°C (102.2°F), with anorexia, headache, chills, sweats, myalgias, and abdominal pain. AR comes to the emergency department with high fever (> 39.8°C [> 103.6°F]), headache, abdominal pain, nausea, stiffness of the neck, and back pain. AR indicates that he did not take antimalarial prophylaxis on this trip.

What are the symptoms in this patient that are consistent with malaria?

Why is this patient at risk for malaria?

Are there any additional information you like to have, to be able to develop a pharmacotherapy plan for this patient?

MALARIA

Malaria is a devastating parasitic disease. Nearly 200 million cases of malaria were reported in 2013 worldwide, with 0.3% resulting in death. Over 1700 cases were diagnosed in the United States that year and, mostly acquired in Africa, followed by Asia, the

LO 4 Carribbean and Americas, and Oceania. KEY CONCEPT The primary reasons for morbidity and death in malaria are failure to take recommended chemoprophylaxis, inappropriate chemoprophylaxis, delay in seeking medical care or in initiating therapy promptly, and misdiagnosis.[3] Evaluation of a patient should include specific travel history, details of chemoprophylaxis, and physical findings (eg, splenomegaly).

Malaria is transmitted by the bites of female *Anopheles* mosquitoes, which introduce into the bloodstream one of five species of sporozoites of the plasmodia (*Plasmodium falciparum, P. ovale, P. vivax, P. malariae,* and *P. knowlesi*). LO 5 Initial symptoms of malaria are nonspecific and may resemble influenza and include chills, headache, fatigue, muscle pain, rigors, and nausea. The onset of the symptoms is between 1 and 3 weeks following exposure. Fever may appear 2 to 3 days after initial symptoms and may follow a pattern and occur every 2 or 3 days (*P. vivax, P. ovale,* and *P. malariae*). *P. falciparum*, which is the most common cause of severe disease, may cause erratic fever that may not follow specific patterns. It is not unusual for patients to have concomitant infections with *P. vivax* and *P. falciparum*.[37,38] Falciparum malaria (or *P. knowlesi*) must always be regarded as a life-threatening medical emergency.[39]

Epidemiology and Etiology

The distribution of the various species of malaria is not strictly defined, but *P. vivax* is reported to be prevalent in the Indian subcontinent, Central America, North Africa, and the Middle East, whereas *P. falciparum* is predominantly in Africa (including sub-Saharan Africa), both East and West Africa, Haiti, the Dominican Republic, the Amazon region of South America, Southeast Asia, and New Guinea.[3,37,38] Most *P. ovale* infections occur in Africa, whereas the distribution of *P. malariae* is worldwide. Most infections in the United States are reported in American travelers, recent immigrants, or immigrants who have visited friends and family in an endemic area.[3,38] Placental transmission and blood transfusions are uncommon sources of malaria.[3]

Pathophysiology

Within minutes after the bite of the *Anopheles* mosquito, sporozoites begin to distribute to hepatocytes where they incvade and begin an asexual phase called schizonts (exoerythrocytic stage or schizogony). This asexual phase is about 48 hours for *P. falciparum, P. vivax,* and *P. ovale,* and 72 hours for *P. malariae*. The patient may be asymptomatic during this period. After a lapse of between 5 and 15 days (depending on the species), schizonts rupture to release daughter cells (merozoites) into the blood, which then invade erythrocytes. In erythrocytes, the merozoites undergo various forms: a ring form, trophozoite, schizont, and merozoite, which then invade new erythrocytes. The merozoites develop into gametocytes and undergo a sexual phase (sporogony). After a mosquito bite of an infected person and ingestion of blood containing gametocytes, the gametocytes undergo a number of stages: zygote, ookinete, and oocyst, and finally transform into sporozoites in the salivary glands, where they can infect the next host. Unlike *P. falciparum* and *P. malariae*, which only remain in the liver for about 3 weeks before invading erythrocytes, *P. ovale* and *P. vivax* can remain in the liver for extended periods in a latent stage (as hypnozoites); this can result in the recurrence of the infection after weeks or months.[17,37] Primaquine therapy is necessary to eradicate this stage of the infection.[12]

Clinical Presentation and Diagnosis

The clinical presentation of malaria can vary. Normally, the appearance of a prodrome with headache, abdominal pain, fatigue, fever, and chills, which coincides with the erythrocytic phase of malaria, occurs between 8 and 40 days after being exposed.[3,17,37,38] This phase causes extensive hemolysis, which results in anemia and splenomegaly. The most serious complications are caused by *P. falciparum* infections. Infants and children younger than 5 years and nonimmune pregnant women are at high risk for severe complications with falciparum infections.[37,38,40] The complications associated with falciparum malaria are related to two unique features of *P. falciparum*: (a) its ability to produce high parasitism (up to 80%) of red cells of all ages; and (b) the propensity to be sequestered in postcapillary venules of critical organs such as brain, liver, heart, lungs, and kidneys.[38,40] It has been postulated that tissue hypoxia from anemia, together with *P. falciparum*–parasitized red blood cell adherence to endothelial cells in capillaries, contributes to severe ischemia and metabolic derangements.[40] *P. malariae* is implicated in immune-mediated glomerulonephritis and nephrotic syndrome.[41]

Patient Encounter 3, Part 2: Falciparum Malaria

AR presents with fever, nausea, headache, myalgias, chills, and body aches including back pain.

PMH: Otherwise healthy 52-year-old man

FH: Father died of colon cancer at age 62 years; mother, who is 82-year-old, has osteoarthritis and lives with his sister

SH: Works for a nonprofit organization providing water filters to communities in India

Meds: Multivitamin

ROS: In addition to the complaints noted previously, he complains of severe nausea and fatigue

Gen: Patient is slightly agitated and febrile

VS: BP 132/86 mm Hg; P 120 beats/min, RR 36 breaths/min, T 40.1°C (104.2°F)

Skin: Warm and dry to touch

HEENT: Slightly dry oral mucosa

ABD: Splenomegaly

Rest of the systems were WNL.

Labs: Sodium 148 mEq/L (148 mmol/L), hemoglobin 10.2 g/dL (102 g/L or 6.33 mmol/L), potassium 4.1 mEq/L (4.1 mmol/L), hematocrit 31% (0.31), chloride 96 mEq/L (96 mmol/L), WBC $14.8 \times 10^3/mm^3$ ($14.8 \times 10^9/L$), BUN 28 mg/dL (10.0 mmol/L), total bilirubin 1.8 mg/dL (30.8 µmol/L), Scr 1.4 mg/dL (124 µmol/L), platelets $110 \times 10^3/mm^3$ ($110 \times 10^9/L$), glucose 77 mg/dL (4.3 mmol/L), aspartate aminotransferase 87 U/L (1.45 µkat/L), albumin 3.2 g/dL (32 g/L), alanine aminotransferase 94 U/L (1.57 µkat/L), blood smear (Giemsa stain): *P. falciparum*.

Based on the above findings, what is your approach in the management of AR?

Describe the specific steps one needs to take to ensure a good outcome and minimize the associated complications with P. falciparum *infection.*

Thick and thin blood smears should reveal malaria parasites with the Giemsa stain being preferred, and rapid diagnostic tests should be used if microscopy is not available. KEY CONCEPT One negative set of blood smears does not rule out malaria.[17,42] Malaria can also be detected with DNA or RNA probes by PCR and monoclonal antibody testing.[3,38,43]

Treatment

Prevention of malaria is key in those traveling to regions with endemic malaria. Prophylaxis must be started prior to travel and continued through 1 week after travel. Drug selection is based on resistance patterns in the region. The primary goal in the management of malaria is to rapidly eradicate the infection to prevent complications such as hypoglycemia, pulmonary edema, and renal failure.[3,37,40,44]

Rapid identification of the *Plasmodium* species by blood smears is important. Antimalarial therapy should be initiated promptly to eradicate the infection within 48 to 72 hours.

Pharmacologic Therapy

Treatment of malaria is based on the species and resistance patterns in the region from which it was acquired. See Table 78–4 for treatment regimens. See Table 78–6 for adverse reactions related to drugs.[12,13]

KEY CONCEPT In severe illness or falciparum malaria, patients should be admitted to an acute care unit, and quinidine gluconate should be started. KEY CONCEPT Patients often cannot tolerate quinidine due to QTc prolongation. Artesunate may be used in place of quinidine, followed by oral therapy. Artesunate is available from the Centers for Disease Control and Prevention [CDC] under an investigational new drug application (www.cdc.gov/malaria/features/artesunate_now available.htm).[12]

LO 6 Mefloquine is associated with sinus bradycardia, confusion, hallucinations, and psychosis and should be avoided in patients with a history of epilepsy, cardiovascular problems, or depression. IV quinidine gluconate followed by quinine plus doxycycline or clindamycin should be administered for severe illness as

Table 78–4

Treatment Regimens for Malaria

Drug	Adult Dosing	Pediatric Dosing
Oral (Uncomplicated/Mild)		
No chloroquine resistance		
Chloroquine phosphate	1 g (600 mg base[a]), followed by 500 mg at 6, 24, and 48 hours	10 mg/kg (base[a]), followed by 5 mg/kg at 6, 24, and 48 hours
Chloroquine-resistant* P. falciparum *or unidentified species		
• Atovaquone/proguanil	4 tablets (250 mg/100 mg) daily for 3 days	5–8 kg: 2 pediatric tablets (62.5 mg/25 mg) daily; 9–10 kg: 3 peds tabs daily; 11–20 kg: 1 adult tab daily; 21–30 kg: 2 adult tabs daily; 31–40 kg: 3 adult tabs daily; > 40 kg: adult dose (all for 3 days)
• Artemether/lumefantrine	4 tablets per dose at 0, 8, 24, 36, 48, 60 hours	Same as adult
• Quinine sulfate PLUS	650 mg every 8 hours for 3–7 days	30 mg/kg/day in 3 doses for 3–7 days
doxycycline	100 mg twice daily	4 mg/kg/day in 3 doses
OR tetracycline	250 mg 4 times daily	25 mg/kg/day in 4 doses
OR clindamycin	20 mg/kg/day in 3 doses (all for 7 days)	20 mg/kg/day in 3 doses (all for 7 days)
Alternative:		
• Mefloquine	750 mg followed by 500 mg 12 hours later	15 mg/kg followed by 10 mg/kg 12 hours later
***Chloroquine-resistant* P. vivax**		
• Quinine sulfate PLUS	Same dosing as above	Same dosing as above
• Doxycycline	Same dosing as above	Same dosing as above
Alternative:		
• Atovaquone/proguanil	Same dosing as above	Same dosing as above
• OR Mefloquine	Same dosing as above	Same dosing as above
EITHER PLUS		
• Primaquine phosphate	30 mg base/day for 14 days	0.5 mg/kg/day for 14 days
Parenteral (Severe)		
All* Plasmodium *species		
• Quinidine gluconate	10 mg/kg IV loading dose (max 600 mg) over 1–2 hours followed by 0.02 mg/kg/min until PO can be used	Same as adult
• OR quinine dihydrochloride	20 mg/kg IV loading dose over 4 hours followed by 10 mg/kg over 2–4 hours every 8 hours (max 1800 mg/day) until PO can be used	Same as adult
• OR artesunate PLUS an oral drug	2.4 mg/kg/dose for 3 days at 0, 12, 24, 48, and 72 hours	Same as adult

[a]Tablets available as 250 mg of chloroquine phosphate, which is equivalent to 150 mg of chloroquine base.

Clinical Presentation and Diagnosis of Malaria[37]

Initial Presentation

Take a careful travel history, physical findings, and details of antimalarial chemoprophylaxis.

Erythrocytic Phase

1. Prodrome: Headache, anorexia, malaise, fatigue, and myalgia.
2. Nonspecific complaints include abdominal pain, diarrhea, chest pain, and arthralgia.
3. Paroxysm: High fever, chills, and rigor.
4. Cold phase: Severe pallor, cyanosis of the lips and nail beds.
5. Hot phase: Fever between 40.5°C (104.9°F) and 41.0°C (105.8°F) (seen more frequently with *P. falciparum*).
6. Sweating phase: Follows the hot phase by 2 to 6 hours
7. When fever resolves, it is followed by marked fatigue and drowsiness, warm dry skin, tachycardia, cough, headache, nausea, vomiting, abdominal pain, diarrhea and delirium, anemia, and splenomegaly.

KEY CONCEPT *P. falciparum* malaria is a life-threatening emergency. Complications include hypoglycemia, acute renal failure, pulmonary edema, severe anemia (high parasitism), thrombocytopenia, heart failure, cerebral congestion, seizures, coma, and adult respiratory distress syndrome.

Diagnostic Procedures for Malaria

1. To ensure a positive diagnosis, blood smears (both thick and thin films) should be obtained every 12 to 24 hours for 3 consecutive days.
2. The presence of parasites in the blood 3 to 5 days after initiation of therapy suggests resistance to the drug regimen.

Patient Care Process: Malaria

Collect Information:

- Based on physical examination and review of systems, determine whether patient has acute malaria.
- Review all laboratory tests and take note of blood work that identifies species of *Plasmodium*.
- Conduct a **medical history review** to identify **travel history and medication allergies.**

Assess the Information:

- Determine, based on patient presentation, travel history, and use of prophylaxis, if acute malaria is chloroquine sensitive or resistant.

Develop a Care Plan:

- Use the CDC malaria website for recommendations.
- Develop regimen, considering the region the patient traveled to and therapeutic options, as well as drug interactions.

Implement the Care Plan:

- Inform patient of regimen (or begin regimen if critically ill), and counsel patient on adherence, drug interactions, or side effects.

Follow-up: Monitor and Evaluate:

- Monitor for efficacy and toxicity.
- Repeat smear if necessary to detect level of parasitemia and improvement.

LO 7 indicated previously. The IV quinidine regimen requires close monitoring of the ECG (QT-segment) and other vital signs (hypotension and hypoglycemia). An alternative oral treatment for *P. falciparum* infections in adults, especially those with history of seizures, psychiatric disorders, or cardiovascular problems, is the combination of atovaquone and proguanil.[13] KEY CONCEPT LO 8 Since falciparum malaria is associated with serious complications, including pulmonary edema, hypoglycemia, jaundice, renal failure, confusion, delirium, seizures, coma, and death, careful monitoring of fluid status and hemodynamic parameters is essential.

Outcome Evaluation

Acute *P. falciparum* malaria resistant to chloroquine should be treated with IV quinidine. The loading dose of quinidine should be omitted in patients who have received quinine or mefloquine. Hypoglycemia, associated with both *P. falciparum* and quinidine administration, should be assessed every 6 hours and corrected with dextrose when necessary. Quinidine infusions should be slowed or stopped if the QT interval is greater than 600 msecs, the increase in the QRS complex is greater than 25%, or if hypotension unresponsive to fluid challenge results. Quinidine levels should be maintained at 3 to 7 mg/dL (9.2–21.6 µmol/L).[44]

When advising potential travelers on prophylaxis for malaria, be aware of the incidence of chloroquine-resistant *P. falciparum* malaria and the countries where it is prevalent.[44] In patients who have *P. vivax* or *P. ovale* malaria (note that some patients can have *P. falciparum* and one of these species), following the treatment of the acute phase of malaria and screening for glucose-6-phosphate dehydrogenase deficiency, patients should receive a regimen of primaquine for 14 days to ensure eradication of the hypnozoite stage of *P. vivax* or *P. ovale*.[44] Malaria prophylaxis recommendations are available from the CDC Yellow Book based on region, which can be viewed at https://wwwnc.cdc.gov/travel/page/yellowbook-home. Vaccines for malaria are under investigation.[6]

AMERICAN TRYPANOSOMIASIS

Epidemiology and Etiology

Two distinct forms of the genus *Trypanosoma* occur in humans. One is associated with African trypanosomiasis (sleeping sickness) and the other with American trypanosomiasis (Chagas disease). *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* are the causative organisms for the East African and West African trypanosomiasis, respectively. *T. brucei rhodesiense* causes the acute disease and is the more virulent of the two species. Both East and West African trypanosomiasis are transmitted by various species of tsetse fly belonging to the genus *Glossina*. Further discussion of this subject will focus on American trypanosomiasis.

Trypanosoma cruzi is the agent that causes American trypanosomiasis. American trypanosomiasis is transmitted by different species of reduviid bugs (*Triatoma infestans* and *Rhodium prolixus*) that live in wall cracks of houses in rural areas of North, Central, and South America.[45–47]

Pathophysiology

The reduviid bug ("kissing bug") is infected by sucking blood from animals (eg, opossums, dogs, and cats) or humans infected with circulating trypomastigotes. Patients who are carriers of *T. cruzi* can transmit the parasite via blood or organ donation. Patients may be asymptomatic or experience mild symptoms such as local inflammation and fever. Less commonly, the disease may present as CNS infection in patients with AIDS or cause death due to arrhythmias or heart failure.[46,48,49] Diagnosis of trypanosomiasis depends on trypomastigotes in the blood, in addition to other signs, and may be undetectable in chronic disease.[17]

LO 9

▶ *Pharmacologic Therapy*

The drugs used for *T. cruzi* include nifurtimox and benznidazole. See Table 78–5 for treatment regimens. Nifurtimox is available from the CDC, but benzinidazole was FDA-approved in 2017 in the United States for treatment of Chagas Disease in children aged 2–12 years.[13,46,50] Benznidazole and nifurtimox both act by producing free radicals that damage parasitic DNA. Since children may tolerate the dose better than adults, the pediatric dose is higher.[12,13] Nifurtimox requires monitoring of liver function tests (LFTs), complete blood count (CBC), and chemistries.

Table 78–5

Treatment Regimens for Trypanosomiasis

Trypanosomiasis		
Drug	**Adult Dosing and Duration**	**Pediatric Dosing**
Nifurtimox	8–10 mg/kg/day in 3–4 doses × 90 days	1–10 years: 15–20 mg/kg/day in 3–4 doses 11–16 years: 12.5–15 mg/kg/day in 3–4 doses
Benznidazole	5–8 mg/kg/day in 2 doses × 60 days	Same as adults (children > 2 years)

Benznidazole requires CBC and chemistry monitoring.[12,13] Symptomatic treatment for heart failure associated with Chagas disease should be initiated. The GI complications may require surgical revisions and reconstruction.[45,46] See Table 78–6 for adverse reactions related to drugs.

Outcome Evaluation

Treatment of the acute phase of the disease (ie, fever, malaise, edema of the face, and hepatosplenomegaly) is nifurtimox. The congestive heart failure associated with cardiomyopathy of Chagas disease is treated the same way as cardiomyopathy from other causes.[46,47]

Clinical Presentation and Diagnosis of Trypanosomiasis[17,46]

Acute (2 weeks after infection, in 1% of patients)

- Unilateral orbital edema (Romana sign)
- Granuloma (chagoma)
- Fever, hepatosplenomegaly, lymphadenopathy, myocarditis, or CNS involvement

Intermediate Stage

- Resolution of acute illness after 4–8 weeks with detectable antibodies

KEY CONCEPT **Chronic (30% of patients)**

Cardiac: cardiomyopathy and heart failure

ECG: first-degree heart block, right bundle-branch block, and arrhythmias

GI: enlargement of the esophagus and colon ("mega" syndrome)

CNS: meningoencephalitis, strokes, seizures, and focal paralysis

Diagnosis

Positive history of exposure and use of serology: indirect hemagglutination test, ELISA, and complement fixation (CF) test. (*Note:* CF may produce false-positive reactions in those exposed to leishmaniasis, syphilis, and malaria. PCR may be more definitive for diagnosis.)

ECTOPARASITES

A parasite that lives outside the body of the host is called an ectoparasite. Approximately 6 to 12 million subjects become infested with pediculosis (lice infestation) yearly in the United States.

Patient Care Process: Trypanosomiasis (Chagas Disease)

Collect Information:

- Review medical history and laboratory tests including serology to establish the diagnosis for *T. cruzi*.
- Identify common complications associated with *T. cruzi*.

Assess the Information:

- Determine if patient needs to be treated for primary disease and any secondary complications.
- Assess efficacy, safety, and potential drug interactions.

Develop a Care Plan:

- Determine the doses and regimen for pharmacotherapy.

Implement the Care Plan:

- Educate patient on treatment and side effects.

Follow-up: Monitor and Evaluate:

- Review medical history, physical examination findings, and lab tests monthly.
- Determine, after assessing efficacy and toxicities of pharmacotherapy, if changes in regimen are necessary.

Table 78–6

Adverse Effects of Anti-Parasitic Agents

Drug[a]	Adverse Effects
Metronidazole	Gastrointestinal intolerance, metallic taste, disulfiram-like reaction with alcohol use (flushing, tachycardia, and hypotension)
Tinidazole	Gastrointestinal intolerance, metallic taste, disulfiram-like reaction with alcohol use
Nitazoxanide	Gastrointestinal intolerance, discoloration of eyes or urine
Furazolidone	Gastrointestinal intolerance, yellow/brown discoloration of urine, pulmonary infiltrate, headache, fever, hemolysis with G6PD deficiency, hypotension, polyneuropathy, hypoglycemia, agranulocytosis
Paromomycin	Gastrointestinal intolerance. If systemic absorption occurs, nephrotoxicity and ototoxicity can result
Quinacrine	Gastrointestinal intolerance, psychosis, headache, yellow staining of skin, hemolytic anemia, leukopenia, rash, disulfiram-like reaction. Contraindicated if history of psychosis or psoriasis
Albendazole	CNS related, gastrointestinal intolerance, leukopenia
Iodoquinol	CNS related, rash, thyroid enlargement, optic neuritis, peripheral neuropathy
Diloxanide furoate	Gastrointestinal intolerance
Mebendazole	Gastrointestinal intolerance
Pyrantel pamoate	Gastrointestinal intolerance, stool discoloration, rash, dizziness
Ivermectin	Fever, rash, pruritis, inflammatory reaction (due to death of worms), lymphadenopathy, headache
Praziquantel	Dizziness, drowsiness, gastrointestinal intolerance, rash, fever
Niclosamide	Anorexia, gastrointestinal intolerance
Chloroquine phosphate	QTc prolongation, anorexia, gastrointestinal intolerance, headache, dizziness, blurred vision, pruritis
Atovaquone/proguanil	Gastrointestinal intolerance, headache, dizziness, mild AST/ALT increase
Artemether/lumefantrine	Headache, anorexia, dizziness, arthralgia, myalgia
Quinine sulfate	Cinchonism, tinnitus, headache, gastrointestinal intolerance, blurred vision. Less common: blood dyscrasias, drug fever, asthma, hypoglycemia, transient blindness. Contraindicated if prolonged QTc, G6PD deficiency, myasthenia gravis, optic neuritis
Doxycycline	Gastrointestinal intolerance, chelation with cations (separate administration with dairy products, antacids), erosive esophagitis (should take with water), photosensitivity, onycholysis
Tetracycline	Discoloration of tooth enamel, photosensitivity, gastrointestinal intolerance, chelation with cations (separate administration with dairy products, antacids)
Clindamycin	Gastrointestinal intolerance (especially diarrhea, including C. difficile infection), neutropenia, thrombocytopenia, eosinophilia
Mefloquine	Black box warning for neuropsychiatric events (Medication Guide must be dispensed with prescription). Other AE include headache, irritability, insomnia, diarrhea, toxic psychosis, seizures. Less common: prolonged QTc and toxic epidermal necrolysis. Contraindicated with quinine and quinidine
Primaquine phosphate	Avoid in G6PD deficiency (risk of hemolytic anemia, methemoglobinemia). Other AE include nausea/abdominal pain if taken on empty stomach
Quinidine gluconate	Fatal hypotension with rapid IV bolus, hypoglycemia. Can reduce rate of infusion of IV quinidine to reduce QTc prolongation
Quinine dihydrochloride	Fatal hypotension with rapid IV bolus, hypoglycemia, cinchonism, blindness
Artesunate	Hemolysis (decline in hemoglobin after treatment), bradycardia, dizziness, gastrointestinal intolerance. Less common: seizure, cerebellar dysfunction
Nifurtimox	Gastrointestinal intolerance, CNS effects, polyneuropathy, rash. Leukopenia, hepatitis. Hemolysis if G6PD deficiency
Benznidazole	Rash, anorexia, gastrointestinal intolerance, CNS effects, increased AST/ALT, arthralgia

[a]Listed in order of appearance in the chapter.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system.

Pediculosis is usually associated with poor hygiene, though infections are then passed from person to person through social and sexual contact.[51]

Lice

The two species that belong to this group include *Pediculus humanus capitis* (head louse) and *Pediculus humanus corporis* (body louse). The eggs (or nits) remain firmly attached to the hair, and in about 10 days the lice hatch to form nymphs, which mature in 2 weeks. The lice become attached to the base of the hair follicle and feed on the blood of the host. Pubic or crab lice is found on the hairs around the genitals but may occur in other parts of the body (eg, eyelashes or axillae). Hypersensitivity to the secretions from lice can produce macular swellings and lead to secondary bacterial infections.[51]

► *Treatment*

LO 10

KEY CONCEPT The pharmacologic agent of choice for all three infections (body, head, and crab lice) is permethrin, but it is as important to comb hair with a fine tooth comb to remove eggs and dead lice. Permethrin 1% is available over-the-counter and has both pediculicidal and ovicidal activity against *P. humanus capitis*. Individuals with a history of hypersensitivity to ragweed or chrysanthemum may react to permethrin and should avoid this preparation. An alternative agent is oral ivermectin. Permethrin can cause itching, burning, stinging, and tingling with application. Because of the reports of resistance to permethrin, an alternative agent is 0.5% malathion, which should be applied to dry hair, and rinsed after 8 to 12 hours with shampoo. Two applications of malathion, 7 days apart, may be necessary to eradicate the infection.[12,13] Other alternatives for head lice include spinosad

0.9% or benzyl alcohol 5%, for which dosing varies by hair length. For the relief of pruritus, calamine lotion with 0.1% menthol or an equivalent agent may be used. Lindane is no longer recommended due to side effects. KEY CONCEPT All individuals, including immediate family members and sexual partners of the primary host, should be treated. All bedding and clothes should be cleaned in hot water.[13] See Table 78–6 for adverse events related to drugs.

LO 10

Scabies

KEY CONCEPT Scabies is caused by the mite *Sarcoptes scabiei* hominis, which affects both humans and animals. Infection usually affects the interdigital and popliteal folds, axillary folds, the umbilicus, and the scrotum. The infection causes severe itching and excoriations in the interdigital web spaces, buttocks, groin, and scalp. Scabies may also manifest as nodules or crusted scabies (Norwegian scabies), which is a more aggressive form of disease. Diagnosis is made by identifying the mite from skin scrapings on a wet mount.[52]

Treatment

LO 10

KEY CONCEPT The agent of choice for scabies is permethrin 5% cream.[12,13] Alternative agents are crotamiton 10% (Eurax) or oral ivermectin 200 mcg/kg as a single dose. Lindane is only indicated for classic (not crusted) scabies and is contraindicated in pregnant women or children. Before applying permethrin, the skin should be scrubbed in a warm soapy bath to remove the scabs. The permethrin lotion should then be applied to the whole body, avoiding the face, mucous membranes, and eyes, and left on for 8 to 14 hours before washing off. A single application eradicates 97% of scabies. However, in subjects with poor response, permethrin application can be combined with oral ivermectin therapy.[13] All close contacts should be treated appropriately. The pruritus associated with scabies may persist for 2 to 4 weeks because of the remnants of mite parts in the skin. Clothing and bedding must be washed in hot water.[12,13] See Table 78–6 for adverse events related to drugs.

LO 10

Patient Care Process: Ectoparasites

Collect Information:

- Ask the patient about specific symptoms and when they started, and if anyone in the household is experiencing the same symptoms.
- Obtain a travel, medical, and medication history.

Assess the Information:

- Determine if symptoms are consistent with an ectoparasitic infection (ie, specific identifiable rash, identifiable mites).
- Identify treatment options.

Develop a Care Plan:

- Consider if other family members need to be treated and the ability for all members to be treated and adhere to a regimen.

Implement the Care Plan:

- Explain the treatment choice to the patient and counsel them on proper hygiene (eg, washing clothing and linens) and administration of medication.
- Advise patient on possible side effects.

Follow-up: Monitor and Evaluate:

- Instruct patient to follow up at the end of therapy if symptoms are not gone.

Outcome Evaluation

Infections due to arthropods can be controlled by preventing their access to the host. Avoiding sharing common personal items like hats and hair brushes may minimize the spread of these arthropod-transmitted infections. Permethrin is an effective agent for all of them.

Abbreviations Introduced in This Chapter

CDC	Centers for Disease Control and Prevention
CF	Complement fixation
ELISA	Enzyme-linked immunosorbent assay
IgA	Immunoglobulin A
PCR	Polymerase chain reaction

REFERENCES

1. Ross AG, Olds GR, Cripps AW, Farrar JJ, McManus DP. Enteropathogens and chronic illness in returning travelers. N Engl J Med. 2013;368(19):1817–1825.
2. Puthiyakunnon S, Boddu S, Li Y, et al. Strongyloidiasis—an insight into its global prevalence and management. PLoS Negl Trop Dis. 2014;8(8):e3018.
3. Cullen KA, Mace KE, Arguin PM. Malaria Surveillance —United States, 2013. MMWR Morb Mortal Wkly Rep. 2013;65(2):1–22.
4. Schwartz BS, Mawhorter SD, Practice ASTIDCo. Parasitic infections in solid organ transplantation. Am J Transplant. 2013;13(suppl 4):280–303.
5. Yazdanbakhsh M, Sacks DL. Why does immunity to parasites take so long to develop? Nat Rev Immunol. 2010;10(2):80–81.
6. Hill AV. Vaccines against malaria. Philos Trans R Soc Lond B Biol Sci. 2011;366(1579):2806–2814.
7. Diemert DJ, Freire J, Valente V, et al. Safety and immunogenicity of the Na-GST-1 hookworm vaccine in Brazilian and American adults. PLoS Negl Trop Dis. 2017;11(5):e0005574.
8. Hill DR, Nash TE. Giardia lamblia. In: Bennett JE, Dolin R, Blaser MJ, eds. Principles and Practice of Infectious Diseases, 8th ed. New York: Elsevier Churchill-Livingstone; 2015:3154–3160.
9. Bogitsh BJ, Oeltmann TN, Carter CE. Visceral Protozoa II: Flagellates. Human Parasitology. St. Louis, United States: Elsevier Science; 2005.
10. Painter JE, Gargado JW, Collier SA, Yoder JS. Giardiasis Surveillance —United States, 2011–2012. MMWR Morb Mortal Wkly Rep. 2015;64(3):15–25.
11. Hanevik K, Dizdar V, Langeland N, Hausken T. Development of functional gastrointestinal disorders after Giardia lamblia infection. BMC Gastroenterol. 2009;9:27.
12. Drugs for parasitic infections. In: Handbook of Antimicrobial Therapy. Medical Letter. 18th ed. New Rochelle, NY 2013.
13. The Johns Hopkins POC-IT ABX Guide. Bartlett JG, editor. Baltimore, MD: Unbound Medicine; 2015.
14. Kelly P. Intestinal protozoa. In: Farrar J, Hotez PJ, Junghanss T, Kang G, Lalloo D, White N, eds. Manson's Tropical Diseases, 23rd ed. London: WB Saunders; 2014:664–682.
15. Wright SG. Protozoan infections of the gastrointestinal tract. Infect Dis Clin North Am. 2012;26(2):323–339.

16. Petri WA, Haque R. Entamoeba species, including amebic colitis and liver abscess. In: Bennett JE, Dolin R, Blaser MJ, eds. Principles and Practice of Infectious Diseases, 8th ed. New York: Elsevier Churchill-Livingstone; 2015:3047–3058.
17. Garcia LS. Diagnostic Medical Parasitology. Washington, United States: ASM Press; 2006.
18. Choudhuri G, Rangan M. Amebic infection in humans. Indian J Gastroenterol. 2012;31(4):153–162.
19. Athie-Gutierrez C, Rodea-Rosas H, Guizar-Bermudez C, Alcantara A, Montalvo-Jave EE. Evolution of surgical treatment of amebiasis-associated colon perforation. J Gastrointest Surg. 2010;14(1):82–87.
20. Starr MC, Montgomery SP. Soil-transmitted Helminthiasis in the United States: a systematic review—1940–2010. Am J Trop Med Hyg. 2011;85(4):680–684.
21. Maguire JJ. Intestinal nematodes (roundworms). In: Bennett JE, Dolin R, Blaser MJ, eds. Principles and Practice of Infectious Diseases, 8th ed. New York: Elsevier Churchill-Livingstone; 2015:3199–3207.
22. Knopp S, Steinmann P, Keiser J, Utzinger J. Nematode infections: soil-transmitted helminths and trichinella. Infect Dis Clin North Am. 2012;26(2):341–358.
23. Marcos LA, Terashima A, Canales M, Gotuzzo E. Update on strongyloidiasis in the immunocompromised host. Curr Infect Dis Rep. 2011;13(1):35–46.
24. Bartsch SM, Hotez PJ, Asti L, et al. The global economic and health burden of human hookworm infection. PLoS Negl Trop Dis. 2016;10(9):e0004922.
25. Casey GJ, Montresor A, Cavalli-Sforza LT, et al. Elimination of iron deficiency anemia and soil transmitted helminth infection: evidence from a fifty-four month iron-folic acid and de-worming program. PLoS Negl Trop Dis. 2013;7(4):e2146.
26. Casey GJ, Tinh TT, Tien NT, et al. Sustained effectiveness of weekly iron-folic acid supplementation and regular deworming over 6 years in women in rural Vietnam. PLoS Negl Trop Dis. 2017;11(4):e0005446.
27. Krolewiecki AJ, Lammie P, Jacobson J, et al. A public health response against Strongyloides stercoralis: time to look at soil-transmitted helminthiasis in full. PLoS Negl Trop Dis. 2013;7(5):e2165.
28. Buonfrate D, Requena-Mendez A, Angheben A, et al. Severe strongyloidiasis: asystematic review of case reports. BMC Infect Dis. 2012;13(78):1–10.
29. Bogitsh BJ, Oeltmann TN, Carter CE. Intestinal Nematodes. Human Parasitology. Saint Louis, MO: Elsevier Science; 2005.
30. Barda B, Sayasone S, Phongluxa K, et al. Efficacy of moxidectin versus ivermectin against Strongyloides stercoralis infections: a randomized controlled non-inferiority trial. Clin Infect Dis. 2017.
31. Fogang YF, Savadogo AA, Camara M, et al. Managing neurocysticercosis: challenges and solutions. Int J Gen Med. 2015;8:333–344.
32. Gunn A, Pitt SJ. Parasitology: An Integrated Approach. Hoboken: Wiley; 2012.
33. Coyle CM. Neurocysticercosis: an update. Curr Infect Dis Rep. 2014;16(11):437.
34. King CH, Fairley JK. Tapeworms (Cestodes). In: Bennett JE, Dolin R, Blaser MJ, eds. Principles and Practice of Infectious Diseases, 8th ed. New York: Elsevier Churchill-Livingstone; 2015:3227–3236.
35. Cuello-Garcia CA, Roldan-Benitez YM, Perez-Gaxiola G, Villarreal-Careaga J. Corticosteroids for neurocysticercosis: a systematic review and meta-analysis of randomized controlled trials. Int J Infect Dis. 2013;17(8):e583–e592.
36. Del Brutto OH. Neurocysticercosis: new thoughts on controversial issues. Curr Opin Neurol. 2013;26(3):289–294.
37. White N. Malaria. In: Farrar J, Hotez PJ, Junghanss T, Kang G, Lalloo D, White N, eds. Manson's Tropical Diseases, 23rd ed. London: WB Saunders; 2014:532–600.
38. Fairhurst RM, Wellems TE. Malaria (Plasmodium species). In: Dolin R, Bennett JE, Blaser MJ, eds. Principles and Practice of Infectious Diseases, 8th ed. New York: Elsevier Churchill-Livingstone; 2015:3070–3090.
39. Kantele A, Jokiranta TS. Review of cases with the emerging fifth human malaria parasite, Plasmodium knowlesi. Clin Infect Dis. 2011;52(11):1356–1362.
40. Marks M, Gupta-Wright A, Doherty JF, Singer M, Walker D. Managing malaria in the intensive care unit. Br J Anaesth. 2014;113(6):910–921.
41. Badiane AS, Diongue K, Diallo S, et al. Acute kidney injury associated with Plasmodium malariae infection. Malar J. 2014; 13(226):1–5.
42. Diagnosis of Malaria. Guidelines for the treatment of malaria, 3rd ed. Geneva, Switzerland: World Health Organization; 2015:27–30.
43. Lucchi NW, Oberstaller J, Kissinger JC, Udhayakumar V. Malaria diagnostics and surveillance in the post-genomic era. Public Health Genomics. 2013;16(1–2):37–43.
44. Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci. 2014;369(1645):20130434.
45. Andrade DV, Gollob KJ, Dutra WO. Acute chagas disease: new global challenges for an old neglected disease. PLoS Negl Trop Dis. 2014;8(7):e3010.
46. Kirchoff LV. Trypanosoma species (American trypanosomiasis, Chagas' disease): biology of trypanosomes. In: Bennett JE, Dolin R, Blaser MJ, eds. Principles and Practice of Infectious Diseases 1, 8th ed. New York: Elsevier Churchill-Livingstone; 2015:3108–3115.
47. Rassi A, Jr., Rassi A, Marcondes de Rezende J. American trypanosomiasis (Chagas disease). Infect Dis Clin North Am. 2012;26(2):275–291.
48. Kransdorf EP, Czer LS, Luthringer DJ, et al. Heart transplantation for Chagas cardiomyopathy in the United States. Am J Transplant. 2013;13(12):3262–3268.
49. Messenger LA, Gilman RH, Verastegui M, et al. Towards improving early diagnosis of congenital Chagas disease in an endemic setting. Clin Infect Dis. 2017.
50. FDA approves first U.S. treatment for Chagas disease [press release]. Silver Spring, MD: Food and Drug Administration 2017.
51. Diaz JH. Lice (pediculosis). In: Bennett JE, Dolin R, Blaser MJ, eds. Principles and Practice of Infectious Diseases, 8th ed. New York: Elsevier Churchill-Livingstone; 2015:3246–3249.
52. Shimose L, Munoz-Price LS. Diagnosis, prevention, and treatment of scabies. Curr Infect Dis Rep. 2013;15(5):426–431.

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79 Urinary Tract Infections and Prostatitis

Spencer H. Durham

LEARNING OBJECTIVES

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

LO

1. Determine the diagnostic criteria for significant bacteruria, urinary tract infections (UTIs), and catheter-associated UTIs.
2. Recognize the signs and symptoms of urinary tract infections (UTIs), and differentiate asympotomatic bacteriuria from acute cystitis and pyelonephritis, and acute prostatitis from chronic prostatitis.
3. Identify the pathogenic organisms most commonly implicated in different UTIs.
4. Assess the laboratory tests used in the diagnosis of UTIs.
5. Based on clinical signs, symptoms, and laboratory parameters, recommend appropriate empiric and targeted pharmacotherapy for the treatment of acute cystitis, pyelonephritis, and prostatitis, including drug, dose, and duration of therapy.
6. Formulate appropriate monitoring and education information for patients with UTIs.

INTRODUCTION

A urinary tract infection (UTI) is defined as the presence of pathogenic microorganisms in the genitourinary tract with associated signs and symptoms of infection. UTIs represent a diverse array of syndromes based on location within the urinary tract, including acute cystitis, pyelonephtritis, and prostatitis.[1–3] UTIs are one of the most common reasons for the prescribing of antimicrobial therapy.[4]

EPIDEMIOLOGY AND ETIOLOGY

The prevalence and type of UTIs generally vary according to age and gender.[5,6] In adults, bacteriuria is more common in young, nonpregnant women (range, 1%–3%), but uncommon in men (up to 0.1%).[7] Symptomatic UTIs occur most frequently in women of childbearing age. It is estimated that the lifetime risk of UTIs in women is as high as 60%, with 25% of those patients experiencing a recurrence within 1 year.[8] UTIs are much more common in women and men due to their inherently shorter urethra and location in the perineal area. However, older men may experience UTIs due to immunoscenesence and concomitant disease states, such as benign prostatic hypertrophy (BPH).

LO 2

KEY CONCEPT UTIs can be classified as either uncomplicated or complicated. Uncomplicated infections usually occur in women of childbearing age. Complicated UTIs usually occur in patients who have structural or functional abnormalities of the genitourinary tract, and may involve the bladder or the kidneys.[2] Male patients with UTIs are considered complicated, and most older adults will also meet this criterion. Although complicated infections are usually treated similar to uncomplicated infections, a longer treatment duration is typically warranted in complicated infections. UTIs can also be classified as upper and lower depending on their anatomical location. Lower UTIs usually refer to acute cystitis, whereas upper UTIs refer to pyelonephritis. It is important to note that an upper UTI does not necessarily imply complicated UTI, nor does a lower UTI imply uncomplicated UTI.

LO 3

The etiologic pathogens of most UTIs originate from the perirectal area. *Escherichia coli* is implicated in more than 80% of uncomplicated infections, with *Klebsiella pneumoniae* and *Proteus* species being less common.[9] Gram-positive organsisms, such as *Staphylococcus saprophyticus* and *Enterococcus* species, are uncommon but potential causes.[10,11] Although *E. coli* is still implicated in complicated UTIs, it causes less than 50% of these infections. The bacteria responsible for complicated infections can be more varied than with uncomplicated infections, and some complicated infections may be due to highly resistant organisms such as *Enterobacter* species and *Pseudomonas aeruginosa*.[12]

PATHOPHYSIOLOGY

There are three potential ways for bacteria to enter into the urinary tract and cause infection: the ascending, hematogenous, and lymphatic pathways. The most common route of infection is via the ascending pathway. KEY CONCEPT Due to the inherently short urethra and proximity to the perirectal area, bacteria often colonize the female urethra. The ascending pathway of infection involves ascention of colonized bacteria upward into the bladder, leading to acute cystitis[13] (Figure 79–1). Once in the bladder, bacteria may continue to ascend the urinary tract via the ureters and cause upper UTIs as well.

The hematogenous route involves the seeding of the urinary tract with pathogens carried through the blood from a distant site of infection. For example, *Staphylococcus aureus* bacteremia is known to cause UTIs and renal abscesses via the hematogenous route.[14] However, less than 5% of all UTIs are thought to be related to hematogenous spread. The lymphatic pathway is least understood because it is uncertain that bacterial transmission occurs in this manner.

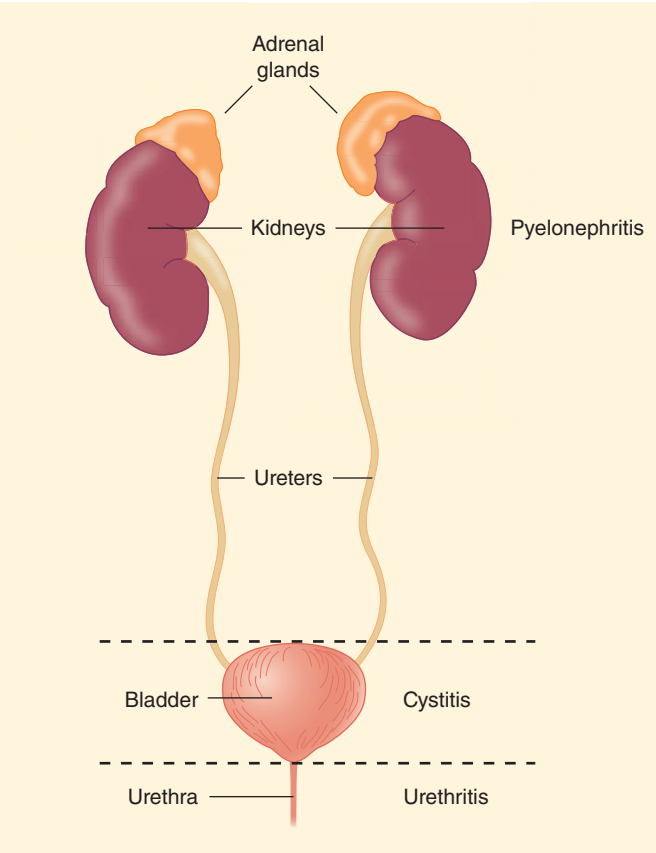

FIGURE 79–1. Anatomy and associated infection of the urinary tract. (From Sprandel KA, Lesch CA, Rodvold KA. Lower urinary tract infection. In: Schwinghammer TL (ed). 6th ed. New York: McGraw-Hill; 2005; 315; with permission.)

Host Defense Mechanisms and Risk Factors

Urine possesses numerous characteristics unsuitable for bacterial metabolism and growth, such as low pH, high urea concentration, and high osmolality. The presence of bacteria in the bladder stimulates an urge to urinate to void the bladder and release the bacteria. In addition, innate host response and adaptive immunity are defense mechanisms against bacterial infections, including UTIs.[15]

There are several risk factors for development of UTIs.[7] Common risk factors for uncomplicated infections in women include sexual intercourse, use of a cervical diaphragm or spermicidal jellies, diabetes, and pregnancy.[16–18] Risk factors in men include not being circumcised and, in older men, prostatic hyperplasia. In complicated infections, urinary tract obstruction is a common risk factor for both men and women. Vesicouretal reflux (VUR), which can result from obstruction or congenital abnormalities, results in urine being forced from the ureters into the kidneys, which can also predispose to infection.[19,20] Other risk factors common to both men and women include urologic instrumentation, urethral catheterization, renal transplantation, and neurogenic bladder.[21,22]

CLINICAL PRESENTATION AND DIAGNOSIS

Signs and symptoms of lower UTIs include increased urinary frequency, urgency, dysuria, nocturia, and supraputic heaviness. Systemic signs and symptoms are uncommon with lower UTIs. By contrast, patients with pyelonephritis often present with systemic signs and symptoms, such as fever, chills, flank pain, nausea and vomiting, and elevated white blood cell count. Older adults often do not present with traditional signs and symptoms of a UTI due to the naturally impaired ability of their immune systems to mount a typical reponse to infections. Instead, they may experience altered mental status, poor appetite, and incontinence.

Table 79–1

Quantitative Diagnostic Criteria for UTIs

Condition	Quantitative Measure
Asymptomatic bacteriuria	• 2 consecutive urine cultures with the same organism greater than or equal to 10^5 CFU/mL in asymptomatic patients
UTI	• ≥ 10^5 CFU/mL in a symptomatic woman[a] • ≥ 10^3 CFU/mL in a symptomatic man • Any growth of bacteria on suprapubic catheterization in a symptomatic patient
Catheter-associated UTI	• ≥ 10^3 CFU/mL of at least 1 pathogenic species in a symptomatic patient • ≥ 10^5 CFU/mL of at least 1 pathogenic species in any patient regardless of symptoms

[a]Some women may have signs and symptoms of a UTI but less organisms on culture results. Treatment is still indicated for these patients.

CFU, colony-forming unit; UTI, urinary tract infection.

The diagnosis of a UTI should generally be based on signs and symptoms in conjunction with laboratory tests to determine bacterial counts in the urine. Bacteriuria, defined as the presence of bacteria in the urine, does not always represent true infection. Asymptomatic bacteriuria is the isolation of a quantitative amount of bacteria from an appropriately collected urine specimen in a patient without signs and symptoms of a UTI.[23] While a full discussion of asymptomatic bacteriuria is beyond the scope of this chapter, it is important to note that it should only be treated with antimicrobial therapy in very selected circumstances, and not in premenopausal, nonpregnant women. To help diagnose true UTIs, quantitative diagnostic criteria have been developed based on the amount of bacteria present in the urine combined with the presence or abscense of infectious signs and symptoms (Table 79–1). A urinalysis is a microscopic examination of the urine and can be helpful to aid in diagnosis. Common abnormalities associated with UTIs seen on urinalysis can be seen in the Clinical Presentation and Diagnosis of UTIs textbox. In particular, the presence of white blood cells (pyuria) and leukocyte esterase (by-products of white blood cells) will almost always be seen in patients with UTIs. In addition, the presence of nitrites, which are formed by many of the etiologic gram-negative pathogens associated with UTIs, is usually seen. A urine culture is considered the gold standard for confirmatory diagnosis of a UTI in symptomatic patients.

TREATMENT

KEY CONCEPT The goals of treatment are to eradicate the causative pathogen, prevent or treat consequences of infection, administer appropriate empiric antimicrobial therapy or targeted therapy based on culture results, and prevent recurrence of infection.

Antimicrobial therapy is the cornerstone of treatment in symptomatic UTIs. Ideally, the selected antimicrobial should be well tolerated, require few total doses, achieve adequate concentrations in the urinary tract, possess few drug interactions, have wide therapeutic index, and have good oral bioavailability.

Clinical Presentation and Diagnosis of UTIs

General

- Most otherwise healthy women present with local signs and symptoms, such as dysuria and increased urgency and frequency.
- Patients with lower UTIs rarely present with systemic signs and symptoms, whereas those with upper UTIs usually do.
- Elderly patients are often asymptomatic or present with altered mental status.
- More than 95% of uncomplicated UTIs are caused by a single organism, most commonly *E. coli*.

KEY CONCEPT Signs and Symptoms of Lower UTIs

LO 2

- Dysuria, gross hematuria, suprapubic heaviness, nocturia, increased urinary frequency, and urgency

KEY CONCEPT Signs and Symptoms of Upper UTIs

LO 2

- Fever, chills, nausea/vomiting, malaise, and flank pain

Laboratory Tests

Urinalysis abnormalities include:

- Pyuria typically greater than 10 white blood cells/mm^3 urine (10×10^6/L)
- Bacteriuria, usually greater than 10^5 CFU organisms/mL (10^8 CFU/L)
- Presence of nitrites
- Presence of leukocyte esterase
- Bacterial urine culture
- Gold standard for diagnosis in a symptomatic patient

In addition, the empiric antimicrobial should be sufficiently narrow in antimicrobial spectrum to be unlikely to cause collateral damage (the ecological adverse effects of antimicrobial therapy).[1]

Nonpharmacologic Therapy

Several nonpharmacologic therapies have been proposed for prevention of UTIs with varying degrees of supportive evidence.

Patient Encounter Part 1

KB is a 32-year-old woman who presents to her primary care physician with complaints of a 3-day history of burning and pain upon urination and increased urinary frequency and urgency. She denies vomiting, fever, nausea, or flank pain. She has no significant past medical history. The physician orders a urinalysis to be done in the office.

What signs and symptoms are suggestive of a lower urinary tract infection (UTI)?

Would you classify this patient as noncomplicated or complicated UTI?

What additional patient information is required before creating an appropriate treatment plan for this patient?

Large volumes of cranberry juice have been associated with a decrease in the number of recurrent UTIs over a year period in small, randomized controlled trials, but efficacy is uncertain in the general population and with smaller intake volumes.[24–26] Probiotics such as *Lactobacillus* spp. lower urinary pH and may reduce the growth of pathogenic bacteria and show promise in preventing recurrent UTIs in women.[27] Although uncommonly used, topical estrogen replacement therapy has been shown to significantly decrease the incidence of UTIs in postmenopausal women as compared with placebo.[28] Methenamine hippurate and methenamine mandelate are hydrolyzed in acidic urine to the antimicrobial formaldehyde and are effective in preventing UTIs in patients without renal tract abnormalities.[29] Although several of these therapies show promise in the treatment of UTIs, their roles in therapy are currently unclear due to overall limited evidence.

Pharmacologic Therapy

Table 79–2 reviews oral and intravenous (IV) antibiotics frequently used to treat UTIs with comments on their use, and Table 79–3 reviews frequency, duration, and doses of oral antibiotics used commonly for outpatient treatment of UTIs.

Table 79–2

Commonly Used Antimicrobial Agents for the Treatment of UTIs

Agent	Comments
Oral Therapy	
Penicillins	
Amoxicillin Amoxicillin-clavulanic acid	Amoxicillin is no longer recommended for empiric therapy due to increasing *E. coli* resistance, but can be considered for targeted therapy. Amoxicillin-clavulanic acid can be considered for empiric therapy if a β-lactam must be used.
Pivmecillinam	Pivmecillinam is a prodrug of mecillinam and is recommended for treatment of acute cystitis. It should be avoided in patients with suspected pyelonephritis. Neither pivmecillinam nor mecillinam is currently approved for use by the US FDA.
Cephalosporins	
Cephalaexin Cefaclor Cefadroxil Cefixime Cefpodoxime Cefuroxime	Oral cephalosporins can be used as alternative therapies for the empiric treatments of UTIs, but they are less effective and have more adverse effects compared to nitrofurantoin and TMP/SMX. Concern also exists for use of these agents as a first-line option for uncomplicated cystitis therapy due to potential selection of cephalosporin-resistant organisms.

(Continued)

Table 79–2

Commonly Used Antimicrobial Agents for the Treatment of UTIs (*Continued*)

Agent	Comments
Fluoroquinolones	
Ciprofloxacin Levofloxacin	Fluoroquinolones are highly effective in the treatment of acute cystitis and pyelonephritis, but bacterial resistance is increasing. They should not be used empirically for acute cystitis due to the risk of collateral damage, unless a first-line agent cannot be used. They are first-line agents for pyelonephritis if *E. coli* resistance in the area is < 10%. Avoid in pregnancy and children. Moxifloxacin should not be used due to limited urinary excretion.
Miscellaneous	
Trimethoprim-sulfamethoxazole	Considered a first-line option for acute cystitis if *E. coli* resistance in the area is < 20%. A 3-day treatment regimen is recommended. It can also be used as prophylaxis for recurrent infections. Generally well tolerated and low cost but increasing resistance rates above 20% in certain regions. Its use may be precluded in patients with sulfa allergies.
Nitrofurantoin	Broad-spectrum agent with a low-risk of collateral damage. Does not penetrate renal tissue well, so should not be used for pyelonephritis. It is considered a first-line agent for acute cystitis and a 5-day treatment is recommended. This agent is effective in treatment and prophylaxis in patients with uncomplicated or recurrent lower tract UTIs. Traditionally, the Beers criteria recommended to avoid use in CrCl < 60 mL/min due to limited urine concentrations, but recent evidence suggests it is effective even with a CrCl as low as 30 mL/min.
Fosfomycin	First-line, single-dose therapy for uncomplicated cystitis. Has been recommended for empiric therapy since resistance rates are low but may have inferior efficacy when compared with short courses of other oral antibiotic agents. Possesses a broad-spectrum of activity, so is sometimes used to treat multidrug-resistant organisms, including ESBL-producing organisms.
Parenteral Therapy	
Aminoglycosides	
Amikacin Gentamicin Tobramycin	Gentamicin and tobramycin given as a consolidated 24-hour dose are recommended as a one-time dose for the treatment of outpatient pyelonephritis, followed by oral antimicrobials, when resistance rates preclude the empiric use of other agents. They can also be used for empiric inpatient treatment of pyelonephritis. Amikacin generally is reserved for multidrug-resistant bacteria.
Penicillins	
Ampicillin Ampicillin-sulbactam Piperacillin-tazobactam	These agents can be used for the treatment of pyelonephritis in the inpatient setting.
Cephalosporins	
Ceftriaxone Ceftazidime Cefepime	Ceftriaxone is recommended as an initial dose for the treatment of outpatient pyelonephritis when resistance rates preclude the empiric use of other agents. Ceftriaxone and other extended-spectrum cephalosporins can be used in the empiric treatment of pyelonephritis in the inpatient setting.
Carbapenems	
Doripenem Ertapenem Imipenem-cilastatin Meropenem	Broad-spectrum agents that can be used in the empiric treatment of pyelonephritis in the inpatient setting when multi-drug resistance is suspected.
Fluoroquinolones	
Ciprofloxacin Levofloxacin	IV dosage forms are considered first-line agents for pyelonephritis if *E. coli* resistance in the area is < 10%. These agents have broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide high urine and tissue concentrations. Switch to oral therapy when possible due to excellent bioavailability. Resistance rates are increasing in the United States, so often cannot actually be used as a first-line therapy.

CrCl, creatinine clearance; ESBL, extended-spectrum β-lactamase; FDA, Food and Drug Administration; IV, intravenous; TMP/SMX, trimethoprim-sulfamethoxazole; UTI, urinary tract infection.

▶ *Uncomplicated UTIs*

Cystitis Because patients with uncomplicated acute cystitis rarely manifest systemic signs and symptoms of infection, treatment is generally provided in the outpatient setting.[1] Patients are subsequently monitored for resolution of signs and symptoms. LO 5 KEY CONCEPT Uncomplicated UTIs are usually managed with a short-course antimicrobial therapy involving one-dose, 3-day, or 5-day regimens depending on the clinical factors involved. Because urine culture results take several days for complete results, empiric treatment in the outpatient setting will often be complete prior to obtaining final culture results. Therefore, urine cultures are rarely obtained.[1,30]

For acute uncomplicated UTIs, there are three primary oral empiric treatment options: one dose of fosfomycin, a 3-day course of trimethoprim-sulfamethoxazole (TMP/SMX), or a 5-day course of nitrofurantoin.[1] Due to increasing antimicrobial resistance to TMP/SMX, empiric therapy with this agent should only be considered if local resistance rate to *E. coli* is less than 20%.[1,9,31] Fluoroquinolone (as 3-day regimens) and oral beta-lactam antimicrobials (3–7-day regimens) can also be used for empiric therapy, but should be relegated for use only when one of the three primary treatment options cannot be utilized. Fluoroquinolones are broad-spectrum antimicrobials and have a high propensity to cause collateral damage. Some β-lactams

Table 79–3

Overview of Outpatient, Oral Antimicrobial Therapy for Acute Cystitis, Pyelonephritis, and Prostatitis

Indications	Antibiotic	Adult Dose[a]	Frequency	Duration[b]
Acute Cystitis				
First-line options	Nitrofurantoin monohydrate/ macrocrystals	100 mg	Every 12 hours	5 days
Alternative options:	Trimethoprim-sulfamethoxazole	One DS[c] tablet	Every 12 hours	3 days
	Fosfomycin	3000 mg	One-time dose	1 day
	Pivmecillinam[d]	400 mg	Every 12 hours	3–7 days
	Ciprofloxacin	250 mg	Every 12 hours	3 days
	Levofloxacin	250 mg	Every 24 hours	3 days
	Amoxicillin-clavulanic acid	500 mg	Every 8 hours	3–7 days
	Cefdinir	100 mg	Every 12 hours	3–7 days
	Cefaclor	250–500 mg	Every 8 hours	3–7 days
	Cefpodoxime-proxetil	100 mg	Every 12 hours	3–7 days
Recurrent infections—continuous prophylaxis	Trimethoprim-sulfamethoxazole	½ SS[e] tablet	Every 24 hours	6 months
	Trimethoprim	100 mg	Every 24 hours	6 months
	Ciprofloxacin	125 mg	Every 24 hours	6 months
	Nitrofurantoin	50 *or* 100 mg	Every 24 hours	6 months
	Cefaclor	250 mg	Every 24 hours	6 months
	Cephalexin	125 mg	Every 24 hours	6 months
Pyelonephritis				
Outpatient treatment	Ciprofloxacin	500 mg	Every 12 hours	7 days
	Ciprofloxacin (extended release)	1000 mg	Every 24 hours	7 days
	Levofloxacin	750 mg	Every 24 hours	5 days
	Trimethoprim-sulfamethoxazole	One DS[c] tablet	Every 12 hours	14 days
Prostatitis	Ciprofloxacin	500 mg	Every 12 hours	2–4 weeks[f]
	Levofloxacin	500 mg *or* 750 mg	Once daily	2–4 weeks[f]
	Trimethoprim-sulfamethoxazole	One DS[c] tablet	Every 12 hours	2–4 weeks[f]

[a]Majority of listed antimicrobial agents require dosage adjustment in patients with significant renal dysfunction.

[b]Duration of therapy may be longer if treating complicated infections.

[c]DS, double strength (160 mg trimethoprim/800 mg sulfamethoxazole).

[d]Not approved for use by the US FDA.

[e]SS, single strength (80 mg trimethoprim/400 mg sulfamethoxazole).

[f]Treatment should be 6–12 weeks if treating chronic prostatitis.

are also broad-spectrum, but are also less efficacious and have a higher incidence of adverse effects compared to the three primary treatments. Ampicillin and amoxicillin should not be considered for empiric therapy due to low efficacy and high rates of resistance.[1]

▶ *Acute Pyelonephritis*

Patients experiencing acute pyelonephritis may be treated in either the outpatient or inpatient settings. In particular, patients who may be dehydrated due to poor fluid intake or severe nausea and vomiting, or those with unstable vital signs should receive inpatient treatment.

Unlike patient with acute cystitis, urine culture and susceptibility testing should always be performed in patients experiencing pyelonephritis. For patients who can be treated as outpatients, oral fluoroquinolones as a 5- or 7-day regimen are the mainstay of therapy if local *E. coli* resistance is less than 10% (see Table 79–3 for specific regimens). A one-time initial dose of IV ciprofloxacin (400 mg) can also be considered. For patients who reside in areas where resistance is greater than 10%, oral fluoroquinolones can still be utilized, but an initial dose of IV ceftriaxone (1 gram) or a consolidated 24-hour dose of an aminoglycoside should be given. The purpose of this initial IV dose is to provide long-acting empiric coverge while awaiting urine culture results. TMP/SMX can be used as a 14-day treatment, but only if susceptibility is confirmed. If TMP/SMX is used empirically, the initial IV dose of ceftriaxone or an aminoglycoside must be given. Another alternative regimen is an oral beta-lactam for 10 to 14 days given with the initial IV dose of ceftriaxone or an aminoglycoside. For patients who require empiric inpatient treatment, therapy with one of four general options is recommended: a fluoroquinolone alone; an aminoglycoside with or without ampicillin; an extended-spectrum penicillin or cephalosporin with or without an aminoglycoside; or a carbapenem. Local resistance patterns should be examined to determine appropriate empiric therapy in this case.[1,32,33]

Special Populations

▶ *Pregnant Women*

Pregnant women are predisposed to UTIs due to changes in the urinary tract, including alterations in amino acid and other nutrient concentrations in the urine and physiologic changes such as reduced bladder tone and dilation of the renal pelvis and ureters.[34,35]

UTIs during pregnancy can result in serious complications, such as fetal death, labor complications, mental retardation, and developmental delay.[36,37] Because of these risks, screening for UTIs during pregnancy is recommended, and patients should receive treatment regardless of symptoms.[16,38] Fluoroquinolones are pregnancy category C and should generally be avoided due to their ability to inhibit cartilage and bone development.

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Overweight (body mass index 28 kg/m^2)

FH: Mother living with hypertension; father living with chronic obstructive pulmonary disease, diabetes mellitus type 2, and dyslipidemia

SH: Unmarried, sexually active with two partners in last 6 months, occupation: elementary school teacher

Allergies: Bactrim (rash)

Meds: Norethindrone 0.5 mg/ethinyl estradiol daily

ROS: (+) dysuria, urinary frequency; (–) fever, nausea, vomiting, flank pain

PE:

VS: BP 122/74 mm Hg, P 78 beats/min, RR 16 breaths/min, T 37.2°C

CV: RRR, normal S1, S2; normal findings

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly, heme (–) stool

Lab: Within normal limits including blood glucose; (–) pregnancy test

Urinalysis: Greater than 200 white blood cells/mm^3 (200 × 10^6/L); urine nitrates positive; leukocyte esterase positive

Urine gram stain: Gram-negative rods, more than 10^5 CFU/mL (10^8 CFU/L)

Local resistance of *E. coli* to TMP/SMX and ciprofloxacin is 18% and 7%, respectively

Given this additional information, what is your assessment of the patient's condition?

Identify your treatment goals for the patient.

What nonpharmacologic and pharmacologic alternatives are available for the patient?

TMP/SMX is pregnancy category D and should also be avoided due to the potential for congenital malformations and an increased risk of neonatal kernicterus. Nitrofurantoin is category B and can be safely used during pregnancy except in the last 30 days, where it should be avoided due to an increased risk of neonatal jaundice. Most β-lactams are pregnancy category B and can be safely used, and are historically considered first-line options for pregnant patients. Fosfomycin is pregnancy category B and can be considered, but less clinical experience exists.[39] In pregnant patients who do experience UTIs, follow-up usually consists of a urine culture 1 to 2 weeks after completion of therapy, then subsequent monthly urine cultures until birth.

► *Catheterized Patients*

Catheter-associated urinary tract infections (CA-UTIs) are common in patient with an indwelling urinary catheter.[21,40] Bacteria may be introduced into the bladder via the catheter by colonization and direct introduction during catheterization. UTIs as a result of an indwelling catheter are common and occur at a rate of 3% to 8% for each day the catheter is present.[40]

The primary treatment of CA-UTIs is removal and discontinuation of the catheter if possible. In patients without signs and symptoms of infection, removal of the catheter is likely sufficient, and antimicrobials may be withheld. In patients who are symptomatic, antimicrobials should be administered. In all patients, if the catheter cannot be permanently discontinued, a new catheter should be inserted if the previous catheter has been in place for longer than 2 weeks. Empiric antimicrobial regimens for the treatment of CA-UTIs have not been well defined, and treatment should be based on local susceptibility patterns. Results from urinalyses are often difficult to interpret in patients with indwelling catheters as the white blood cell count is usually elevated due to the presence of a foreign material. Urine cultures should always be obtained in CA-UTIs to guide ultimate selection of antimicrobials. In general, treatment for 7 days is sufficient if symptoms promptly resolve, and 10 to 14 days if symptoms are slower to resolve.[40]

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient's UTI. Your plan should include:

(a) a statement of the drug-related needs and/or problems,

(b) a patient-specific detailed therapeutic plan, and

(c) monitoring parameters to assess efficacy and safety.

► *UTIs in Men*

KEY CONCEPT UTIs occurring in men are usually due to a structural or functional abnormality of the urinary tract, and are therefore usually treated as a complicated infection.[41] For this reason, men should not generally be treated with a single dose or short course of therapy if diagnosed with a UTI. Antimicrobial therapy selection is similar to that used in otherwise healthy women, but men will usually receive 7 to 14 days of treatment.

LO 5

► *Prostatitis*

KEY CONCEPT Prostatitis is an inflammation of the prostate gland due to infection, usually from bacterial causes. Prostatitis can be acute or chronic, with acute being most common. It is uncommon in young men, but the incidence increases after the age of 30, and as many as half of all men will experience it at some point in their lifetimes. The pathogenesis of prostatitis is not completely understood, but likely involves the reflux of infected urine directly into the prostate gland.[42]

LO 2

Acute prostatitis differs from chronic in their respective signs and symptoms. KEY CONCEPT Patients with acute prostatitis present with fever, chills, localized rectal pain, dysuria, urinary straining, increased urinary frequency, and irritation. By contrast, patients with chronic prostatitis rarely present with these symptoms, but instead have difficulty urinating, perineal pain, recurrent UTIs, epididymitis, urethritis, or low back pain.[42] The pathogenic organisms responsible for prostatitis are similar to those that cause UTIs, with *E. coli* accounting for 75% of cases. *Klebsiella pneumoniae* and *Proteus mirabilis* can also be implicated, with other Enterobacteriaceae, such as *Pseudomonas*, being infrequent causes. *Staphylococcus* is a rare but possible cause as well. Some men may

LO 3

Table 79–4

Monitoring Parameters for Select Antibiotics Used in the Treatment of UTIs

Drug Class or Drug	What to Monitor	Frequency	Endpoint
Aminoglycosides	SCr, urine output	Every 24 hours	Prevention of nephrotoxicity manifested by a rise in SCr
	Aminoglycoside serum concentrations	Depends on duration of therapy. At least once weekly; more frequently if evidence of changing renal function	Trough serum concentrations < 2 mg/L or < 8 mg/L for amikacin, to decrease risk of nephrotoxicity and ototoxicity. Peak goal 5–6 mg/L. If using extended-interval dosing, monitoring should be based on the specific nomogram chosen
Nitrofurantoin	SCr	Only if renal function changing or unstable	Nitrofurantoin metabolites may accumulate in renal insufficiency and lead to neuropathy; avoid if CrCl < 30 mL/min
	Liver profile	Periodic monitoring	Prevention of cholestasis
Nitrofurantoin Tetracyclines Sulfonamides	SCr	Only if renal function changing or unstable	Decreases in glomerular filtrate rate can significantly decrease the urine concentration of these agents

CrCl, creatinine clearance; SCr, serum creatinine.

also experience prostatitis following infection with the sexually transmitted infections *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. The organisms responsible for chronic prostatitis are the same as acute. Chronic prostatitis usually occurs after a patient experiences acute prostatitis when the infecting organsism is not completely removed from the prostate. Therefore, the same pathogens responsible for acute prostatitis also cause chronic.[43]

Acute prostatitis can be readily diagnosed based on symptoms and the presence of significant bacteriuria. The diagnosis of chronic prostatitis is more difficult due to the infrequent prostate symptoms. It is generally diagnosed when a male patient has a recurring UTI with the same organism each time.[42]

The pharmacologic treatment approach to the management of prostatitis is similar to that of UTIs. Antimicrobial penetration of the prostate must be taken under consideration as many antimicrobials do not penetrate well into prostatic tissue and fluids, although concentrations are improved through the inflammatory process in acute prostatitis. KEY CONCEPT Fluoroquinolones and TMP/SMX are considered the treatments of choice for prostatitis due to their activity against the most common organsims and their penetration into prostatic fluid. However, as discussed previously, bacterial resistance to these agents is increasing. Alternative agents to be considered include cephalosporins (such as cephalexin or cefuroxime) and penicillins (such as amoxicillin/clavulanate). Initial therapy with an IV agent may be necessary in some cases of acute prostatitis based on the clinical stability of the patient. Acute prostatitis should be treated for at least 2 weeks and can be extended to 4 weeks if patients are slow to improve. Chronic prostatitis is treated for a longer period of time, usually 6 weeks, but possibly up to 12 weeks.[42,44,45]

LO 5

Outcome Evaluation for UTIs

- Monitor the patient for resolution of symptoms with the goal of 48 to 72 hours to resolution after start of antimicrobial therapy.
- Follow up with urine culture results to deescalate antimicrobial therapy if possible.
- Repeat urine culture is necessary only if symptoms do not acutely abate, reinfection, or recurrence occurs. Resistance rates to *E. coli* are increasing to antibiotics commonly prescribed for UTI, and certain isolates are multidrug resistant.[46]
- Depending on the chosen antibiotic therapy, evaluate the patient based on drug therapy monitoring parameters including those presented in Table 79–4 to optimize therapy and decrease incidence of adverse events.

Patient Care Process

Collect Information:

- Based on physical examination, signs and symptoms, review of systems, and urinalysis, determine whether the patient is experiencing a UTI.
- Obtain the patient's medication history and risk factors for an antibiotic-resistant infection.
- Assess patient renal function and other laboratory tests for antibiotic dosing and systemic complications.
- Identify potential sources of infection, such as indwelling urinary catheters.

Assess the Information:

- Based on urinalysis and gram stain (if available), determine whether the empiric antibiotic selection is appropriate.
- Based on culture and susceptibility data (if available), determine whether any changes should be made from your initial empiric antimicrobial selection (ie, resistance to the regimen initially selected). Also, assess if the empiric antimicrobial selected can be deescalated to a lower-spectrum agent.

(*Continued*)

Patient Care Process (*Continued*)

- Evaluate the patient's symptoms to determine response to the antimicrobial regimen chosen.
- Evaluate the patient for the presence of adverse drug events, drug allergies, and potential drug interactions.

Develop a Care Plan:

- Determine the optimal antibiotic dose and duration of therapy based on the patient and infection type (complicated vs uncomplicated).
- Determine whether the patient may benefit from prophylactic therapy (ie, recurrent UTIs secondary to chronic urinary catheterization due to paraplegia).
- Identify lifestyle modifications as needed to minimize UTI recurrence.

Implement the Care Plan:

- Prescribe and dispense the optimal antibiotic at the correct dose and duration.
- Recommend lifestyle changes, if needed.

Follow-up: Monitor and Evaluate:

- Stress the importance of complying with the prescribed antimicrobial regimen and to follow up with the health care provider if signs and symptoms recur.

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Abbreviations Introduced in This Chapter

BPH	Benign prostatic hypertrophy
CA-UTI	Catheter-associated UTI
CFU	Colony-forming units
CrCl	Creatinine clearance
ESBL	Extended-spectrum β-lactamase
IV	Intravenous
SCr	Serum creatinine
TMP/SMX	Trimethoprim-sulfamethoxazole
UTI	Urinary tract infection
VUR	Vesicouretal reflux

REFERENCES

1. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103–e120.
2. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40:643–654.
3. Fihn SD. Clinical practice. Acute uncomplicated urinary tract infection in women. N Engl J Med. 2003;349:259–266.
4. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014;28:1–13.
5. American Academy of Pediatrics, Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011;128:595–610.
6. Alper BS, Curry SH. Urinary tract infection in children. Am Fam Physician. 2005;72:2483–2488.
7. Ronald AR, Pattullo AL. The natural history of urinary tract infection in adults. Med Clin North Am. 1991;75:299–312.
8. Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: a meta analysis. Int J Antimicrob Agents. 2009;33(2):111–119.
9. Zhanel GG, Hisanaga TL, Laing NM, et al. Antibiotic resistance in *Escherichia coli* outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents. 2006;27:468–475.
10. Ronald A. The etiology of urinary tract infection: traditional and emerging pathogens. Am J Med. 2002;113:S14–S19.
11. Raz R, Colodner R, Kunin CM. Who are you—*Staphylococcus saprophyticus*? Clin Infect Dis. 2005;40:896–898.
12. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269–284.
13. Bran JL, Levison ME, Kaye D. Entrance of bacteria into the female urinary bladder. N Engl J Med. 1972;286:626–629.
14. Freedman LR. Experimental pyelonephritis. VI. Observation on susceptibility of the rabbit kidney to infection by a virulent strain of *Staphylococcus aureus*. Yale J Biol Med. 1960;32:272–279.
15. Medzhitov R. Toll-like receptors and innate immunity. Nat Rev Immunol. 2001;1:135–145.
16. U.S. Preventive Services Task Force. Screening for asymptomatic bacteriuria in adults: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med. 2008;149:43–47.
17. Nicolle LE. Urinary tract infection in diabetes. Curr Opin Infect Dis. 2005;18:49–53.
18. Harding GK, Zhanel GG, Nicolle LE, et al. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. N Engl J Med. 2002;347:1576–1583.
19. Habib S. Highlights for management of a child with a urinary tract infection. Int J Pediatr. 2012;2012:943653.
20. Shand DG, Nimmon CC, O'Grady F, Cattell WR. Relation between residual urine volume and response to treatment of urinary infection. Lancet. 1970;760(1):1305–1306.
21. Niël-Weise BS, van den Broek PJ. Urinary catheter policies for long-term bladder drainage. Cochrane Database Syst Rev. 2005;1:CD004201.
22. Sobel JD, Kaye D. Urinary tract infection. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases, 8th ed. Philadelphia, PA: Elsevier; 2014:74.
23. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40:643–654.
24. Jepson RG, Craig JC. Cranberries for preventing urinary tract infection. Cochrane Database Syst Rev. 2008;1:CD001321.

25. Salo J, Uhari M, Helminen M, et al. Cranberry juice for the prevention of recurrences of urinary tract infections in children: a randomized placebo-controlled trail. Clin Infect Dis. 2012;54:340–346.
26. Barbosa-Cesnik C, Brown MB, Buxton M, et al. Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trail. Clin Infect Dis. 2011;52:23–30.
27. Grin PM, Kowalewska PM, Alhazzan W, Fox-Robichaud AE. Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. Can J Urol. 2013 Feb;20(1): 6607–6614.
28. Raz R, Stamm WE. A controlled trial of intravaginal estriol in post-menopausal women with recurrent urinary tract infections. N Engl J Med. 1993;329:753–756.
29. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev. 2012;10:CD003265.
30. Miller LG, Tang AW. Treatment of uncomplicated urinary tract infections in an era of increasing antimicrobial resistance. Mayo Clin Proc. 2004;79:1048–1054.
31. Gupta K, Sahm DF, Mayfield D, et al. Antimicrobial resistance among uropathogens that cause community-acquired urinary tract infections in women: a nationwide analysis. Clin Infect Dis. 2001;33:89–94.
32. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet. 2012;380:484–490.
33. Rubenstein JN, Schaeffer AJ. Managing complicated urinary tract infections: the urologic view. Infect Dis Clin North Am. 2003;17:333–351.
34. Ovalle A, Levancini M. Urinary tract infections in pregnancy. Curr Opin Urol. 2001;11:55–59.
35. Christensen B. Which antibiotics are appropriate for treating bacteriuria in pregnancy? J Antimicrob Chemother. 2000;46:29–34.
36. McDermott S, Daguise V, Mann H, et al. Perinatal risk for mortality and mental retardation associated with maternal urinary tract infections. J Fam Pract. 2001;50:433–437.
37. Sheiner E, Mazor-Drey E, Levy A. Asymptomatic bacteriuria during pregnancy. J Matern Fetal Neonatal Med. 2009 May; 22(5):423–427.
38. Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40:643–654.
39. Reeves DS. Treatment of bacteriuria in pregnancy with single dose fosfomycin trometamol: a revew. Infection. 1992(suppl 4): S313–316.
40. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:625–663.
41. Naber KG, Bergman B, Bishop MC, et al. EAU guidelines for management of urinary and male genital tract infections. Urinary Tract Infection Working Group of the Health Care Office of the European Associated of Urology. Eur Urol. 2001;40:576–588.
42. Sharp VJ, Takacs EB, Powell CR. Prostatitis: diagnosis and treatment. Am Fam Physician. 2010;82(4):397–406.
43. Murphy AB, Macejko A, Taylor A, Nadler RB. Chronic prostatitis: management strategies. Drugs. 2009;69(1):71:84.
44. Lipsky BA, Byren I, Hoey CT. Treatment of bacterial prostatitis. Clin Infect Dis. 2010;50(12):1641–1652.
45. Wagenlehner FM, Naber KG. Current challenges in the treatment of complicated urinary tract infections and prostatitis. Clin Microbiol Infect. 2006;12(suppl 3):67–80.
46. Johnson JR, Johnston B, Clabots C, et al. *Escherichia coli* sequence type ST131 as the major cause of serious multidrug-resistant *E. coli* in the United States. Clin Infect Dis. 2010;51:286–294.

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80 Sexually Transmitted Infections

Marlon S. Honeywell and Evans Branch III

LEARNING OBJECTIVES

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

1. Analyze the behavioral considerations and assess the importance of contraception with regard to the contributing factors of sexually transmitted infections (STIs).
2. Apply the "patient-delivered partner therapy" method when recommending treatment for STIs.
3. Identify the patient populations that are typically affected by specific STIs.
4. Identify causative organisms for STIs.
5. Devise a list of the clinical signs and symptoms corresponding to each type of STI and classify patients based on recommended criteria.
6. Select appropriate diagnostic procedures for STIs.
7. Identify STI treatment regimens and recommend therapy when appropriate.
8. Design a patient care plan based on the monitoring parameters.

INTRODUCTION

Though we have made significant progress in science and medicine, longstanding problems of infectious disease continue to plague us.[1] Even with the discovery of newly improved antibiotics, sexually transmitted infections (STIs) have not been eradicated. Many have reemerged secondary to modern social trends of sexual activity, and some as a result of the human immunodeficiency virus (HIV) epidemic, socioeconomic concerns, and the global lack of preventive education. KEY CONCEPT Optimal detection and treatment of sexually transmitted diseases depend on counseling by a patient-friendly and knowledgeable clinician who can establish open communication with the patient.

LO 1 Since the correlation between risky sexual behavior and STIs is well documented,[2] most sexually active individuals will contract an infection at some point in their lives. Though inconsistent and incorrect condom use increases the probability of new STIs, counseling patients on the consistent use of condoms, spermicides, or diaphragms is an important component in reducing overall incidence.[3] Additionally, health care providers who manage persons at risk for STIs should counsel women in a timely fashion concerning the option for emergency contraception, when indicated. Mifepristone, misoprostol, oxytocin, and levonorgestrol have been employed in the United States for the prevention of unintended pregnancy.[4]

In addition to an increasing number of adolescents engaging in unsafe sexual practices, there is a high incidence of men who have sex with men (MSM) and women who have sex with women (WSW). Many MSM do not disclose their HIV status. In fact, MSM is documented as the risk group most severely affected by HIV in the United States. However, new infections within this group recently stabilized at approximately 26,000 new infections each year.[5] Although limited data are available with regard to STIs in WSW, transmission generally occurs through fisting, fingering, oral sex, or the use of sexual toys. Sharing penetrative items or employing practices involving digital vaginal or digital anal contact most likely represent the most common modes of transmission. This possibility is supported by reports of metronidazole-resistant trichomoniasis and genotype-specific HIV transmitted sexually between women who reported such behaviors and an increased prevalence of bacterial vaginosis (BV) among monogamous WSW.[6]

Sexual abuse in adolescents and children is becoming more ubiquitous in the United States. Children or adolescents with an STI should be evaluated for sexual abuse.[7] The identification of an STI in a child can have serious medical and legal implications; and is used to support the presence or allegation of abuse. In cases of abusive contact, commonly found infections include *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Abusive cases should be reported to Child Protective Services.

LO 3 Defined as a person who engages in the exchange of spouses for sexual activities, the emergence of "swingers" as a new category of at-risk patients has been seen in STI clinics throughout the world. In one Canadian clinic, swingers composed 40.8% of patients that rarely accessed STI health services.[8] Most swingers are likely to be diagnosed with HIV, herpes, chlamydia, or gonorrhea. To this end, although little data exists, swingers now represent a group with risky behaviors that must be identified and treated, when necessary.

LO 2 KEY CONCEPT Optimally, both sex partners should be treated simultaneously for an STI; however, this is difficult to accomplish. Clinics and health departments often proactively attempt dual treatment by providing a prescription for the partner to the index patient (the patient who is evaluated by a clinician), a practice commonly known as patient-delivered partner therapy. Medications or prescriptions should be accompanied by treatment instructions and appropriate warnings. Counseling regarding the appropriate use of condoms, cervical diaphragms, spermicides, and emergency contraception is also important to mitigate the occurrence of reinfection.

Accurate reporting of STIs is imperative to the evaluation of trends in sexual behaviors; reporting may be provider- or laboratory-based. State and local health departments may assist with the mechanism by which STI cases are reported in accordance with statutory requirements. Confidentiality should always be exercised in such cases.[9,10]

GONORRHEA

LO 4

A curable STI caused by the gram-negative diplococcus *Neisseria gonorrhoeae*, gonorrhea may be the second most commonly reported bacterial STI. Proper therapeutic management with antimicrobial agents is essential to eradicate this infection and prevent the development of associated sequelae such as a urethritis, cervicitis, or dysuria.

In the United States, over the past 5 years, an increase in the gonorrhea infections has been observed in both males and females; the increase was larger among males. The highest rate of gonococcal infection is seen within the 15- to 24-year-old age groups for both sexes; although more cases are reported in men. Approximately 700,000 new cases occur annually in the United States.[9,10] In 2015, approximately 3.95 cases per person were reported. Factors associated with an increased risk of infection include ethnicity, low socioeconomic status, illicit drug use, and age. Targeted screening of young women, less than 25 years of age, who are at an increased risk has been correlated to gonorrhea control in the United States.[9] In fact, the risk of a cervical infection after a single episode of vaginal intercourse is approximately 50% and increases with multiple exposure. Furthermore, rates of reinfection are significantly higher among ethnic minorities.

PATHOPHYSIOLOGY

Attachment to mucosal epithelium, mediated in part by pili and opa (outer membrane opacity proteins), is followed by penetration of *N. gonorrhoeae* through epithelial cells into the submucosal tissue within 24 to 48 hours. A vigorous response by neutrophils begins with sloughing of the epithelium, development of submucosal microabscesses, and exudation of pus. Stained smears usually reveal large numbers of gonococci within a few neutrophils, whereas most cells contain no organisms.[11]

DIAGNOSIS

LO 6

Several laboratory tests are available to aid in the diagnosis of gonorrhea and include Gram-stained smears, endocervical or vaginal specimens, culture, or the DNA hybridization probe.

Patient Encounter 1, Part 1

RT is a 58-year-old man who visits a clinic complaining of profuse urethral discharge, increased frequency of urination, a persistent sore throat, and swollen testicles for the past several days. The patient admits to having sexual intercourse with his wife and three other women without barrier contraception (condoms). He also admits to having sexual intercourse with one of the other women for more than 12 months.

What information is suggestive of gonorrhea?

What potential risk factors for STIs are present?

What other diagnostic tests should be ordered?

Clinical Presentation of Gonorrhea[9,10]

LO 5

General

- Purulent discharge
- Greater urinary frequency
- Persistent sore throat

Signs

- Painful or swollen testicles
- Tubal scarring

Symptoms

Men:

- May be asymptomatic, though acute urethritis is the predominant manifestation
- Urethral discharge and dysuria, usually without urinary frequency or urgency
- When compared with nongonococcal urethritis, the discharge in gonococcal urethritis is generally more profuse and purulent
- Pain during urination

Women:

- Cervicitis, urethritis, increased vaginal discharge, dysuria, and intermenstrual bleeding
- Pain during urination
- Abdominal pain

Patient Encounter 1, Part 2

PMH: Hypertension, diabetes, hyperlipidemia, asthma; no prior history of STIs; no drug allergies noted

Meds: Amlodipine 10 mg by mouth daily; furosemide 40 mg by mouth daily; metformin 500 mg by mouth three times daily; glipizide XL 5 mg by mouth daily; simvastatin 40 mg by mouth at bedtime; Advair HFA 250/50 2 inhalations by mouth twice daily

FH: Mother has diabetes and hypertension. Father is deceased.

SH: Admits to having unprotected sex with wife and another woman. Does not smoke; drinks alcohol occasionally

ROS: C/o urethral discharge and swollen testicles

PE:

VS: BP 150/88 mm Hg, post prandial glucose 132 mg/dL (7.3 mmol/L), total cholesterol 198 mg/dL (4.86 mmol/L), P 73 beats/min, T 37.0°C (98.6°F)

Lab: Urethral discharge swab revealed *N. gonorrhoeae*; rapid plasma reagin (RPR) test was positive

Given this additional information, what is your assessment of the patient's condition?

What consideration should be given to other STIs?

Identify your treatment goals for this patient.

What pharmacologic alternatives are available for this patient?

A gram stain of a male urethral specimen that demonstrates polymorphonuclear leukocytes with intracellular gram-negative diplococci may be considered diagnostic in symptomatic men. A gram-negative stain is insufficient for ruling out infection in asymptomatic men.[9] Additionally, gram stain of endocervical, pharyngeal, or rectal specimens are also insufficient to detect infections. All patients who test positive for gonorrhea should be tested for other STIs, including chlamydia, syphilis, and HIV.

TREATMENT

The desired outcome is complete eradication of *N. gonorrhoeae* and avoidance of sequelae.

Pharmacologic Therapy[4,9,12,13]

KEY CONCEPT Patients infected with gonorrhea are often coinfected with *C. trachomatis* and should receive concurrent therapy to eradicate both organisms. Treatment is now complicated by the development of resistance to *N. gonorrhoeae.* To mitigate the probability of resistance, the most recent guidelines recommend the combination of cephalosporins and azithromycin.[9] Use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages associated with single dose therapy; and the substantially higher resistance of gonococcus to tetracyclines. Ceftriaxone and azithromycin should be administered together on the same day to improve results. However, treatment failures involving cephalosporins have been noted in Hawaii and Asian countries. As such, clinicians should determine whether sexual activity may have occurred in these countries before recommending antibiotic therapy. Fluoroquinolones should not be prescribed for infections in MSM, in those with a history of recent foreign travel or for infections acquired in California, Hawaii, and Asian countries or for infections in other areas with increased gonococcal resistance.[14,15] First-line treatment for gonorrhea in most countries is third-generation cephalosporins, and in some cases, spectinomycin and azithromycin have been used.[16]

LO 7

Though unavailable in the United States, spectinomycin is expensive and has poor efficacy against pharyngeal infections. Doxycycline 100 mg orally (PO) twice daily for 7 days may be used in combination with ceftriaxone when an allergy to azithromycin is noted. The mechanism of resistance appears to be associated with a mosaic penicillin-binding protein in addition to other chromosomal mutations previously found to confer resistance to β-lactam antimicrobials. To reduce the prevalence of cephalosporin resistance, strong antimicrobial management programs, expanding surveillance networks and procedures, and STI control and prevention are warranted.

Oral hormonal contraception has been evaluated to determine if it deters the acquisition of gonococcal infections in women. Though transmission of *N. gonorrhoeae* is poorly understood, one study suggested that oral hormonal contraception may lessen the probability of infection.[17] More studies are required to support this theory as a viable option for prevention.

Treatment of gonorrhea may vary according to clinical presentation and is indicated as follows[9]:

Uncomplicated Gonococcal Infection of the Cervix, Urethra, and Rectum[a]: Ceftriaxone 250 mg intramuscularly (IM) *or* cefixime 400 mg PO *or* single-dose injectable cephalosporin regimens *plus* azithromycin 1 g PO *or* doxycycline 100 mg PO twice daily for 7 days. When ceftriaxone is unavailable, ceftizoxime 500 mg IM *or* cefoxitin 2 g IM with probenecid 1 g *or* Cefotaxime 500 mg IM have also been used.[15] Though several alternative agents possess notable activity, they should not be used if pharyngeal infection is suspected. Spectinomycin has also been prescribed.

Uncomplicated Gonococcal Infection of the Pharnyx: Ceftriaxone 250 mg IM plus azithromycin 1 g PO.

MSM or Heterosexuals with a History of Recent Travel[a]: Ceftriaxone 250 mg IM *or* cefixime 400 mg PO *plus* treatment for chlamydial infection, if it has not been ruled out.

Uncomplicated Gonococcal Infection of the Pharyngeal, Cervix, Urethra, or Rectum: Ceftriaxone 250 mg IM plus azithromycin 1 g PO or doxycycline 100 mg PO twice daily for 7 days. Single-dose injectable cephalosporins which are generally effective against uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime 500 mg IM, cefoxitin 2 g IM with probenecid 1 g PO, and cefotaxime 500 mg IM. None of the aforesaid injectable cephalosporins offer any advantage over ceftriaxone.

Coverage for Coinfection with *C. trachomatis*: Azithromycin 1 g PO as a single dose *or* doxycycline 100 mg PO twice daily for 7 days. Since most gonococcal infections in the United States are susceptible to azithromycin and doxycycline, routine cotreatment might hinder the development of resistance.

Treatment of Gonorrhea in Special Situations

Uncomplicated infections of the cervix, urethra, and rectum can be treated with one of the following regimens in adults:

▶ *Recommendations During Pregnancy*

- Pregnant women should be treated with a recommended or alternative cephalosporin. For women who cannot tolerate a cephalosporin, azithromycin 2 g PO may be prescribed. For treatment of presumptive or diagnosed *C. trachomatis*, azithromycin or amoxicillin is recommended. When allergies or other issues preclude treatment, consultation with an infectious diseases specialist is recommended.

▶ *Allergy, Tolerance, or Adverse Reactions*

- When cephalosporin allergy is a consideration, single doses of PO or IM gemifloxacin 320 mg *plus* azithromycin 2 g may be used.
- Doxycycline and fluoroquinolones are contraindicated.

[a]Regimens are given for one dose only.

Patient Encounter 1, Part 3

Unprotected sex is a major risk factor for contracting STIs. Although the purulent discharge and pain during urination are consistent with gonorrhea infection, a positive urethral swab coupled with an incubation period consistent with gonorrhea confirms the diagnosis. A serologic test for HIV should be performed. Although gonorrhea has been confirmed in this patient, infection with *C. trachomatis* occurs commonly in this setting. The expedited partner treatment approach should be employed, and treatment should effectively cover gonorrhea and chlamydia.

If this patient has a true allergy to penicillin and cephalosporins, how would the therapeutic management of the identified problems change?

Recommendations for Disseminated Gonococcal Infection (Regimens Should Be Continued for 24–48 Hours): Ceftriaxone 1 g IM or intravenous (IV) every 24 hours *plus* azithromycin 1 g PO *or* cefotaxime 1 g IV every 8 hours *or* ceftizoxime 1 g IV every 8 hours plus azithromycin 1 g PO. Continue regimens for 24 to 48 hours after improvement is noted.

Uncomplicated Infections of the Cervix, Urethra, and Rectum in Children Less Than 45 kg: Ceftriaxone 250 mg IM as a single dose *or* spectinomycin 40 mg/kg IM as a single dose (not to exceed 2 g).

Gonococcal Conjunctivitis: Ceftriaxone 1 g IM once plus azithromycin 1 g PO for adults has demonstrated excellent response rates. Lavage of the infected eye(s) once with saline solution should also be considered. Since gonococcal conjunctivitis is uncommon and data is limited, consultation with an infectious-disease specialist should be considered.

Ophthalmia Neonatorum Prophylaxis: Erythromycin 0.5% ophthalmic ointment in each as a single application at birth. This medication should be instilled into both eyes, regardless of whether delivery is vaginal or cesarean. If erythromycin is unavailable, ceftriaxone may be used at a dose of 25–50 mg/kg IV or IM, not to exceed 125 mg in a single dose.

Gonococcal Scalp Access in Newborns: Ceftriaxone 25 to 50 mg/kg/day IV or IM in a single daily dose for 7 days or cefotaxime 25 mg/kg IV or IM every 12 hours for 7 days may be used. Both medications may be used for a duration of 10–14 days if meningitis is documented.

Outcome Evaluation

- Order diagnostic test for gonorrhea. If positive, recommend antibiotics that cover gonorrhea and chlamydia.
- Subsequent to treatment, expect the eradication of organisms responsible for gonorrhea and chlamydia.
- Monitoring is generally not required.

CHLAMYDIA

EPIDEMIOLOGY

LO4 LO3 Infection with *C. trachomatis* has increased dramatically in recent years. This bacterium is the most common cause of nongonococcal urethritis, accounting for as many as 40% of cases. In 2015, 1,526,658 cases of chlamydia were reported to the CDC; and an estimated 2.86 million infections occur annually. Many cases remain unreported because most people are asymptomatic and do not seek testing. Chlamydia is most common among young people. Almost two-thirds of new chlamydia infections occur among youth aged 15 to 24 years.

Substantial racial disparities in chlamydia infection exist, with a prevalence among non-Hispanic blacks 5.9 times the prevalence among non-Hispanic whites. Chlamydia is also common among MSM. Among MSM screened for rectal chlamydia infection, 3% to 10.5% were positive.

PATHOPHYSIOLOGY

C. trachomatis possesses characteristics resembling both bacteria and viruses. Its major membrane is comparable to that of gram-negative bacteria, although it lacks a peptidoglycan cell wall and requires cellular components from the host for replication. Chlamydia transmission risk is thought to be less than that of gonorrhea.

CLINICAL PRESENTATION AND DIAGNOSIS

LO6 Common tests used to diagnose *C. trachomatis* include the nucleic acid amplification test, culture, enzyme immunoassay, DNA hybridization probe, or the direct fluorescent monoclonal antibody test. Diagnosis has been confirmed in women through urine or swab specimen collected from the endocervix and in men using a urethral swab or urine specimen. Most women are asymptomatic; therefore, an annual screening or physical is necessary, as early detection may reduce rates of transmission.

TREATMENT[9,18]

Uncomplicated Genital

LO7 Azithromycin 1 g PO as a single dose *or* doxycycline 100 mg PO twice daily is suggested. Alternative recommendations include erythromycin 500 mg PO four times daily for 7 days *or* erythromycin ethylsuccinate 800 mg four times daily *or* levofloxacin 500 mg once daily for 7 days *or* ofloxacin 300 mg twice daily (or 600 mg once daily) for 7 days.

Anorectal Infection

Treatment for anorectal infection includes doxycycline 100 mg PO twice daily for 7 days or azithromycin 1 g PO as a single dose.

Chronic Reactive Arthritis

Doxycycline 100 mg PO twice daily plus rifampin 300 mg once daily for 6 months.

Uncomplicated Urethral, Endocervical, or Rectal Infection in Adults

The recommended adult regimen is azithromycin 1 g PO in a single dose *or* doxycycline 100 mg PO twice daily for 7 days. An alternate regimen *is* erythromycin ethylsuccinate 800 mg PO four times daily for 7 days *or* erythromycin base 500 mg PO four times daily for 7 days *or* levofloxacin 500 mg PO once daily for 7 days *or* ofloxacin 300 mg PO twice daily for 7 days.

The recommended regimen for pregnant patients is Azithromycin 1 g PO as a single dose *or* Amoxicillin 500 mg three times daily for 7 days *or* Erythromycin 500 mg four times daily for seven days *or* 250 mg four times daily for 14 days.

Alternate regimens include erythromycin base 500 mg PO four times daily for 7 days *or* 250 mg PO four times daily for 14 days *or* erythromycin ethylsuccinate 800 mg PO four times daily for 7 days *or* 400 mg PO four times daily for 14 days.

C. trachomatis Infection in Infants

Treatment of ophthalmia neonatorum or infant pneumonia should be with erythromycin base or ethylsuccinate 50 mg/kg/day PO divided into four doses daily for 14 days. An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants aged less than 6 weeks who were treated with this drug. Infants treated with erythromycin should be monitored for signs and symptoms of IHPS.

▶ *Infant Pneumonia Caused by* C. Trachomatis

Erythromycin base or ethylsuccinate 50 mg/kg/day PO divided into four doses daily for 14 days.

Clinical Presentation of Chlamydia[9,10,13]

General

- Asymptomatic

LO 5

Signs

- Beefy red cervix that bleeds easily (women)

Symptoms

- When present, the urethral discharge is watery and less purulent than that seen with acute gonococcal urethritis. Complications resulting from lack of treatment or inadequate treatment include: epididymitis (in males), and pelvic inflammatory disease (PID) including associated complications in women.

Other Diagnostic Tests

- Culture is usually positive for both chlamydia and gonorrhea.

Outcome Evaluation

- Order diagnostic test for chlamydia. If positive, recommend antibiotics that cover gonorrhea and chlamydia.
- Subsequent to treatment, expect the eradication of organisms responsible for gonorrhea and chlamydia.
- Monitoring is generally not required.

SYPHILIS

LO 4

Attributed to the spirochete *Treponema pallidum*, syphilis can have numerous and complex manifestations. Clinician familiarity, stage-specific diagnosis, and effective treatment are vital. Missed or inappropriately treated syphilis may result in cardiovascular complications, neurologic disease, or congenital syphilis.

EPIDEMIOLOGY AND ETIOLOGY

LO 3

Since the 1940s, the incidence of syphilis declined drastically following the introduction of penicillin; however, prevalence rose when HIV arrived from obscurity in the 1980s. In 2009, rates of primary and secondary syphilis increased for the tenth consecutive year, reaching the highest rate reported since 1995. Although increases have occurred mostly among men, in 2013, the rate of reported primary and secondary syphilis in the United States was 5.3 cases per 100,000 population. Additionally, from 2005 to 2015, the number of primary and secondary cases nearly doubled. The primary and secondary syphilis rate among black men was 5.2 times that among white men; the rate among black women was 13.3 times that among white women, emphasizing the need for enhanced preventive measures among blacks and MSM. The disparity among men and women has been observed across racial and ethnic groups and is highest in the South and among non-Hispanic blacks.[19]

PATHOPHYSIOLOGY

T. pallidum rapidly penetrates intact mucous membranes or microscopic dermal abrasions, and within a few hours, the organism enters the lymphatics and blood to produce systemic illness. During the secondary stage, examinations commonly demonstrate abnormal findings in the cerebrospinal fluid (CSF). As the infection progresses, the parenchyma of the brain and spinal cord may subsequently be damaged.

DIAGNOSIS AND CLINICAL PRESENTATION

Stages of Syphilis

▶ *Primary Syphilis*

LO 5 LO 6

Usually manifests as a solitary, painless chancre. Primary syphilis develops at the site of infection approximately 3 weeks after exposure to *T. pallidum*; the chancre is highly infectious.[9,20]

▶ *Secondary Syphilis*

Without appropriate treatment, primary syphilis will advance to secondary syphilis—a stage usually apparent from its clinical symptomatology. Symptoms include fatigue, diffuse rash, fever, lymphadenopathy, and genital or perineal condyloma latum. Additionally, the skin is most often affected, and a rash may present as macular, macropapular, or pustular lesions or may involve skin surfaces including the palms of the hands and soles of the feet.

▶ *Latent Syphilis*

Early Latent Usually occurs during the first year after infection and may be established in patients who have seroconverted, who had symptoms of primary or secondary syphilis, or who had sex with a partner with primary, secondary, or latent syphilis.

Late Latent Patients should be considered to have late latent syphilis if the aforementioned criteria (early latent) are not met. In both stages, patients are usually asymptomatic and the lesions noted in the primary and secondary phase usually resolve; however, individuals are still seropositive for *T. pallidum*.

Tertiary Syphilis Develops years after the initial infection and may involve any organ in the body.

Congenital Syphilis

Congenital syphilis is a condition in which the fetus is infected with *T. pallidum* as a result of the hematogenous spread from an infected mother, although transmission may also occur from direct contact with the infectious genitalia of the mother. Since the primary stage of syphilis is characterized by spirochetemia, infectious rates of the fetus are nearly 100% if the mother has primary syphilis.[20,21]

Diagnostic procedures include dark-field microscopy, nontreponemal exams[9,20] (ie, the Venereal Disease Laboratory [VDRL] and the rapid plasma reagin [RPR] test), and treponemal exams (ie, enzyme immunoassay, the *T. pallidum* hemagglutination test, the fluorescent treponemal antibody test, and the enzyme-linked immunosorbent assay [ELISA]).

TREATMENT

After confirming the diagnosis of syphilis, the desired outcome is a fourfold decrease in quantitative nontreponemal titers over a 6-month period and within 12 to 24 months after treatment of latent or late syphilis. An algorithm for the treatment of syphilis is shown in Figure 80–1.

With regard to neurosyphilis, a reduction in neurologic manifestations is desired, which may include seizures, paresis, meningitis, stroke, hyperreflexia, visual disturbances, hearing loss, neuropathy, or loss of bowel and bladder function. In late neurosyphilis, vascular lesions (meningovascular neurosyphilis) may also be observed; thus, a reduction in the number of

LO 6 LO 7

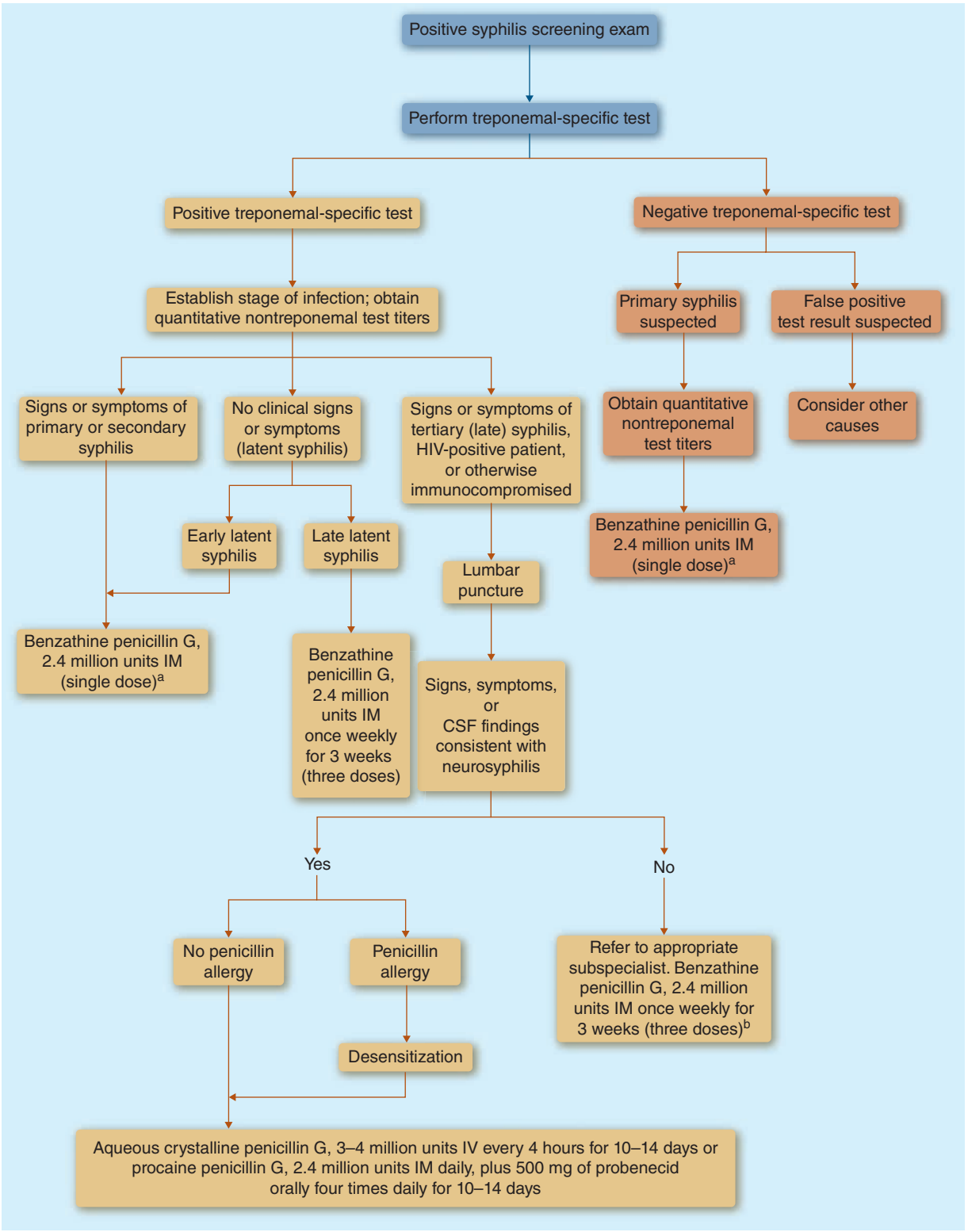

FIGURE 80–1. Treatment of syphilis. [a]Alternative treatments for nonpregnant penicillin-allergic patients: doxycycline 100 mg PO twice daily for 2 weeks, or tetracycline 500 mg four times daily for 2 weeks; limited data support ceftriaxone 1 g once daily IM or IV for 8 to 10 days; or azithromycin, 2 g PO (single dose). [b]Alternative treatments for nonpregnant penicillin-allergic patients: doxycycline, 100 mg PO twice daily for 4 weeks, or tetracycline 500 mg PO four times daily for 4 weeks. (CSF, cerebrospinal fluid; IM, intramuscularly.) (Reprinted with permission from Diagnosis and Management of Syphilis, July 15, 2003, Vol 68, No 2, American Family Physician Copyright © 2003 American Academy of Family Physicians, All Rights Reserved.)

Patient Encounter 2

JN is an HIV-positive man who complains of first observing the appearance of a "round sore" on his penis. He admits to disregarding the lesion; however, he is now experiencing fatigue, diffuse rash, fever, and perineal condyloma latum. He reports having unprotected sexual intercourse with one female and two male partners. He denies pain or itching at the original site of the lesion, dysuria, or frequent urination. Additionally, there appears to be no vesicles in the genital area.

What information is suggestive of syphilis?

What stage of syphilis is present?

What potential risk factors for STIs are present?

How should the diagnosis of syphilis be confirmed in this patient?

If the diagnosis of syphilis is confirmed, what therapeutic options exist for this patient?

observed lesions is warranted. A diminution in CSF white blood cell (WBC) (< $10 \times 10^3/mm^3$ [$10 \times 10^9/L$]) or protein levels (0.05 g/dL [0.5 g/L]) is also preferred.

Pharmacologic Therapy

KEY CONCEPT Parenterally administered penicillin is recommended for all stages of syphilis (Table 80–1). Although penicillin is the drug of choice, combinations of benzathine penicillin with procaine penicillin or oral penicillin preparations are not considered appropriate treatment regimens. Several reports demonstrated the misuse of the benzathine–procaine combination (Bicillin C-R) instead of the standard benzathine penicillin (Bicillin L-A) for treatment of syphilis.[20,22] Clinicians and purchasing agents should be aware of the similarities in product names to avoid errors in the prescribing and administration of these agents. Pertinent information germane to benzathine penicillin G is found in Table 80–1.

Alternative agents may be used in allergic individuals and include doxycycline, minocycline, tetracycline, or erythromycin base or stearate. Some patients (such as young children or pregnant women) may not respond favorably to alternative modalities or should not receive tetracyclines. Therefore, in patients who must be administered penicillin (ie, patients who are pregnant or have central nervous system [CNS] involvement) and are allergic, **desensitization** should be performed because penicillin as a treatment modality is far superior to alternatives.

Patients may experience fever, chills, tachycardia, and tachypnea, a condition commonly known as the Jarisch-Herxheimer reaction, an acute febrile reaction accompanied by headache, myalgia, fever, and other symptoms within the first 24 hours after the initiation of therapy. This reaction is postulated to occur secondary to spirochete lysis and proinflammatory cytokine cascades. Treatment is supportive and may include antipyretic and anti-inflammatory agents, as well as fluid resuscitation and bed rest.

▶ *Primary Syphilis*

Drug of Choice

Adults Benzathine penicillin, 2.4 million units IM as a single dose. Additional doses of benzathine penicillin or other antibiotics do not enhance efficacy, regardless of HIV status.[9]

Children Benzathine penicillin 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose. Infants less than 1 month of age diagnosed with syphilis should have a CSF test to determine if asymptomatic neurosyphilis is present. Patient records should be reviewed to decipher whether syphilis is congenital or acquired.

Alternatives Oral doxycycline 100 mg twice daily for 2 weeks *or* tetracycline 500 mg by mouth four times daily for 2 weeks. Limited literature also supports the use of ceftriaxone 1 g IM or IV once daily for 10 days *or* oral azithromycin as a single 2 g dose.[9,21]

Table 80–1

Benzathine and Procaine Penicillin G Informational Chart

Categories	Benzathine Penicillin G	Procaine Penicillin G
Potential adverse reactions	CNS: convulsions, confusion, drowsiness, myoclonus, fever Dermatologic: rash Metabolic: electrolyte imbalance; Hematologic: positive Coombs test, hemolytic anemia Local: pain, thrombophlebitis Renal: acute interstitial nephritis Miscellaneous: anaphylaxis, hypersensitivity, Jarisch-Herxheimer reaction	CNS: seizures, confusion, drowsiness, myoclonus, CNS stimulation Cardiovascular: myocardial depression, vasodilation, conduction disturbances Hematologic: positive Coombs test, hemolytic anemia, neutropenia Local: thrombophlebitis, sterile abscess at injection site Renal: interstitial nephritis Miscellaneous: pseudoanaphylactic reactions, hypersensitivity, Jarisch-Herxheimer reaction, serum sickness
Monitoring parameters	Observe for anaphylaxis during first dose	Periodic renal and hematologic function tests with prolonged therapy; fever, mental status, WBC
Pregnancy category	B	B
Lactation	Enters breast milk	Enters breast milk
Availability	Bicillin L-A: 600,000 units/mL (1, 2, and 4 mL) Permapen isoject: 600,000 units/mL (2 mL)	Injection, suspension: 600,000 units/mL (1, 2 mL)
Combination	Bicillin C-R: (1, 2, 4 mL) Bicillin C-R: 900/300: (2 mL)	Same

CNS, central nervous system; IM, intramuscular.

Data from Lacy C, Armstrong L, Goldman M, Lance L. Lexi-Comp's Drug Information Handbook, 19th ed. Hudson, OH: Lexi-Comp; 2010:1128–1132.

LO 7

▶ *Secondary and Early Latent Syphilis*

Treatment modalities administered in primary syphilis are also effective in secondary syphilis and early latent syphilis (< 1-year duration).

Children with early latent syphilis should receive benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose.

LO 7

▶ *Late Latent Syphilis*

Benzathine penicillin, 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-week intervals.

Children with late latent syphilis should be treated with benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as three doses at 1-week intervals (total 150,000 units/kg up to the adult dose of 7.2 million units).

LO 7

▶ *Tertiary Syphilis*

Drug of Choice Benzathine penicillin 2.4 million units administered IM once weekly for 3 weeks. A total of 7.2 million units should be administered.

Alternatives In nonpregnant patients with a penicillin allergy, alternative regimens include doxycycline 100 mg PO two times daily for 4 weeks *or* tetracycline 500 mg PO four times daily for 4 weeks.

▶ *Gummatous and Cardiovascular Syphilis*

As long as no evidence of CNS involvement exists, antibiotic therapy for gummatous and cardiovascular syphilis is identical to that for tertiary syphilis.

LO 7

▶ *Neurosyphilis*

As an effective treatment for neurosyphilis, the Centers for Disease Control and Prevention (CDC) endorse two regimens of penicillin. Alternatively, ceftriaxone may also be prescribed.[25]

The regimens of choice are aqueous penicillin G 3 to 4 million units administered IV every 4 hours or continuous infusion for 10 to 14 days *or* procaine penicillin G 2.4 million units administered IM once daily, plus probenecid 500 mg PO four times daily, both for 10 to 14 days.

Congenital Syphilis[23–25]

The decision to treat an infant should be based on a diagnosis of syphilis in the mother and confirmation of adequacy of maternal treatment. Clinical, laboratory, or radiographic evidence of syphilis in the infant should be documented. Maternal nontreponemal titers (at delivery) should be compared with the infant's nontreponemal titers. Since diagnosis based on neonatal serologic testing is complicated by the transplacental transfer of maternal immunoglobulin G (IgG) antibodies, which can cause a positive test in the absence of infection, neonatal titers are assessed. A titer greater than four times the maternal titer would not generally result from passive transfer and diagnosis is considered confirmed or highly probable.

The following regimens are recommended for treatment of maternal syphilis: benzathine penicillin G 2.4 million units or 7.2 million units IM over 3 weeks if the duration of syphilis has been at least a year. An alternative regimen is procaine penicillin 0.6 to 0.9 million units IM for 10 to 14 days, or ceftriaxone 1 g daily IM or IV for 8 to 10 days.

In women who experience uterine cramping, pelvic pain, or fever, administer acetaminophen to combat these symptoms. Additionally, the patient should be well hydrated and rested.

Treatment of asymptomatic neonates is with 50,000 units/kg of benzathine penicillin G in a single IM dose. Symptomatic neonates should receive 50,000 units/kg of aqueous crystalline penicillin G every 12 hours IM for the first 7 days of life, then every 8 hours for 3 days *or* procaine penicillin G 50,000 IU/kg IM as a single dose daily for 10 days.

Outcome Evaluation

LO 8

The CDC has provided patient care monitoring guidelines for syphilis (Figure 80–2).[9,11,20]

Primary and Secondary Syphilis

- After 6, 12, and 24 months of treatment, reexamine the patient and recommend a follow-up quantitative nontreponemal titer. More frequent assessment might be sensible if follow-up is uncertain. If the patient is asymptomatic and a fourfold increase in nontreponemal titer or persistent or recurrent symptoms are observed, order an HIV test and a lumbar puncture; if the patient is HIV-positive, suggest an infectious disease consult.
- In patients who are both negative for HIV and the lumbar puncture, administer benzathine penicillin G 2.4 million units IM once weekly for 3 additional weeks. Perform a patient follow-up in 6 months including a clinical examination and another nontreponemal titer. In HIV-negative patients with lumbar puncture findings compatible with neurosyphilis, treat the patient accordingly for neurosyphilis.
- Six months after the original diagnosis, institute a standard clinical follow-up examination in patients who show no symptomatology and a fourfold decrease in nontreponemal titers. By testing and observing the patient for signs of remission, you may be able to initiate proper treatment or recommend a consult in a timely fashion, thereby decreasing the propensity of the patient's condition to advance to a higher stage.
- If serologic titers do not decline despite a negative CSF examination and a repeated course of therapy, it is unclear whether additional therapy or CSF examinations are needed; additional testing or repeated therapy is not generally recommended.

Early and Late Latent Syphilis

- Order nontreponemal titers 6, 12, and 24 months after instituting treatment for early or late latent syphilis. Neurosyphilis should be strongly considered in patients who show a fourfold increase in titers, patients who have an initially high titer (1:32 or greater) that fails to decline at least fourfold within 12 to 24 months of therapy, HIV-infected patients, and patients who develop signs or symptoms associated with neurosyphilis.

Neurosyphilis

- Follow-up is dependent on the CSF findings. If pleocytosis is present, reexamine the CSF every 6 months until the WBC count normalizes. Consider recommending a second

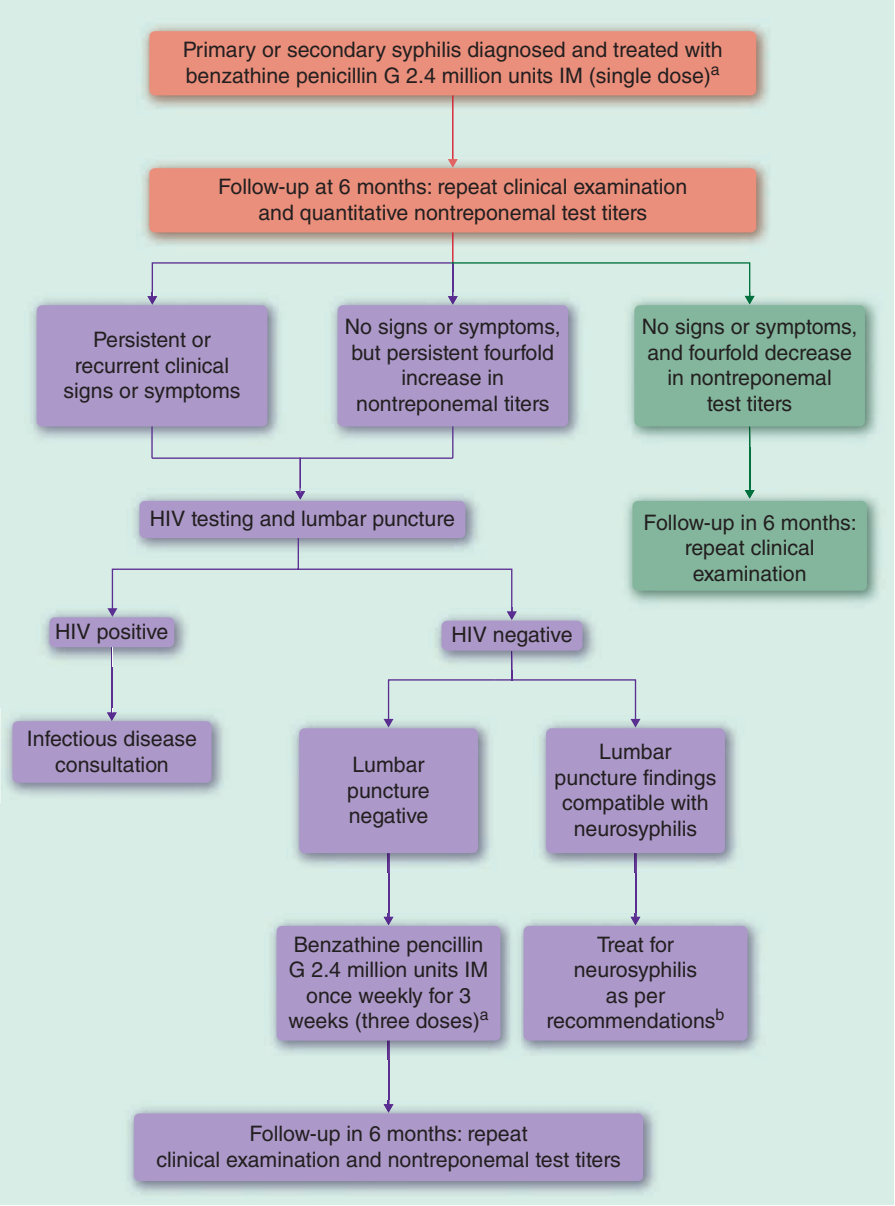

FIGURE 80–2. Patient care monitoring for syphilis. [a]See text for alternative treatment recommendations for nonpregnant penicillin-allergic patients. [b]See text for treatment recommendations for neurosyphilis. (Reprinted with permission from Diagnosis and Management of Syphilis, July 15, 2003, Vol 68, No 2, American Family Physician Copyright © 2003 American Academy of Family Physicians, All Rights Reserved.)

course of treatment if the CSF white count does not decline after 6 months or completely normalize after 2 years.[4,9,20] Failure to normalize may require retreatment; most treatment failures occur in immunocompromised patients.

Congenital Syphilis

- Observe the patient for changes in clinical features; hepatomegaly, jaundice, and bone changes will usually resolve in 3 months.
- Monitor elevated serologic markers (nontreponemal tests) for reduction in titer levels. Given effective treatment, clinical features will usually disappear after 6 months. On this basis, evaluate seropositive infants periodically for at least 6 months.[24]

TRICHOMONIASIS

LO 4

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis* and is far more prevalent than *C. trachomatis* or *N. gonorrhoeae*. In the United States, approximately 5 million new cases appear annually, compared with 3 million chlamydial and 650,000 gonococcal cases annually.[26]

PATHOPHYSIOLOGY

T. vaginalis, a protozoa, may be isolated from the vagina, urethra, and Bartholin or Skene glands. After attachment to the host cells, it ignites an inflammatory response exhibited as a discharge containing elevated levels of polymorphonuclear leukocytes. The pathogen causes direct damage to the epithelium, leading to microulcerations.

CLINICAL PRESENTATION AND DIAGNOSIS

LO6 Diagnosis is usually performed with a wet mount or Papanicolaou smear. In women, symptoms are characterized by diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation. Some women may be asymptomatic.

TREATMENT

The desired outcome is the complete eradication of *T. vaginalis* in both partners and elimination of the signs and symptoms observed.

Pharmacologic Therapy

KEY CONCEPT The 5-nitroimidazoles (metronidazole and tinidazole) have been the standard therapy for trichomoniasis for over 45 years. When using these agents, advise patients to avoid the consumption of alcohol.

▶ *Metronidazole*

LO7 Metronidazole may be administered PO as a single 2 g dose or 500 mg twice daily for 7 days.[9,26] Pregnant women should be prescribed the single dose of metronidazole. Cure rates are greater than 90% when metronidazole is administered as either a single 2 g dose or a 7-day regimen. Possible adverse effects include an unpleasant metallic taste, reversible neutropenia, urticaria, rash, flushing, dry mouth, darkened urine, and a disulfiram-like reaction.

▶ *Tinidazole*

Tinidazole is a second-generation nitroimidazole with protozoal and anaerobic activity.[27] As a single 2 g dose, tinidazole has an efficacy equivalent to a 2-g dose of metronidazole. Tindazole also has a longer half-life than metronidazole, 14 and 7 hours, respectively, and penetrates into male reproductive tissue better than metronidazole.

Tinidazole is effective for metronidazole-resistant trichomoniasis.[26,27] Possible side effects include an unpleasant metallic taste, dizziness, loss of coordination, seizures, severe diarrhea, darkened urine, nausea, vomiting, and a swollen or discolored tongue.

Outcome Evaluation

- Order diagnostic test for trichomoniasis. If positive, recommend antibiotics that cover *T. vaginalis*.
- Subsequent to treatment, expect the eradication of the protozoa.
- Monitoring is generally not required.

Clinical Presentation of Trichomoniasis[9,26]

General

- Asymptomatic

LO5

Signs

- Strawberry cervix (women)
- Colpitis macularis (women)
- Prostatitis or epididymitis (men)

Symptoms

- Vaginal/vulvar erythema
- Excessive yellow-green discharge
- Vulvar itching
- Vaginal odor
- Urethral discharge or irritation
- Dysuria
- Vaginal pH greater than 4.5

GENITAL WARTS

LO4 Genital warts, caused by the human papillomavirus (HPV), usually appear in the genital area as very contagious, small bumps. Responsible for various visible, keratotic, and nonkeratotic manifestations, HPV has more than 150 noted strains, some of which have been linked to squamous cell carcinoma.[28] More than 40 strains have been linked to the genital area.[29]

EPIDEMIOLOGY AND ETIOLOGY

LO3 Genital warts are caused by several strains of HPV and spread by skin-to-skin contact (ie, vaginal, anal, or oral) during sexual activity with an infected person.[30,31] HPV can be passed when an infected person has no signs or symptoms. Affecting over 79 million Americans, HPV is the most common, newly diagnosed STI in the United States, with prevalence of approximately 52%. Almost 14 million new HPV infections occur every year in the United States.[28] Nearly half of new infections occur among persons aged 15 to 24 years. Condoms offer incomplete (grade B, level II [fair research-based evidence to support the recommendation]) protection against HPV because HPV can infect areas not covered by a condom.[30,31]

The frequency of cervicovaginal HPV infection among sexually active women has been observed at 43%, with the greatest incidence noticed in men with three or more sex partners and women whose most recent regular sexual partner had two or more lifetime partners. Most people with HPV do not develop symptoms. At least half of sexually active persons will become infected at least once in their lifetime. In 90% of the cases, the body immune system clears HPV naturally within 2 years. Routine testing of HPV DNA infection is not recommended because test results would not alter clinical management of the condition. KEY CONCEPT HPV types 16 and 18 cause 99.7% of all cervical cancer while HPV types 6 and 11 are responsible for about 90% of genital warts.[30,32]

PATHOPHYSIOLOGY

HPV replicates in terminally differentiated squamous cells in the intermediate layers of the genital mucosa. Hence, these effects of the viral early region genes on DNA synthesis are critical for viral survival. Genital warts are the clinical manifestation of active viral replication and virion production at the infection site.

CLINICAL PRESENTATION AND DIAGNOSIS

LO6
- A definitive diagnosis of HPV is based on DNA, RNA, or capsid protein detection.
- Diagnosis is generally made from the clinical presentation or by visual inspection. It may be classified into several

Clinical Presentation of Genital Warts[9,32,33]

General

- Appear as rough, thick, cauliflower-like lesions

LO 6

Signs

- Black dots within warts
- Disrupted surface

Symptoms

- Anogenital pruritus
- Burning
- Vaginal discharge or bleeding
- Although rare, dyspareunia may occur with vulvovaginal condyloma

categories: classic condyloma acuminata, which are pointed or cauliform; keratotic warts with a thick, horny surface resembling common skin warts; and flat warts, which are frequently observed on the surface.

- Tissue biopsy or viral typing is only indicated if the diagnosis is uncertain and is not recommended for patients with routine or typical lesions.
- Since HPV is highly associated with cervical cancer and has more than 20 different cancer-associated HPV types, patients who are diagnosed with HPV should be tested for cervical cancer.

TREATMENT

Genital warts are usually asymptomatic but can be painful or pruritic. Approximately 40% to 60% of untreated warts will spontaneously resolve in 9 to 12 months if left untreated.[30] Treatment of benign, symptomatic genital warts is aimed at alleviation of physical symptoms and cosmetic improvement. Removal of visible warts and reduction of infectivity are the goals of treatment.

A comparison of adverse effects related to treatment options may be found in Table 80–2.[34]

Table 80–2

Comparison of Adverse Effects Seen with Treatments for Genital Warts

Treatment	Adverse Effects
Podofilox	Burning at site of application, pain, inflammation
Imiquimod	Erythema, irritation, ulceration, pain, burning, edema, pigmentary changes
Sinecatechins	Burning at site of application, erythema, pruritus, edema
Podophyllin resin	Local irritation, erythema, burning, soreness at application site; possibly oncogenic
Bichloroacetic and trichloroacetic acid	Local irritation and pain, minimal systemic effects
Cryotherapy	Pain or blisters at application site
Surgical excision	Pain, bleeding, scarring; possible burning or allergic reaction to local anesthetic
Vaporization	Pain, bleeding, scarring; risk of HPV spreading via smoke plumes
Intralesional interferon	Burning, itching, irritation at injection site, systemic myalgia, headache, fever, chills, leukopenia, elevated liver enzymes, and thrombocytopenia

HPV, human papillomavirus.

Data from Refs. 9, 28, and 31.

Patient-Applied Treatment

▶ *Podofilox*

LO 7

Available as a 0.5% gel or solution containing purified extract of the most active compound of podophyllin, podofilox inhibits the formation of the mitotic spindle, prevents cell division, and may also induce damage in blood vessels within the warts. The surface area treated must not exceed 10 cm^2, and a maximum of 0.5 mL should be used on a daily basis.

Apply podofilox twice daily for 3 consecutive days, followed by 4 consecutive days without treatment. This cycle may be repeated until there are no visible warts or for a maximum of 4 weeks. Side effects are generally local and may include erythema, swelling, and erosions. Podofilox is not recommended for use in the vagina, anus, or during pregnancy.

▶ *Imiquimod*

Imiquimod is a cell-mediated immune-response modifier, available as a topical 5% cream in single-dose application packets. There are two recommended dosage regimens:

a. Apply at bedtime, three times a week for up to 16 weeks.
b. Apply every other day for three applications.

The treatment area should be washed with soap and water 6 to 10 hours after application. Mild to moderate erythema has been noted with imiquimod use; however, this generally suggests that the drug is reaching a therapeutic range and may be clearing the lesion.[35,36]

▶ *Sinecatechins*

A green tea extract with an active product (catechins) is available as a 15% ointment. Apply a thin layer (0.5 cm) using a finger to each wart three times a day until complete clearance of warts. Do not wash off after use and all sexual contact should be avoided while ointment is on the skin. This product should not be continued for longer than 16 weeks.[9]

Physician-Applied Treatments

▶ *Podophyllin Resin*

A 10% to 25% solution of podophyllin resin in a compound tincture of benzoin has been the standard in-office treatment for genital warts. Because podophyllin is neurotoxic and systemically absorbed, only a small amount (no > 0.5 mL) should be applied. Application should be limited to less than 0.5 mL of podophyllin on an area of less than 10 cm^2 of warts per session and no open lesions or wounds should exist in the area to which treatment is administered. The affected area will likely become erythematous and painful within 48 hours of application.[36]

Topical podophyllin is applied once weekly; and the area should be allowed to dry. Immediately following treatment, the dried drug should be removed using alcohol or soap and water. Topical podophyllin is contraindicated in pregnant patients.

▶ *Bichloroacetic (BCA) and Trichloroacetic (TCA) Acids*

These caustic agents are available in 80% to 90% concentrations and are not systemically absorbed. The products are effective when used to treat a few small, moist lesions. Apply once a week until the wart is resolved. They may be applied to both keratinized epithelial and mucosal surfaces and may be used in pregnancy.

A noted reaction to these medications is transient burning; contact with surrounding epithelium may prove to be painful, producing significant local erythema and swelling. To avoid these effects, place petroleum jelly around the external lesion, including unaffected skin, and carefully apply the agent with a small applicator. If an excess amount of acid is used, talc or sodium bicarbonate (baking soda) or liquid soap preparations may be administered to neutralize unreacted acid.

▶ *Other Treatments*

Other treatments may include fluorouracil/epinephrine/bovine collagen gel, an intralesional injection that has been proven effective in clinical trials for refractory patients or an intralesional injection of interferon.[33]

Ablative Therapy

Several ablative options have been employed in the treatment of genital warts and include cryotherapy with liquid nitrogen or cryoprobe, surgical removal by excision, and vaporization.

Special Therapeutic Issues[34–37]

▶ *Large Warts*

Treat warts greater than 10 mm in diameter with surgical excision. Use imiquimod for three to four treatment cycles to reduce the number of warts and improve surgical outcomes. Fifty percent reduction in wart size after four treatment cycles warrants continued use of imiquimod until warts clear or eight cycles have been completed; less than 50% reduction warrants surgical excision or other ablative therapy.

▶ *Subclinical Warts*

Subclinical warts may be identified through colonoscopy, biopsy, acetic acid application, or laboratory serology. However, early treatment has not been linked to a favorable effect during the course of therapy in the index patient or the partner with regard to reduction of the transmission rate.

▶ *Pregnancy*

Agents contraindicated in pregnancy include podofilox, sinecatechins, fluorouracil, and podophyllin. Imiquimod is not approved for use in pregnancy, although it has been considered after signed consent has been obtained. Bichloroacetic and trichloroacetic acids have been used without problems. Ablative therapy is also a viable option.

Vaccinations

Several HPV genotypes have been linked to the development of cervical cancer. Gardasil, a quadrivalent vaccine developed to protect against HPV genotypes 6, 11, 16, and 18, was the first vaccine employed to prevent cervical cancer, precancerous genital lesions, and genital warts due to HPV. Cervarix, a bivalent vaccine, prevents cervical cancer and precancers caused by HPV types 16 and 18. Additionally, Gardasil 9, a 9-valent vaccine, protects against infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The CDC recommends the HPV vaccine for all 11- and 12-year-old girls and boys. Vaccination is also recommended for females aged 13 through 26 years and males 13 to 21 years old who have not been previously vaccinated or who have not completed the full series of shots.[28,38] The quadrivalent vaccine, Gardasil, is Food and Drug Administration (FDA)-approved for females and males 9 to 26 years old.[39]

In the past, inactivated vaccines were given in a series of three IM injections over a 6-month period. Second and third doses were given at 2 and 6 months (respectively) after the first dose. However, the CDC guidelines now recommend that 11–12-year olds receive two doses of the HPV vaccine rather than the previously mentioned three doses. The second dose should be given 6–12 months after the first. HPV vaccine may be given at the same time as other vaccines. Vaccines are efficacious in preventing genital warts; however, they will not clear those that are already present. Either vaccine is recommended for girls/women, whereas only one vaccine (Gardasil) is recommended for boys/men.[28]

Outcome Evaluation

LO 8

- Monitor the patient for any visible warts and relief of symptoms.
- Apply powder with talc, baking soda, or liquid soap to remove unreacted trichloracetic or bichloroacetic acid.
- Dry area before contact with normal mucosa after application of podophyllin.
- Repeat TCA, BCA, podophyllin treatment weekly if necessary.
- Administer a different agent if warts persist after one type of therapy.
- Refer all recalcitrant patients to local STI clinic, gynecologists, dermatologists, or urologists.

GENITAL HERPES

LO 4

Genital herpes (GH) is caused by herpes simplex virus (HSV) types 1 and 2. HSV is a chronic, lifelong viral infection, for which there is no cure. Once latency is established, neither competent host immunity nor therapeutic agents can eradicate the virus.[9] Currently, there is no vaccine available for HSV, and it seems that the development of one is unlikely in the near future. HSV-1 is mainly transmitted by oral to oral contact to cause oral herpes (cold sores) but can also cause GH through oral sex. HSV-2 is an STI that causes GH.[40]

EPIDEMIOLOGY AND ETIOLOGY

LO 3

Approximately 50 million Americans have GH. HSV-2 is the most common cause of recurrent GH. Roughly 1 in 6 people in the United States (16.2%) aged 14–49 is infected with HSV-2. Prevalence of HSV-2 infection has grown by approximately slightly since the late 1970s (16.4%–17.2%), and currently over 500,000 new cases of HSV-2 occur annually.[9] Many persons infected with HSV-2 have not been diagnosed; therefore most GS infections are transmitted by persons unaware of their status.[36]

PATHOPHYSIOLOGY

KEY CONCEPT Nearly all HSV-2 infections are sexually acquired.

LO 3

Since HSV is only found in humans, infection may only be transmitted from infectious secretions onto mucosal surfaces (ie, cervix or urethra) or direct contact with an active lesion

(abraded skin). The virus may survive for a limited amount of time on environmental surfaces. Most sexual transmission occurs while the source case is asymptomatic. Most patients with asymptomatic or unrecognized genital HSV infections will still shed virus intermittently in the genital tract. Patients will have small, painful blisters that are filled with fluid. The first outbreak takes 2 to 4 weeks to heal, and later attacks are less severe. Because there is no cure for this illness, treatment will only help reduce the signs, symptoms, and number of attacks.[9] Persons with GS should be tested for HIV infection because of their epidemiological synergy.[36]

CLINICAL PRESENTATION AND DIAGNOSIS

LO 6

Ulcerative or multiple vesicular lesions are absent in many infected persons. Laboratory confirmation is vital to effective treatment of HSV, especially in individuals in whom a clinical diagnosis cannot be obtained. There are several methods by which a definitive diagnosis may be acquired, and these include virologic typing, serologic diagnosis, rapid point-of-care antigen detection, ELISA, immunoblot, and DNA polymerase chain reaction.[41] Glycoprotein G-based assays may also be used to aid in the diagnosis of HSV.

TREATMENT

Management of genital HSV should address the chronic nature of the disease rather than focusing solely on treatment of acute episodes of genital lesions. The desired outcome is to curtail the number of episodic prodromes and to minimize any side effects experienced due to the antivirals. Counseling of infected persons and their partners is vital to the management of HSV.

First Episode

The first episode is a systemic illness associated with the vesicular lesions, may last up to 21 days, usually has an uncomplicated course of infection, and, in severe cases, may require hospitalization. This initial presentation occurs 4 to 7 days after sexual exposure. Several agents are effective during this period (Table 80–3).[42–44] At the cited dosages, these agents produce excellent outcomes with regard to lesion healing time, viral shedding, and reduction in pain. Common adverse effects are nausea, headache, and diarrhea. It is important to note that the first episode does not necessarily indicate recent infection and the genital symptoms may develop several years after the infection was acquired. Condom use in new or uninfected partners, particularly in the 12 months after the first attack, is recommended.

Clinical Presentation of Genital Herpes[9,41,42]

General

- Asymptomatic

LO 5

Classic Sign

- A cluster of painful vesicles on an erythematous base

Symptoms

- Itching
- Burning
- Tingling
- Groin lump
- Dysuria
- Dyspareunia
- Increased urinary frequency

Other Symptoms

- Ulcerative lesions, fissures, cervicitis

Episodic Therapy

In a patient with a previous diagnosis of GS, the appearance of new vesicular lesions is synonymous with HSV reactivation. For most patients, GS recurrence is self-limiting and short-lived, lasting approximately 6 to 7 days.

Suppressive Therapy

Suppressive therapy is effective for controlling all symptoms related to the disease and may impact troublesome complications of infection. Before beginning suppressive therapy, discuss patient expectations. Encourage patients to record any breakthrough episodes, as this may require treatment reevaluation and adjustment.

Preventive Therapy

Valacyclovir 500 mg PO once daily has been used to prevent the sexual transmission of HSV to an uninfected partner. In addition to pharmacologic therapy, counsel patients regarding safe sex practices.

Drug Resistance

All acyclovir-resistant strains are resistant to valacyclovir and the majority are resistant to famciclovir. Foscarnet, cidofovir, and trifuridine have been administered in acyclovir-resistant patients.[45] These agents are usually reserved for use after other medications have failed because of their associated toxicities.

Pregnancy

Women who are pregnant may transmit the virus to the neonate during delivery. There are two management strategies: caesarean section and antiviral therapy. Acyclovir 200 to 400 mg every 8 hours has been administered from 38 weeks' gestation until delivery. Acyclovir, famciclovir, and valcyclovir are all classified as category B (no evidence of risk in humans) for use during pregnancy. Suppressive treatment includes the use of acyclovir or valacyclovir from week 36 until delivery. The goal of therapy is to reduce the number of lesions and asymptomatic shedding at delivery.

Neonates

The risk for transmission from an infected mother to a neonate is highest among women who acquired GH near time of delivery. Women who have GH prior to pregnancy are at very low risk of transmitting HSV to their infants. HSV infections should be considered in all neonates who present with nonspecific symptoms such as fever, poor feeding, lethargy, or seizures in the first month of life. Infants suspected to have or who are diagnosed with an HSV infection should be treated parenterally. Acyclovir 20 mg/kg/day in three divided doses IV for 21 days for disseminated and CNS disease or 14 days for disease limited to skin, eyes, and mucous membranes.

Table 80–3

Comparison of Antiviral Agents Used for Herpes Simplex Infection

Agent	Dose	Side Effects
First Episode		
Acyclovir	*200 mg PO five times a day × 7–10 days* ***or*** 400 mg PO three times daily × 7–10 days	Headache, confusion, nausea, vomiting, thrombocytopenia, renal insufficiency, rash, pruritus, fever, arthralgias, myalgia, thrombotic thrombocytopenic purpura, hallucinations, somnolence, depression
Valacyclovir	*1 g PO two times daily × 7–10 days*	Refer to acyclovir
Famciclovir	250 mg PO three times daily × 7–10 days	Refer to acyclovir
Episodic		
Acyclovir	*200 mg PO five times daily × 5 days* ***or*** 400 mg PO every 8 hours × 5 days ***or*** 800 mg PO two times daily × 5 days ***or*** 800 mg PO three times daily × 2 days	Refer to acyclovir (WHO)
Valacyclovir	*500 mg PO two times daily × 3 days* ***or*** 1 g PO once daily × 5 days	Refer to acyclovir
Famciclovir	125 mg PO two times daily × 5 days ***or*** 1000 mg PO twice daily × 1 day	Refer to acyclovir
Suppressive		
Acyclovir	400 mg PO two times daily continuously ***or***	Refer to acyclovir
Valacyclovir	500 mg PO once daily continuously ***or***	Refer to acyclovir
Valacyclovir	1000 mg PO once daily continuously ***or***	Refer to acyclovir
Famciclovir	250 mg PO two times daily continuously	Refer to acyclovir
Reserved Agents		
Foscarnet	40 mg/kg IV every 8 hours until clinical resolution is attained	Renal insufficiency, metabolic disturbances, hypophosphatemia
Cidofovir	1% topical agent (gel) used daily on a compassionate basis for acyclovir-resistant herpes lesions for 5 days	Application site reactions, lesion recrudescence
Imiquimod	Topical alternative used daily on a compassionate basis for acyclovir-resistant herpes lesions for 5 days	Application site reactions, lesion recrudescence

Italicized data indicate preferred dosages.

Data from Refs. 9 and 33.

HIV Infection

Lesions caused by HSV are common among persons with HIV infection and may have prolonged episodes of GH. HSV shedding is increased in persons with HIV infection. Oral antiviral agents are effective in decreasing the clinical manifestations of HSV among people with HIV infection.[9]

Outcome Evaluation

LO 8

- Monitor for systemic symptom improvement and a decrease in viral shedding in initial HSV treatment.
- Take lukewarm baths three to four times a day to ease itching and pain. Pat dry affected areas.
- Wear loose-fitting underwear to help the sore dry.
- Avoid sexual contact until treatment is finished.
- Consider stopping suppressive therapy after 1 year to assess recurrence rate.
- Compound topical 1% cidofovir gel in acyclovir-resistant strains where IV foscarnet is not preferred.

PELVIC INFLAMMATORY DISEASE

LO 4

Pelvic inflammatory disease (PID) usually affects young, sexually active women. PID includes a spectrum of inflammatory disorders of the upper female genital tract. In the majority of cases, the pathogens responsible are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*; although anaerobes, enteric gram-negative rods, and cytomegalovirus have also been implicated in the pathogenesis.[46] PID has been correlated with ectopic pregnancy, infertility, tubo-ovarian abscess, and chronic pelvic pain.[47]

EPIDEMIOLOGY AND ETIOLOGY

LO 3

PID is most common in minority women younger than 25 years of age, who have more than one sex partner. Approximately 800,000 women are diagnosed with PID each year in the United States. The estimated prevalence of self-reported lifetime PID was 4.4% in sexually experienced women of reproductive age (18–44 years). The highest rates of PID occur in

Patient Encounter 3

MB is a 21-year-old Haitian woman whose native tongue is French Creole. She confides in her physician about her profession as an escort. She comes into the clinic because of a vaginal discharge and the recurrence of small bumps in her genital area. MB explains that some of her clients pay extra money to have unprotected sex. Her boyfriend gave her a gel to apply that he received from his doctor because of a past STI in the past.

What information is suggestive of genital herpes?

What potential risk factors for STIs are present?

What additional information is required to initiate a treatment plan?

What is your opinion about the use of the Gardasil vaccine in this patient?

teenagers and first-time mothers. Up to 10% to 15% of these women may become infertile as a result of PID.[9] Since many cases of PID are asymptomatic or inadequately treated, the potential for damage to the reproductive health of women is increased. There is an elevated risk for women with past STIs and for those who have more than one partner. However, over the past decade, there is evidence suggesting of a decline in PID diagnoses in the United States.[48]

PATHOPHYSIOLOGY

PID is an infection that occurs when bacteria move upward from a woman's vagina into her reproductive organs. Normally, the cervix prevents bacteria from entering the vagina and spreading to the reproductive organs. However, when the cervix is exposed to STIs such as chlamydia and gonorrhea, bacteria are disseminated into female internal organs. Chlamydia may produce a heat-shock protein that causes tissue damage through a delayed hypersensitivity reaction. *Chlamydia trachomatis* may also possess DNA evidence of toxin-like genes that code for high-molecular-weight proteins with structures similar to *Clostridium difficile* cytotoxins, enabling inhibition of immune activation. This may explain the observation of a chronic chlamydia infection in subclinical PID.

Patient Encounter 4

TC is a 25-year-old former heroin abuser. She works long hours for little pay at a local pub as a cocktail waitress and constantly worries about not being able to pay her bills. She has four children from three different men. Her PHM includes depression, schizophrenia, and delusions. Social history includes smoking ½ pack/day of Newports and occasional drinking.

She presents at the clinic because of a stinging sensation while urination and painful blisters in the genital area.

What information is suggestive of HSV?

Identify your treatment goals for this patient.

CLINICAL PRESENTATION AND DIAGNOSIS[46,49]

LO 6

Because many women with PID have subtle or mild symptoms, delays in diagnosis and treatment may lead to inflammatory sequelae in the upper reproductive tract. All women who receive a diagnosis of acute PID should be tested for HIV, as well as gonorrhea and chlamydia. To be diagnosed with PID, patients must have uterine tenderness, cervical motion tenderness, painful urination, lower abdominal pain, painful intercourse, and adnexal tenderness with no other cause of these signs. Additional criteria include:

- Oral temperature greater than 38.3°C (101°F)
- Abnormal cervical or vaginal discharge or that has an unusual color (green or yellow)
- WBC presence on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

TREATMENT

LO 8

Presumptive treatment of PID should be initiated in young, sexually active women if they are experiencing pelvic or lower abdominal pain with one or more of the minimum clinical criteria present on the pelvic examination. KEY CONCEPT The removal of causative bacteria and reduction of any related sequelae are the desired goals of treatment. Resolution of infection (ie, *N. gonorrhoeae, C. trachomatis*, *Streptococcus* spp., and gram-negative facultative bacteria) and mitigation of sequelae should be the main goal of pharmacologic therapy. Treatment regimens for PID must provide empiric, broad-spectrum coverage of likely pathogens. Parenteral and oral regimens appear to have similar efficacy in women with PID of mild or moderate clinical severity. CDC-approved treatment regimens are shown in Table 80–4.[9,46]

Though outpatient management remains contentious, many feel that outpatient management should be limited to individuals who remain afebrile, tolerate oral nourishment, or have a WBC counts less than $11 \times 10^3/mm^3$ ($11 \times 10^9/L$), minimal evidence of peritonitis, or active bowel sounds. Nonetheless, outpatient therapy with a parenteral cephalosporin followed by doxycycline and metronidazole is recommended.

Outcome Evaluation

LO 8

- Reevaluate any patient who does not respond significantly within 72 hours of parenteral/oral treatment.
- Initiate parenteral therapy (inpatient or outpatient) for patients that do not respond to oral treatment.
- Continue parenteral therapy for 14 days; however, it may be stopped 24 hours after clinical improvement and doxycycline continued to complete 14 days of therapy.
- Hospitalization and reassessment of the antimicrobial regimen and diagnostics are recommended in women without clinical improvement.
- Repeat testing of all women who have been diagnosed with chlamydia or gonorrhea is recommended 3 to 6 months after treatment, regardless of whether their sex partners were treated.
- Inform the patient that an alteration in sexual behavior should be the first concern, as promiscuous sexual activity augments the probability of infection.

Table 80–4

Treatment Regimens for Pelvic Inflammatory Disease

LO 7

Parenteral Option A
Cefotetan 2 g IV every 12 hours
or
Cefoxitin 2 g IV every 6 hours plus doxycycline 100 mg PO or IV every 12 hours

Parenteral Option B
Clindamycin 900 mg IV every 8 hours plus gentamicin, loading dose IV or IM (2 mg/kg) followed by maintenance dose (1.5 mg/kg) every 8 hours. A single daily dose of gentamicin (3–5 mg/kg) may be used

Alternative Parenteral treatment
Ampicillin-sulbactam 3 g IV every 6 hours plus doxycycline 100 mg PO or IV every 12 hours

Oral
Ceftriaxone 250 mg intramuscular single dose plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days
or
Cefoxitin 2 g intramuscular single dose and probenecid 1 g single dose, plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days
or
Third-generation cephalosporin (ceftizoxime or cefotaxime) plus doxycycline 100 mg PO twice daily for 14 days with or without metronidazole 500 mg PO twice daily for 14 days

Data from Refs. 9, 45, and 46.

Abstinence is the best course of action, especially in patients with herpes during lesional episodes. However, compliance in some may be minimal, in which case, appropriate condom use should always be recommended. To alleviate any possible misconceptions about condom application, either demonstrate how to apply a condom or ask the patient to demonstrate. During the demonstration, explicitly educate the patient with regard to application, storage, and the use of lubricants.[49] Additionally, a woman's sexual partner(s) should be treated to decrease the risk of reinfection, even if the partner(s) has no symptoms.

Clinical Presentation of Pelvic Inflammatory Disease[9,49]

General

- Signs and symptoms may vary from mild to severe.

LO 5

Signs

- Vague

Symptoms

- Lower abdominal or pelvic pain
- Malodorous vaginal discharge
- Abnormal uterine bleeding
- Dyspareunia
- Dysuria
- Nausea and/or vomiting
- Fever

Patient Care Process

Collect Information:

- Review current and past medications.
- Verify sexual history and identify lifestyle habits.
- Review all medical conditions.
- Document allergies and adverse drug reactions to medications.

Assess the Information:

- Test for pregnancy, complete blood count, gonorrhea, chlamydia, and bacterial vaginosis.
- Based on a physical examination that includes a pelvic examination, determine if the patient is experiencing any pain in the lower belly or back, vagina discharge with or without color, painful sex, fever, or burning during urination.
- Determine if any current drug–drug interactions will affect efficacy of treatment therapy.
- Identify comorbidities that may exacerbate current condition.

Develop a Care Plan:

LO 8

- Optimal management of STI should be individualized based on clinical setting and patient characteristics but will typically involve antibiotic therapy.
- For some patients, hospitalizations, IV antibiotics, and surgical treatment of complications may be needed.

Implement the Care Plan:

- If no clinical improvement has occurred after parenteral or outpatient oral therapy, perform further assessment.
- Educate the patient about the goals of monitoring patients which include both short- and long-term outcomes.
- Partners should be counseled and depending on the STI treated simultaneously.

Follow-up: Monitor and Evaluate:

- Advise a combination of prevention efforts.
- The primary approach should be prevention and education of at-risk patients.

Abbreviations Introduced in This Chapter

CSF	Cerebrospinal fluid
ELISA	Enzyme-linked immunosorbent assay
GH	Genital herpes
HPV	Human papillomavirus
HSV	Herpes simplex virus
L-A	Long Acting
MSM	Men who have sex with men
PID	Pelvic inflammatory disease
RPR	Rapid plasma reagent
STI	Sexually transmitted infection
WSW	Women who have sex with women

REFERENCES

1. Birley H, Duerden B, Hart CA, et al. Sexually transmitted diseases: microbiology and management. J Med Microbiol. 2002; 51:793–807.
2. Satterwhite C, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sex Transm Dis. 2013 Mar;40(3):187–193.
3. Kann L, Kinchen S, Shanklin SL, et al. Youth risk behavior surveilliance—United States in 2013. MMWR Surveill Summ. 2014 Jun 13; 63(suppl 4):1–168.
4. Moss D., Snyder M, Lu L. et al. Options for women with unintended pregnancy. Am Fam Physician. 2015 Apr 15; 91(8):544–549.
5. HIV among gay and bisexual men. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/hiv/group/msm/index.html. Accessed February 24, 2017.
6. Fethers K, Marks C, Mindel A, et al. Sexually transmitted infections and risk behaviors in women who have sex with women. Sex Transmit Infect. 2000;76:345–349.
7. Hammerschlag M, Guillen C. Medical and legal implications of testing for sexually transmitted infections in children. Clin Microbiol Rev. 2010 Jul;23(3):493–506.
8. O'Byrne P, Watts JA. Exploring sexual networks: a pilot study of swingers' sexual behaviour and health-care-seeking practices. Can J Nurs Res. 2011;43(1):80–97.
9. Sexually transmitted diseases. MMWR Treatment Guidelines. 2015. Available from: https://www.cdc.gov/std/tg2015/default.htm. Accessed June 24, 2017.
10. Terry N, Francis L. Ensuring the privacy and confidentiality of health records. Available from: https://www.illinoislawreview.org/wp-content/ilr-content/articles/2007/2/Terry.pdf. Accessed July 1, 2017.
11. Mandell, Douglas, and Bennett's principles and practice of infectious disease. JAMA. 2010;304(18):2067–2071.
12. Barbee L, Dombrowski J. Control of Neisseria gonorrhoeae in an era of evolving antimicrobial resistance. Infect Dis Clin North Am. 2013;27(4):723–737.
13. Center for Disease Control and Prevention. Recommendations for the laboratory-based detection of *Chlamydia* and *Neisseria gonorrhoeae*—2014. MMWR Recomm Rep. 2014 Mar 14; 63(RR-02):1–19.
14. Unemo M, Shafer W. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st century: past, evolution, and future. Clin Microbiol Rev. 2014 Jul;27(3):587–613.
15. Barbee L. Preparing for an era of untreatable gonorrhea. Curr Opin Infect Dis. 2014;27(3):282–287.
16. Antibiotic resistant gonorrhoea on the rise, new drugs needed. World Health Organization. Available from: http://www.who.int/mediacentre/news/releases/2017/Antibiotic-resistant-gonorrhoea/en. Accessed August 3, 2017.
17. Gursahaney PR, Meyn LA, Hiller SL, Sweet RL, Wiesenfeld HC. Combined hormonal contraception may be protective against Neisseria gonorrhoeae infection. Sex Transm Dis. 2010;37(6):356–360.
18. Young F. Sexually transmitted infections. Genital chlamydia: practical management in primary care. J Fam Health Care. 2005;15:19–21.
19. MMWR: summary of notifiable diseases in the United States 2016. Available from: https://www.cdc.gov/mmwr/index2016.html. Accessed July 2, 2017.
20. Clement M, Okeke N, Hicks C. Treatment of syphilis: a systematic review. JAMA. 2014;312(18):1905–1917.
21. Cohen SE, Klausner JD, Engelman J, Philip S. Syphilis in the modern era: an update for physicians. Infect Dis Clin North Am. 2013;27(4):705–722.
22. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report. Inadvertent Use of Bicillin C-R to Treat Syphilis Infection—Los Angeles, California, 1999-2004. March 11, 2005;54(09):217–219.
23. Matthias J, Rahman M, Newman D et al. Effectiveness of prenatal screening and treatment to prevent congenital syphilis, Louisiana and Florida (2013–2014). Sex Transm Dis. 2017 Aug;44(8): 498–502.
24. Tsimis M, Sheffield J. Update on Syphilis and pregnancy. Birth Defects Res. 2017 Mar 15;109(5):347–352.
25. Rac M, Revell P, Eppes C. Syphilis during pregnancy: a preventable threat to maternal-fetal health. Am J Obstet Gynecol. 2017 Apr; 216(4):352–363.
26. Bouchemal K, Bories C, Loiseau P. Strategies for prevention and treatment of Trichomonas vaginalis infections. Clin Microbiol Rev. 2017 Jul;30(3):811–825.
27. Randomized, Dounble-Blind, Comparative Study of oral metronidazole and tinidazole in treatment of bacterial vaginosis. Indian J Pharmacol. 2016 Nov-Dec;48(6):654–658.
28. Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2014; 63(RR-05): 1–30.
29. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol. 2012;5(6):25–36.
30. Kodner CM, Nasraty S. Management of genital warts. Am Fam Physician. 2004;70:2335–2342.
31. Lopaschuk CC. New approach to managing genital warts. Can Fam Physician. 2013;59(7):731–736.
32. Ault K. Epidemiology and natural history of human papillomavirus infections in the female genital tract. Infect Dis Obstet Gynecol. 2006;(2006 suppl):40470.
33. Smith GD, Travis L. Getting to know human papillomavirus (HPV) and the HPV vaccines. J Am Osteopath Assoc. 2011;111 (3 suppl 2):S29–S34.
34. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. Am J O bstet Gynecol. 2003;189:S3–S11.
35. Bowden FJ, Tabrizi SN, Garland SM, Fairley CK. Sexually transmitted infections: new diagnostic approaches and treatments. Med J Aust. 2002;176:551–557.
36. Guidelines for the management of sexually transmitted infections. World Health Organization. Available from: http://www.who.int/HIV/pub/sti/en/STIGuidelines2016.pdf. Accessed March 14, 2017.
37. Woodward C, Fisher MA. Drug treatment of common STDs: Part II. Vaginal infections, pelvic inflammatory disease and genital warts. Am Fam Physician. 1999;60:1716–1722.
38. Gardasil. Available from: http://www.cdc.gov/vaccines/vpd-vac/hpv/vac-faqs.html. Accessed August 1, 2014.
39. Genital warts. Women's Health 2013. Available from: https://www.womenshealth.gov/a-z-topics/genital-warts. Accessed August 9, 2014.
40. Guidelines for the treatment of Genital Herpes Simplex Virus 2017. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs400/en/. Accessed.
41. Patel R. Progress in meeting today's demands in genital herpes: an overview of current management. J Infect Dis. 2002;186(suppl 1): S47–S56.
42. Alexander L, Naisbett B. Patient and physician partnerships in managing genital herpes. J Infect Dis. 2002;186(suppl 1):S57–S65.
43. Lacy C, Armstrong L, Goldman M, Lance L. Lexi-Comp's Drug Information Handbook, 19th ed. Hudson, OH: Lexi-Comp; 2013:1128–1132.
44. Kimberlin DW, Rouse DJ. Clinical practice. Genital herpes. N Eng J Med. 2004;350:1970–1977.

45. Wald A. New therapies and prevention strategies for genital herpes. Clin Infect Dis. 1999;28(suppl 1):S4–S13.
46. Miller KE, Ruiz DE, Graves JC. Update on the prevention and treatment of sexually transmitted diseases. Am Fam Physician. 2003;67(9):1915–1922.
47. Epperly AT, Viera AJ. Pelvic inflammatory disease. Clin Fam Pract. 2005;7:67–78.
48. Das B, Ronda J, Trent M. Pelvic inflammatory disease: improving awareness, prevention, and treatment. Infect Drug Resist. 2016;9:191–197.
49. Condoms and sexually transmitted diseases. FDA. Available from: http://www.fda.gov/oashi/aids/condom.html. Accessed August 24, 2011.

81 Osteomyelitis

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LEARNING OBJECTIVES

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

1. List common risk factors for osteomyelitis.
2. Discuss the pathophysiology of osteomyelitis.
3. Compare and contrast the classic signs and symptoms of acute and chronic osteomyelitis.
4. Evaluate microbiology culture data and other laboratory tests and imaging studies utilized for diagnosis of osteomyelitis.
5. List the most common pathogens isolated in acute and chronic osteomyelitis.
6. Develop a treatment plan for osteomyelitis.
7. Recommend parameters to monitor antimicrobial therapy for effectiveness and toxicity.
8. Describe how principles of antimicrobial stewardship can be applied to the management of osteomyelitis.
9. Educate patients regarding lifestyle modifications that may impact disease outcomes.

INTRODUCTION

KEY CONCEPT Osteomyelitis is an infection of the bone that may be either an acute or chronic process. The inflammatory response associated with acute osteomyelitis can lead to bone necrosis and subsequent chronic infection.[1] Bacterial pathogens, such as *Staphylococcus aureus*, are most commonly responsible for both acute and chronic infections.[1–8] Diagnosis and treatment present significant challenges to clinicians due to the complex nature of osteomyelitis.[1,2] Medical management is considered the cornerstone of treatment for acute infections; however, surgical intervention in addition to antimicrobial therapy is necessary to achieve cure for chronic infections.[1,2]

KEY CONCEPT Osteomyelitis is most often classified by duration of disease and route of infection.[1,2,9]

Two major osteomyelitis classification schemes exist. The Cierny-Mader classification focuses on the affected portion of bone, physiologic status of the patient, and factors impacting local vascularity.[1] In contrast, the Waldvogel classification scheme categorizes disease based on route of infection (**hematogenous** or **contiguous**) and duration of disease (acute versus chronic).[9] Using this classification scheme, osteomyelitis secondary to a contiguous focus can be further subdivided into infections with or without vascular insufficiency. Typical bone involvement in osteomyelitis depends on the route of infection.

- Hematogenous: long bones (femur, tibia) in children and vertebra in the elderly[2–5,10]
- Contiguous with vascular insufficiency: lower extremities[2,11,12]
- Contiguous without vascular insufficiency: bones affected by trauma, surgery, or adjacent soft-tissue infection[1,5]

A single pathogen is most often isolated in hematogenous osteomyelitis, whereas multiple organisms are often isolated in contiguous infections.[7,10,11,13]

While there are no validated definitions delineating acute versus chronic infection,[1,9,10] acute infection is often defined as the first episode or onset of symptoms within 2 weeks.[2,9–11] In comparison, chronic osteomyelitis is generally defined as disease relapse or symptoms persisting beyond 2 months.[2,9] Because there is no abrupt temporal demarcation, but rather a gradual shift from acute to chronic infection, many describe chronic osteomyelitis as the presence of necrotic bone.[1,2,10,11]

EPIDEMIOLOGY AND ETIOLOGY

The most common origin of osteomyelitis is dependent on the age of the patient. Children are more likely to suffer from hematogenous disease while adults are more likely to develop osteomyelitis due to contiguous spread.[1–4,6] However, hematogenous osteomyelitis can also be seen in older adults and in patients with a history of intravenous (IV) drug abuse, with the spine (vertebral osteomyelitis) being the most common site of infection.[1,2,5]

KEY CONCEPT *S. aureus* is the predominant pathogen seen in all types of osteomyelitis, with methicillin-resistant *S. aureus* (MRSA) being increasingly reported.[1–4,6,10] Patient-specific risk factors have the greatest impact on the potential pathogens including the following:

LO 1

- Uncontrolled diabetes and/or peripheral vascular disease (polymicrobial including MRSA, Enterobacteriaceae, and *Pseudomonas aeruginosa*).[11,14]
- Sickle cell patients (*Salmonella* spp.).[1,2,7]
- Individuals with prosthetic implants (coagulase-negative staphylococci).[7]

- Neonates (*E. coli* or group B streptococci).[2]
- Patients with pressure sores (polymicrobial).[2,7]

Regardless of patient-specific risk factors all patients with deep or extensive wounds, particularly those that are nonhealing should be evaluated for underlying osteomyelitis.[11,14]

PATHOPHYSIOLOGY

Both microbial and patient-specific factors are important determinants in the development of osteomyelitis.[1] Healthy bone tissue is normally resistant to infection but may become susceptible under certain conditions.[1,2] Bone can become infected: (a) via the presence of bacteria in the bloodstream (hematogenous), (b) by direct inoculation from trauma or surgery, and (c) by spread from an adjacent site (eg, soft-tissue infection) (contiguous).[1] The latter is particularly problematic in patients with implantable devices (eg, hip replacement), vascular insufficiency, and chronic skin ulcers.[1,11] LO 2

Staphylococcus species possess bacterial adhesins, which promote their attachment to tissues and prosthetic material.[1] Microbial adherence to bone elicits an inflammatory response.[1] The subsequent release of leukocytes and cytokines leads to local edema and **ischemia** facilitating bone necrosis.[1] Pieces of dead bone may become separated, forming **sequestra**.[1] The presence of sequestra is often indicative of chronic disease. These areas typically cannot be penetrated by antimicrobials or phagocytic cells due to poor blood supply and thus require surgical intervention to eradicate the bacterial **nidus**.[1,11] LO 2

CLINICAL PRESENTATION AND DIAGNOSIS

General

The clinical presentations of osteomyelitis may vary depending on route and duration of infection, as well as patient-specific factors such as infection site, age, and comorbidities.[1–4,7,11,14]

KEY CONCEPT Bone biopsy is the gold standard for confirmatory diagnosis of osteomyelitis. A bone biopsy allows for isolation of microorganism(s) from culture in addition to the presence of inflammatory cells and osteonecrosis on histologic exam.[1,2,11–14] Due to the invasive nature of the bone biopsy, the diagnosis of osteomyelitis is often based on clinical findings, laboratory tests, and imaging studies.[1,12,13]

KEY CONCEPT Typical signs and symptoms of osteomyelitis include local pain and tenderness over the affected bone, as well as inflammation, erythema, edema, and decreased range of motion.[1,3,4,6,9] Patients with acute hematogenous osteomyelitis may also present with systemic symptoms such as fever, chills, and/or malaise.[1,3,4,9] A cardinal sign of chronic osteomyelitis is the formation of a sinus tract (a channel from the infected site to the skin) with purulent drainage.[1] LO 3

Laboratory Tests

LO 4

Though no single noninvasive laboratory test is currently available for the diagnosis of osteomyelitis, several nonspecific tests are commonly used to aid in the diagnosis and to monitor response to therapy.

Nonspecific inflammatory markers for infection include:[1,2,4–6]

- White blood cell (WBC) count
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Procalcitonin

WBC, ESR, and CRP are often elevated, but may also be within normal limits. An elevated WBC is mostly seen in patients with acute osteomyelitis.[1,3,6,9] CRP rises faster than ESR during early stages of infection and also returns to normal levels more quickly than ESR. This makes CRP a more useful tool for both diagnosis and monitoring of therapeutic response.[4–6] Similar to CRP, procalcitonin may be useful for both diagnosis and monitoring of therapeutic response; however, it is often more expensive and may not be as readily available.[4]

Microbiologic Evaluation

LO 4

Isolation of a causative pathogen from bone biopsy samples is essential for definitive antimicrobial therapy.[1–3,5,7,11,12] If bone biopsy cannot be performed, quality specimens (eg, two consecutive samples with bone contact [deep samples] in patients with contiguous osteomyelitis[12,15] or blood cultures in patients with acute hematogenous osteomyelitis)[1,3,5] may assist in pathogen identification. Superficial swabs often represent colonization rather than infecting organism(s) and thus have little value in selecting therapy.[1,7,12,14]

Imaging Studies

LO 4

Various imaging studies are used to assist in the diagnosis of osteomyelitis.[1,3,12,14,16,17]

- Magnetic resonance imaging (MRI) is considered the gold standard imaging modality for diagnosing of osteomyelitis.[1,3,4,11,13,14,16,17] Advantages include early detection (3–5 days after onset of symptoms), no radiation exposure, and high resolution.[1,6,16,17] Disadvantages include expense, inconvenience to patients (long examination time), movement artifacts, and the limitations to scanning patients with pacemakers and other implantable metal devices.[3,17]
- Plain film radiographs (x-rays) are the initial imaging study of choice for skeletal infections.[1,5,6,12,16] Although changes in soft tissue may appear within 3 days of infection, bone lesions may not be visible for 10 to 21 days.[1,4,6,11,12,16] Advantages of radiographs are accessibility, cost, low radiation exposure, and they are easily repeatable.[5,16] A disadvantage is the inability to detect early bone infections.[1,3,4,6,11,16]
- Computed tomography (CT) scans have high resolution and reproducibility.[17] CT scans have reduced sensitivity compared to MRI and should not be routinely used to diagnose osteomyelitis.[1,5,16] Advantages are that it is useful for the identification of sequestra, and it is less expensive than MRI.[3,16,17] Disadvantages include patient exposure to radiation and inability to use contrast medium to enhance images in patients with impaired renal function or previous allergic reactions.[3,4,17]
- Radionuclide imaging is also used for the early diagnosis of bone infections.[16] The most widely used nuclear medicine test is the three-phase bone scan.[16,17] An advantage is early detection within 24 to 48 hours after onset of symptoms.[5,6,16] Disadvantages include low specificity (increased risk of false positives) in patients with recent trauma, surgery, orthopedic prosthesis, diabetes, and ischemia, and high radiation dose required.[1,16] Using a labeled WBC scan in combination with the three-phase bone scan can increase sensitivity and specificity.[14,16]

TREATMENT

KEY CONCEPT The treatment goals for osteomyelitis are to eradicate the infection and prevent recurrence.[6–8,14,18]

Patient Encounter Part 1

A 42-year-old man limps into the emergency department complaining of pain and swelling in his left lower leg. He states that he also has a fever and feels tired. After questioning him, you discover that he was discharged from the hospital approximately 1 week ago following surgery for an open fracture of his left tibia. He had undergone debridement and irrigation, followed by internal fixation and treatment with IV vancomycin. He was discharged home on oral ciprofloxacin due to a history of reported penicillin allergy. On physical examination, the area above the fracture is red and swollen (erythematous and inflamed).

What information is suggestive of osteomyelitis?

What risk factors, if any, does he have for osteomyelitis?

General Approach to Treatment

KEY CONCEPT Antimicrobial therapy alone is the mainstay of treatment for acute osteomyelitis.[3–5,7] In comparison, treatment for chronic osteomyelitis typically requires a combination of antimicrobial therapy and surgical intervention.[7,11,14] If the patient is not a candidate for surgical intervention, prolonged antimicrobial therapy is generally necessary.[11–14]

▶ *Nonpharmacologic Therapy*

LO 9

In addition to medical and surgical management, nonpharmacologic interventions for health promotion such as smoking cessation, weight-control, and good nutrition should be emphasized to the patient. Additionally, patients with diabetes should be counseled regarding the importance of frequent blood glucose monitoring and control, routine care and self-examination of lower extremities, and aggressive wound care.[14] Patients with chronic immobility should be counseled on skin care and techniques to prevent the development of pressure ulcers.[7]

▶ *Pharmacologic Therapy*

KEY CONCEPT Empiric antimicrobial therapy should target common pathogen(s) based on patient-specific risk factors and route of infection.[6] Empiric antimicrobial coverage against *S. aureus*, including MRSA, should be considered for all classifications of osteomyelitis.[1,2,6,7,19,20] In addition to MRSA coverage, patients with contiguous osteomyelitis with vascular insufficiency (eg, diabetic) should also receive empiric coverage for Enterobacteriaceae, *P. aeruginosa,* and anaerobes.[11,14] Specific recommendations may vary based on factors such as patient allergies, potential for harboring resistant organisms, institution formulary, and cost considerations.[2,3,11]

LO 5

Patient Encounter Part 2

The medical team suspected osteomyelitis and ordered laboratory tests and imaging studies and consulted orthopedic surgery service.

How would you classify the infection in this patient?

What laboratory test(s) should be ordered for this patient?

What imaging study(s) should be ordered for this patient?

LO 6

Antimicrobial therapy should be guided by culture and susceptibility data of appropriately collected specimens when available (Table 81–1).[4,6,11,14] If MRSA is isolated, vancomycin is considered first-line therapy with desired troughs between 15 and 20 mcg/mL. However, if the minimum inhibitory concentration is greater than 2 mcg/mL (2 mg/L), alternative agents should be considered.[10,21,22] Alternative agents include daptomycin, linezolid, trimethoprim-sulfamethoxazole in combination with oral rifampin, or clindamycin.[21] Other MRSA active agents (tigecycline, telavancin, ceftaroline, dalbavancin, tedizolid, oritavancin) lack robust clinical data to support their routine use in osteomyelitis.[10,23] Clindamycin is commonly used in pediatric patients.[3,4,8,21] However, microbiology laboratories must screen with a disk diffusion test (D-test) for inducible resistance via the macrolide-lincosamide-streptogramin gene, as clindamycin failures have been associated with infections caused by isolates that are D-test positive.[3,24] If methicillin-sensitive *S. aureus* (MSSA) is isolated and the patient has no β-lactam allergy, therapy should be changed to nafcillin/oxacillin or cefazolin.[1,2,5–7]

In comparison to acute hematogenous osteomyelitis, chronic osteomyelitis is associated with higher failure rates, largely due to the presence of necrotic bone.[1,8,14,25] These patients typically require surgical intervention to remove the necrotic bone and tissue, and if applicable, to replace infected hardware.[7] Comorbidities such as vascular insufficiency can further contribute to poor treatment outcomes seen with chronic osteomyelitis.[1,7] Due to the high failure rates, treatment in this patient population may require prolonged courses of therapy, with the primary goal of preventing amputation of infected area(s).[1,11,14]

KEY CONCEPT Treatment is initiated with IV antimicrobials in the inpatient or outpatient setting to optimize drug concentrations in bone.[7,14,16] Following initial IV therapy, a switch to oral antibiotics may be considered in patients with good clinical response, strict adherence, and reliable outpatient follow-up.[3,4,6,8,11,14,21] Ideally, oral agents should possess characteristics such as high bioavailability, good bone penetration, and long half-life (eg, extended dosing interval).[1,3,5–7,10,11,21,25] Commonly used oral antimicrobials include fluoroquinolones, clindamycin, linezolid, and trimethoprim-sulfamethoxazole.[1,6,7,19,21] Additionally, oral rifampin may be used in combination with another antibiotic in patients with osteomyelitis associated with prosthetic material or as part of step-down therapy for MRSA osteomyelitis in combination with trimethoprim-sulfamethoxazole.[1,7,11,21,25] For chronic osteomyelitis, some clinicians recommend placement of antibiotic impregnated beads or cement.[3,7,11,14] This enables antibiotics such as aminoglycosides and vancomycin to be delivered in high concentrations at the site of infection.[3,7]

KEY CONCEPT The duration of treatment is typically 4 to 8 weeks for acute and chronic osteomyelitis.[1–5,8,14,21] Shorter regimens (3 weeks) are often recommended for uncomplicated acute hematogenous infections due to *S. aureus* in children greater than 3 months of age.[4,6,8] Infectious Diseases Society of America (IDSA) MRSA guidelines recommend a minimum of 8 weeks for treatment of MRSA osteomyelitis in adults.[21] Suppressive therapy (> 3 months) may be necessary for certain populations such as patients with vascular insufficiency or patients with recalcitrant infections that do not respond to 4 to 8 weeks of therapy.[1,5,11,14,21]

Antimicrobial Stewardship Implications in the Management of Osteomyelitis

Stewardship programs have become increasingly common in an attempt to ensure appropriate antimicrobial use as well

Table 81–1

Pathogen-Targeted Antimicrobial Therapy and Dosing Recommendations in Adults and Pediatrics

Microorganism	Antimicrobial Agent	Adult Dose	Pediatric Dose[a]
S. aureus			
MRSA	Vancomycin[b]	15–20 mg/kg IV every 8–12 hours	15 mg/kg IV every 6 hours
	Daptomycin[b]	6 mg/kg IV every 24 hours	6–10 mg/kg IV every 24 hours
	Linezolid	600 mg IV/oral every 12 hours	10 mg/kg IV/oral every 8 hours (< 12 years old)
	Clindamycin[c]	600 mg IV/oral every 8 hours	10–13 mg/kg/dose IV/oral every 6–8 hours
	Trimethoprim-sulfamethoxazole[b] (+ rifampin[c] 600 mg oral daily)	3.5–4.0 mg/kg of trimethoprim component IV/oral every 8–12 hours (trimethoprim-sulfamethoxazole single strength tablet is 80 mg/400 mg; double strength tablet is 160 mg/800 mg)	—
MSSA	Nafcillin[d]/oxacillin[b]	1–2 g IV every 4–6 hours	100–200 mg/kg/day IV in divided doses every 4–6 hours
	Cefazolin[b]	1–2 g IV every 6–8 hours	50–100 mg/kg/day IV in divided doses every 6–8 hours
***Enterococcus* spp.**			
Ampicillin-sensitive	Ampicillin[b]	2 g IV every 4–6 hours	100–400 mg/kg/day IV in divided doses every 6 hours
Ampicillin-resistant Vancomycin-resistant	Vancomycin[b]	15–20 mg/kg IV every 8–12 hours	15 mg/kg IV every 6 hours
	Daptomycin[b]	6 mg/kg IV every 24 hours	—
	Linezolid	600 mg IV/oral every 12 hours	10 mg/kg IV/oral every 8 hours (< 12 years old)
***Streptococcus* spp.**	Penicillin G[b]	2–4 million units IV every 4–6 hours	250,000–400,000 units/kg/day IV in divided doses every 4–6 hours
	Ceftriaxone[d]	1–2 g IV every 24 hours	50–100 mg/kg/day IV in divided dose every 12–24 hours
P. aeruginosa			
	Doripenem[b]	500 mg IV every 8 hours	—
	Imipenem/cilastatin[b]	500 mg IV every 6 hours	25 mg/kg IV every 6 hours
	Meropenem[b]	1 g IV every 8 hours	10–20 mg/kg IV every 8 hours
	Ceftazidime[b]	2 g IV every 8 hours	50 mg/kg IV every 8 hours
	Cefepime[b]	2 g IV every 12 hours	50 mg/kg IV every 8–12 hours
	Piperacillin/tazobactam[b]	4.5 g IV every 6 hours	100 mg/kg IV piperacillin component every 8 hours
	Ciprofloxacin[b,e]	400 mg IV every 8–12 hours; 750 mg oral every 12 hours	—
	Levofloxacin[b,e]	750 mg IV/oral every 24 hours	—
Enterobacteriaceae (in addition to antipseudomonal agents listed above)	Ceftriaxone[d]	1–2 g IV every 24 hours	50–100 mg/kg/day IV in divided doses every 12–24 hours
	Cefotaxime[b,d]	1–2 g IV every 8 hours	50–200 mg/kg/day IV in divided doses every 6–8 hours
	Ertapenem[b]	1 g IV every 24 hours	—
	Moxifloxacin[c,e]	400 mg IV/oral every 24 hours	—
Anaerobes[f]	Clindamycin[c]	600–900 mg IV every 8 hours; 300–450 mg oral every 6–8 hours	25–40 mg/kg/day IV in divided doses every 6–8 hours
	Metronidazole[b,c]	500 mg IV/oral every 6–8 hours	30 mg/kg/day IV/oral in divided doses every 6–8 hours

[a]Refer to specialized pediatric reference for maximum neonatal and pediatric dosing recommendations.

[b]Dosage adjustment necessary in renal dysfunction.

[c]Dosage adjustment necessary in severe hepatic dysfunction.

[d]Dosage adjustment necessary in patients with concomitant renal and hepatic dysfunction.

[e]Fluoroquinolones: Not approved by the US FDA for use in children except for anthrax (ciprofloxacin, levofloxacin) and complicated UTI and pyelonephritis (ciprofloxacin).

[f]May consider β-lactam/β-lactamase inhibitor or carbapenem for broad-spectrum activity including anaerobes.

Data from Refs. 1, 3, 4, 7, 8, 10, 11, 19, and 21–26.

LO 8 as to combat emerging resistance. Patients with osteomyelitis are typically subject to prolonged durations of therapy and thus much of the stewardship focus should be on appropriate de-escalation of empiric therapy and duration without sacrificing successful outcomes. As mentioned above, compliant patients with an identified organism may be switched to oral therapy and those who require IV therapy should receive an agent with the narrowest spectrum. Stewardship opportunities may arise throughout the treatment course and thus opportunities to optimize patient care should be continually evaluated.

OUTCOME EVALUATION

LO 7 Therapeutic success is measured by the extent to which the care plan (a) resolves signs and symptoms, (b) eradicates the microorganism(s), (c) prevents relapses, and (d) prevents complications such as amputation.[8,11,14] Patients should be evaluated for resolution of clinical signs and symptoms and normalization of laboratory tests (WBC, CRP, ESR, procalcitonin, and cultures).[3–6,8,10,14] Improvement in clinical manifestations may be seen within 2 to 4 days of initiation of IV antimicrobial therapy in patients with acute osteomyelitis.[4,8] A reduction in CRP should be seen within 1 week of therapy and should be monitored weekly throughout therapy for a continued downward trend.[3,4,6] ESR can also be monitored weekly, although normalization will be slower than for CRP.[3,6] Patients should also be monitored for antimicrobial tolerability and toxicity[2] (Table 81–2). If poor response is noted, the following should be evaluated: (a) patient adherence, (b) significant drug–drug or drug–food interactions, (c) appropriate dosage to achieve therapeutic concentrations, (d) development of antimicrobial resistance necessitating a change in the treatment regimen, (e) need for additional imaging studies, and (f) diagnostic reevaluation.[8,14] Treatment is considered successful if all clinical signs and symptoms are resolved and

Patient Encounter Part 3: The Medical History, Physical Examination, and Diagnostic Tests

PMH: Type 2 diabetes mellitus, dyslipidemia, depression/generalized anxiety disorder

SH: Tobacco smoker (one pack per day for 10 years), two to three cans of beer daily. Employed as mechanic

Allergies: Penicillins (hives)

Meds: Ciprofloxacin 500 mg orally two times a day; rosuvastatin 20 mg orally at bedtime; glargine 10 units subcutaneously at bedtime; fluoxetine 20 mg orally daily; OTC ibuprofen 200 mg orally every 4 hours

PE:

Gen: Moderate distress with pain and tenderness in lower left leg; limps

Skin: Erythema and inflammation

VS: BP 150/70 mm Hg, P 95 beats/min, RR 20 breaths/min, T 38.4°C (101.2°F), Ht 5′ 7″ (170 cm), Wt 73 kg (161 lb)

Labs: WBC 16.4 × 10^3/mm^3 (16.4 × 10^9/L), hemoglobin 13.0 g/dL (130g/L; 8.07 mmol/L), hematocrit 37.0% (0.37), platelets 220 × 10^3/uL (220 × 10^9/L), BUN 23 mg/dL (8.2 mmol/L), serum creatinine (Scr) 1.3 mg/dL (115 µmol/L), total bilirubin 1.1 mg/dL (18.8 µmol/L), alkaline phosphatase 82 U/L (1.37 µkat/L), AST 28U/L (0.47 µkat/L), ALT 13 U/L (0.22 µkat/L), albumin 3.7 g/dL (37 g/L), fasting blood glucose 210 mg/dL (11.6 mmol/L), ESR 110 mm/h, CRP 24 mg/dL (240 mg/L)

Microbiology: Culture from bone aspirate is pending

Based on the information presented, create a care plan for this patient's osteomyelitis. Your plan should include: (a) goals of therapy, (b) patient-specific detailed therapeutic plan, (c) nonpharmacologic interventions, and (d) follow-up plan to determine whether outcomes have been achieved.

Table 81–2

Monitoring Considerations for Select Antistaphylococcal Agents

Antimicrobial	Monitoring Considerations
Daptomycin	Muscle pain or weakness particularly of the distal extremities; monitor CPK weekly with more frequent monitoring in patients with renal insufficiency or receiving (or recent discontinuation) of HMG-CoA reductase inhibitors; consider temporarily discontinuing HMG-CoA reductase inhibitors while patient receiving daptomycin. Peripheral neuropathy: Monitor for neuropathy. Decreased efficacy was observed in patients with moderate baseline renal impairment.
Linezolid	Myelosuppression: Monitor CBC once weekly. MAO inhibitors; evaluate for potential drug–drug interactions. Linezolid should not be used concomitantly or within 2 weeks of medications that inhibit monoamine oxidases A or B. Serotonin syndrome; evaluate for potential drug–drug and drug–food interactions. Patients taking serotonergic antidepressants should receive linezolid only if no other therapies are available. Discontinue serotonergic antidepressants and monitor patients for signs and symptoms of both serotonin syndrome and antidepressant discontinuation. Peripheral and/or optic neuropathy has been reported with long-term therapy; perform routine neurologic and ophthalmic evaluations in these patients. Elevation of blood pressure in certain patients (eg, uncontrolled hypertension): monitor blood pressure. Hypoglycemia in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents: monitor glucose.
Vancomycin	Targeted steady state trough is 15–20 mcg/mL (15–20 mg/L; 10–14 µmol/L) for serious infections such as osteomyelitis. Renal dysfunction: monitor weekly renal function (BUN/SCr) and troughs in stable patients; more often in nonstable patients. Potential for additive renal toxicity if being coadministered with a nephrotoxic agent (eg, aminoglycoside, piperacillin-tazobactam).

BUN, blood urea nitrogen; CBC, complete blood count; CPK, creatine phosphokinase; MAO, monoamine oxidase; SCr, serum creatinine.

Data from Refs. 1, 7, 11, 19, and 21–26.

Patient Encounter Part 4

Culture from the bone aspirate grows *S. aureus* (sensitive to daptomycin, linezolid, rifampin, trimethoprim-sulfamethoxazole, and vancomycin but resistant to clindamycin, erythromycin, and oxacillin). The patient received 2 weeks of empiric IV antimicrobial therapy following debridement. The patient has shown clinical and laboratory improvement. The multidisciplinary medical team plans to complete therapy with an oral antibiotic(s).

What oral antimicrobial therapy would you recommend for this patient?

Evaluate the patient's medication profile for drug–drug interactions.

Counsel the patient regarding this drug therapy.

Patient Care Process

Collect Information:

- Review the medical history for osteomyelitis risk factors.
- Based on physical examination and review of systems, determine whether the patient is experiencing signs or symptoms of osteomyelitis.
- Review available imaging studies and laboratory tests, especially WBC, ESR, and CRP.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.

Assess the Information:

- Review culture data for antimicrobial drug selection and stewardship.
- Evaluate drug allergies or intolerance, as well as drug–drug interactions that would impact antimicrobial selection.
- Assess available imaging studies and laboratory data to differentiate acute versus chronic disease.

Develop a Care Plan:

- Select an appropriate antimicrobial regimen, including drug, dose, and duration, given patient-specific information.
- Identify criteria for possible de-escalation to oral therapy during treatment course.
- Establish monitoring parameters based on the antimicrobial regimen selected.

Implement the Care Plan:

- Provide patient education with regard to disease state and drug therapy. Stress the importance of adherence to the therapeutic regimen.

Follow-up: Monitor and Evaluate:

- Determine whether the antibiotic dosage regimen is optimal based on patient-specific factors and site of infection.
- Patients should be monitored for clinical and laboratory response, development of adverse drug reactions, and potential drug–drug interactions. Patients should also be closely monitored for adherence in the outpatient setting.

all laboratory tests have returned to normal following 4 to 8 weeks of appropriate treatment. Due to high rates of relapse, patients should have medical follow-up for at least 1 year following resolution of symptoms.[4] Patients should be evaluated at predefined follow-up intervals (3- to 6- to 12-months) for any clinical manifestations of recurring infection and continued normalization of laboratory tests.[8,11] Follow-up imaging studies at 1 to 2 years may be useful in some patients to confirm therapeutic success.

Abbreviations Introduced in This Chapter

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CBC	Complete blood count
CRP	C-reactive protein
CPK	Creatine phosphokinase
CT	Computed tomography
ESR	Erythrocyte sedimentation rate
IDSA	Infectious Diseases Society of America
IV	Intravenous
MAO	Monoamine oxidase
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
Scr	Serum creatinine
WBC	White blood cell

REFERENCES

1. Chihara S, Segreti J. Osteomyelitis. Dis Mon. 2010;56:6–31.
2. Howell WR, Goulston C. Osteomyelitis: an update for hospitalists. Hosp Pract (Minneap). 2011;39(1):153–160.
3. Harik NS, Smeltzer MS. Management of acute hematogenous osteomyelitis in children. Expert Rev Anti infect Ther. 2010; 8(2):175–181.
4. Peltola H, Pääkkönen M. Acute osteomyelitis in children. N Engl J Med. 2014;370:352–360.
5. Zimmerli W. Vertebral osteomyelitis. N Engl J Med. 2010; 362:1022–1029.
6. Conrad DA. Acute hematogenous osteomyelitis. Pediatr Rev. 2010;31:464–471.
7. Rao N, Ziran BH, Lipsky BA. Treating osteomyelitis: antibiotics and surgery. Plast Reconstr Surg. 2011;127(suppl 1):S177–S187.
8. Howard-Jones AR, Isaacs D. Systemic review of duration and choice of systemic antibiotic therapy for acute haemetagenous bacterial osteomyelitis in children. J Pediatr Child Health. 2013:49:760–768.
9. Waldvogel FA, Medoff G, Swartz MN. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med. 1970;282:198–206.
10. Senneville E, Nguyen S. Current pharmacotherapy options for osteomyelitis: convergences, divergences, and lessons to be drawn. Expert Opin Pharmacother. 2013;14:723–734.
11. Peters EJ, Lipsky BA. Diagnosis and management of infection in the diabetic foot. Med Clin N Am. 2013;97:911–946.
12. Game FL. Osteomyelitis in the diabetic foot: diagnosis and management. Med Clin N Am. 2013;97:947–956.
13. Game F. Management of osteomyelitis of the foot in diabetes mellitus. Nat Rev Endocrinol. 2010;6:43–47.
14. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54;132–173.

15. Bernard L, Assal M, Garzoni C, Uckay L. Predicting the pathogen of diabetic toe osteomyelitis by two consecutive ulcer cultures with bone contact. Eur J Clin Microbiol Infect Dis. 2011;30:279–281.
16. Hankin D, Bowling FL, Metcalfe SA, et al. Critically evaluating the role of diagnostic imaging in osteomyelitis. Foot Ankle Spec. 2011;4(2):100–105.
17. Gotthardt M, Bleeker-Rovers CP, Boerman OC, Oyen WJG. Imaging of inflammation by PET, conventional scintigraphy, and other imaging techniques. J Nucl Med. 2010;51:1937–1949.
18. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev. 2013;9:CD004439.
19. Boucher H, Miller LG, Razonable RR. Serious infections caused by methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis. 2010;51(suppl 2):S183–S197.
20. Bhavan KP, Marschall J, Olsen MA, et al. The epidemiology of hematogenous vertebral osteomyelitis: a cohort study in a tertiary care hospital. BMC Infect Dis. 2010;10:158.
21. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis. 2011;52:1–38.
22. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009;66:82–98.
23. Moenster RP, Linneman TW, Call WB, et al. The potential role of newer gram-positive antibiotics in the setting of osteomyelitis of adults. J Clin Pharm Ther. 2013;38:89–96.
24. Eleftheriadou I, Tentolouris N, Argiana V, et al. Methicillin-resistant *Staphylococcus aureus* in diabetic foot infections. Drugs. 2010;70(14):1785–1797.
25. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012:54:393–407.
26. Lexi-Drugs Online. Available from: www.crlonline.com. Accessed September 1, 2014.

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82 Sepsis and Septic Shock

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LEARNING OBJECTIVES

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

LO

1. Compare and contrast the definitions of syndromes related to sepsis.
2. Identify the pathogens associated with sepsis.
3. Discuss the pathophysiology of sepsis as it relates to pro- and anti-inflammatory mediators.
4. Identify patient symptoms as early or late sepsis and evaluate diagnostic and laboratory tests for patient treatment and monitoring.
5. Assess complications of sepsis and discuss their impact on patient outcomes.
6. Design desired treatment outcomes for septic patients.
7. Formulate a treatment and monitoring plan (pharmacologic and nonpharmacologic) for septic patients.
8. Evaluate patient response and devise alternative treatment regimens for nonresponding septic patients.

INTRODUCTION

KEY CONCEPT Sepsis occurs across a continuum of physiologic stages in response to infection which manifests as systemic inflammation, coagulation, and tissue hypoperfusion, potentially leading to organ dysfunction.[1] The Third International Consensus Definitions for Sepsis and Septic Shock were published in 2016 and included updated nomenclature to standardize sepsis terminology. Previous definitions focused largely on inflammatory changes that may not necessarily be associated with organ dysfunction. Currently, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response represented by an increase of at least 2 points in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Table 82–1). Septic shock is defined as a subset of patients with further increases in mortality resulting from underlying circulatory, cellular, and/or metabolic abnormalities. These patients require the use of vasopressor support in addition to adequate volume resuscitation to maintain a mean arterial pressure of at least 65 mm Hg and have an elevated serum lactate level greater than 2 mmol/L. Adult patients with suspected sepsis may be screened using a bedside clinical scoring system known as the quickSOFA (qSOFA) to rapidly identify patients who may need further diagnostic workup and intervention (Table 82–2).[2,3]

LO 1

EPIDEMIOLOGY AND ETIOLOGY

Sepsis is the leading cause of morbidity and mortality for critically ill patients and the tenth leading cause of death overall.[4,5] Mortality rates remain high for patients with sepsis and septic shock with septic shock and multiorgan failure as the most common causes of death.[1] There are approximately 750,000 cases of sepsis diagnosed every year in the United States which continues to increase.[1]

Risk factors for developing sepsis include increased age, cancer, immunodeficiency, chronic organ failure, genetic factors (male gender and nonwhite ethnic origin in North America), and the presence of bacteremia.[5–9] Pulmonary infections cause approximately half of all sepsis cases, followed by intraabdominal and genitourinary infections.[2] In approximately one-third of sepsis cases, a pathogen is not identified making de-escalation from broad spectrum to a more narrowed antimicrobial regimen difficult.[2]

KEY CONCEPT Gram-positive and gram-negative bacteria, fungal species, and viruses may cause sepsis (Table 82–3). Gram-positive infections account for 30% to 50% of sepsis and septic shock cases.[5–7] The percentages of gram-negative, polymicrobial, and viral sepsis cases are 25%, 25%, and 4%, respectively.[5–7,10] A multinational study of 14,000 critically ill patients showed an increase in gram-negative bacterial causes of sepsis compared to gram-positive bacterial and fungal causes.[2] Multidrug-resistant (MDR) bacteria are responsible for approximately 25% of sepsis cases, are difficult to treat due to fewer antimicrobial options, and increase mortality.[6,7] The rate of fungal infections has significantly increased with *Candida albicans* as the most common fungal species identified; however, nonalbicans species (*C. glabrata, C. krusei,* and *C. tropicalis*) have increased from 24% to 46%.[5,10,11] Other fungi identified as causes of sepsis include species of *Cryptococcus, Coccidioides, Fusarium*, and *Aspergillus*.

LO 2

PATHOPHYSIOLOGY

The development of sepsis is complex and multifactorial. The normal host response to infection is designed to localize and control microbial invasion and initiate repair of injured tissue through phagocytic cells and inflammatory mediators.[4] KEY CONCEPT Sepsis results when the interplay between the host's immune, inflammatory, and coagulant responses becomes exaggerated, extending to normal tissue distant from the initial tissue site.

Table 82–1

The SOFA Score

SOFA Score	1	2	3	4
Respiration				
PaO_2/FiO_2, mm Hg	< 400	< 300	< 200 ——with respiratory support——	< 100
Coagulation				
Platelets x $10^3/mm^3$	< 150	< 100	< 50	< 20
Liver				
Bilirubin, mg/dL (μmol/L)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	≥ 12.0 (> 204)
Cardiovascular				
Hypotension	MAP < 70 mm Hg	Dopamine ≤ 5 or dobutamine (any dose)[a]	Dopamine > 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system				
Glasgow Coma Score	13–14	10–12	6–9	< 6
Renal				
Creatinine, mg/dL (μmol/L) or urine output	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–400) or < 500 mL/day	≥ 5.0 (> 440) or < 200 mL/day

[a]Adrenergic agents administered for at least 1 h (doses given are in μg/kg/min).

Source: Reproduced, with permission, from Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996 Jul;22(7):707–10.

Pro- and Anti-inflammatory Mediators

LO 3

The key factor in the development of sepsis is inflammation, which is intended to be a local and contained response to infection or injury. Infection or injury is controlled through proinflammatory and anti-inflammatory mediators. Proinflammatory mediators facilitate clearance of the injuring stimulus, promote resolution of injury, and are involved in processing of damaged tissue.[4,14–17] To control the intensity and duration of the inflammatory response, anti-inflammatory mediators are released that act to regulate proinflammatory mediators.[16,17] The balance between pro- and anti-inflammatory mediators localizes infection/injury of host tissue.[14–17] However, systemic responses ensue when equilibrium in the inflammatory process is lost.

The inflammatory process in sepsis is linked to the coagulation system. Proinflammatory mediators may have procoagulant and antifibrinolytic effects, whereas anti-inflammatory mediators may have **fibrinolytic** effects. A key factor in the inflammation of sepsis is activated protein C, which enhances fibrinolysis and inhibits inflammation. Protein C levels are decreased in many septic patients.

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of sepsis varies, and the rate of development of clinical manifestations may differ from patient to patient.

Table 82–2

Quick SOFA (qSOFA) Criteria

- Respiratory rate ≥ 22 breaths/min
- Altered mentation
- Systolic blood pressure ≤ 100 mm Hg

Positive qSOFA score indicated by meeting ≥ 2 criteria

A physical examination should be performed rapidly and efficiently when sepsis is suspected, with efforts directed toward uncovering the most likely cause of sepsis. The patient may not provide any medical history; therefore, historical data may

Table 82–3

Pathogens in Sepsis

Organism	Frequency (%)
Gram-positive bacteria	30–50
Methicillin-susceptible *Staphylococcus aureus*	14–24
Methicillin-resistant *Staphylococcus aureus*	5–11
Other *Staphylococcus* species	1–3
Streptococcus pneumoniae	9–12
Other *Streptococcus* species	6–11
Enterococcus species	3–13
Anaerobes	1–2
Other gram-positive bacteria	1–5
Gram-negative bacteria	25–30
Escherichia coli	9–27
Pseudomonas aeruginosa	8–15
Klebsiella pneumoniae	2–7
Enterobacter species	6–16
Haemophilus influenzae	2–10
Anaerobes	3–7
Other gram-negative bacteria	3–12
Fungi	
Candida albicans	1–3
Other *Candida* species	1–2
Parasites	1–3
Viruses	2–4

Data from Refs. 5, 12, and 13.

Possible Physical Examination Results in Sepsis

HEENT: Scleral icterus, dry mucous membranes, pinpoint pupils, dilated and fixed pupils, nystagmus

Neck: Jugular venous distention, carotid bruits

Lungs: Crackles (rales), consolidation, egophony, absent breath sounds

CV: Irregular rhythm, S_3 gallop, murmurs

Abd: Tense, distended, tender, rebound, guarding, hepatosplenomegaly

Rectal: Decreased tone, bright red blood

Exts: Swollen calf, disparity of blood pressure between upper extremities

Neurologic: Agitation, confusion, delirium, obtundation, coma

Skin: Cold, clammy, or warm; hyperemic skin; rashes

be obtained from medical records and/or family. The patient's medical condition, recent illnesses, infections, or activities may provide valuable information about the cause of sepsis.

Diagnostic and Laboratory Tests

LO 4

Microbiologic cultures should be obtained before antimicrobial therapy is initiated as long as this does not significantly delay the start of therapy. However, cultures take 6 to 72 hours for results to be completed and often are negative (no growth of bacterial organisms). Negative cultures do not rule out the presence of infection. Administering antimicrobials before obtaining cultures may lead to a false-negative culture. Rapid diagnostics of blood cultures allows for identification of specific pathogens within as little as 20 minutes to 3 hours after initial growth is identified. However, not all health care systems have this technology available.

At least two sets of blood cultures should be obtained to rule out contamination, with at least one set drawn percutaneously and one set drawn through each vascular access device present for greater than 48 hours.

Cultures of urine (with urinalysis), respiratory secretions, cerebrospinal fluid, and wounds should be obtained if the clinical presentation suggests infection of these specific fluids, tissues, or organs. Laboratory tests should be performed to evaluate infection or complications of sepsis, including complete blood count (CBC) with differential, coagulation parameters, comprehensive metabolic panel (CMP), serum lactate concentration, arterial blood gas (ABG), and appropriate diagnostic radiographic imaging studies.

The use of biomarkers of sepsis, such as endotoxin and procalcitonin, has been controversial. Measurement of endotoxin, procalcitonin, or other markers in blood or serum is not routinely recommended. Concentrations of procalcitonin in serum are usually increased in sepsis, but fail to differentiate between infection and inflammation. However, procalcitonin has a high negative predictive value and may allow for the discontinuation of antibiotics. It is important to note that the measurement of any biomarker, including procalcitonin, should be used in conjunction with the patient's overall clinical assessment and should never be used as the sole indicator for altering microbial therapy.

Complications of Sepsis

KEY CONCEPT Recognition and treatment of sepsis complications, particularly organ failure, is essential to improve outcomes. The cumulative burden of sepsis complications is the leading factor

Clinical Presentation and Diagnosis of Sepsis

LO 4

The signs and symptoms of septic patients are referred to as early and late sepsis.

Signs and Symptoms

The initial clinical signs and symptoms represent early sepsis, and they include fever, chills, and change in mental status. Other signs and symptoms include:

- Tachycardia
- Tachypnea
- Nausea and vomiting
- Hyperglycemia
- Myalgias
- Lethargy and malaise
- Proteinuria
- Leukocytosis
- Hypoxia
- Hyperbilirubinemia

Septic patients may have an elevated, low, or normal temperature. The absence of fever is common in neonates and elderly patients. Hypothermia is associated with a poor prognosis. Hyperventilation may occur before fever and chills and may lead to respiratory alkalosis. Disorientation and confusion may develop early in septic patients, particularly in the elderly and patients with preexisting neurologic impairment. Disorientation and confusion may be related to the infection or due to sepsis signs and symptoms (eg, hypoxia).

Late sepsis represents a slow process that develops over several hours of hypoperfusion. Signs and symptoms of late sepsis include:

- Lactic acidosis
- Oliguria
- Leukopenia
- Thrombocytopenia
- Myocardial depression
- Pulmonary edema
- Hypotension
- Hypoglycemia
- Gastrointestinal hemorrhage

Oliguria often follows hypotension because of decreased renal perfusion. Metabolic acidosis ensues because of diminished clearance of lactate by the kidneys and liver.

Patient Encounter Part 1

A 64-year-old woman with history of hypertension, diabetes, and end-stage renal disease presents to the emergency department with complaints of fever and chills during hemodialysis. The patient is becoming increasingly lethargic and is unable to answer simple questions, such as her name and the year.

What information is suggestive of infection and/or sepsis?

What information do we need in order to confirm or diagnose sepsis in this patient?

of mortality. The risk of death increases 20% with failure of each additional organ. The most common complications are respiratory and cardiovascular compromise, usually seen as **acute respiratory distress syndrome** (ARDS), hemodynamic compromise, and elevated serum lactate levels. Other complications include altered mentation, acute kidney injury (AKI) which may require renal replacement therapy, paralytic ileus, **disseminated intravascular coagulation** (DIC), and adrenal insufficiency.[2]

LO 5

TREATMENT AND OUTCOME EVALUATION

Desired Outcomes

KEY CONCEPT The primary treatment goal of sepsis is to prevent morbidity and mortality through rapid recognition and intervention. Treatment is aimed at early implementation of therapies, such as fluid resuscitation and antimicrobials, reducing or eliminating organ dysfunction, eliminating the source of infection, avoiding adverse reactions of treatment, and providing cost-effective therapy.[18–24]

LO 6

General Approach to Treatment

Similar to the emphasis placed on the expedited treatment of patients with acute myocardial infarction and cerebrovascular accidents, rapid intervention with appropriate therapies, once a diagnosis of sepsis has been made, is crucial to decrease morbidity and mortality.[18,20]

LO 7

Pertinent approaches in the management of septic patients are as follows (**Figure 82–1**)[24]:

1. Prompt recognition of the septic patient and early implementation of therapies.
2. Fluid therapy, using crystalloids initially, to restore intravascular volume depletion.
3. Early administration of broad-spectrum antimicrobial therapy.
4. Vasopressor therapy, using norepinephrine initially, to maintain hemodynamic stability (on average a mean arterial pressure of 65 mm Hg [8.6 kPa]) in patients with septic shock refractory to fluid resuscitation.
5. Intravenous (IV) hydrocortisone may be considered for patients who remain hemodynamically unstable despite adequate fluid resuscitation and vasopressor support.
6. Glycemic control via infusion of regular insulin to maintain glucose levels between 140 and 180 mg/dL (7.8 and 10.0 mmol/L).
7. Adjunctive therapies: blood product administration, sedation, analgesia, neuromuscular blockade, renal replacement therapy, deep vein thrombosis (DVT) prophylaxis, stress ulcer prophylaxis, and nutrition.

Treatment for sepsis focuses on infection, inflammation, hypoperfusion, and widespread tissue injury. Septic patients may require multiple simultaneous treatment regimens to achieve desired outcomes of decreased morbidity and mortality.

Initial Resuscitation

A landmark study of early goal directed therapy (EGDT) using a standardized protocol that required the use of a special catheter for central venous oxygen saturation monitoring decreased 28-day mortality in septic patients by approximately 16%.[23] Three subsequent randomized controlled studies comparing EGDT to groups of patients receiving contemporary care (with or without the use of protocols) found no differences in mortality.[25–27] These results demonstrate that continued focus on early recognition and treatment of these patients may play a more important role than protocol-based therapy; however, the use of EGDT was not associated with harm.

Upon recognition of sepsis, resuscitation should begin immediately. Within the first 3 hours, at least 30 mL/kg of crystalloid fluid should be administered intravenously. Subsequent fluid administration should be guided by frequent reassessment of hemodynamic status and dynamic variables to predict fluid responsiveness. The use of static variables, such as central venous pressure (CVP), to assess the need for additional fluid administration should not be used alone. Rather, these variables in conjunction with other dynamic measures, such as the passive leg raise technique, fluid challenges, and pulse pressure variation, may be better predictors of fluid responsiveness.[20,23,24,28]

Emerging noninvasive techniques, such as the use of cardiac ultrasound, have recently shown reliability in assessing intravascular volume status through measuring inferior vena cava diameter changes and collapsibility.[29,30] Resuscitation should also target the normalization of blood lactate levels in patients with an initially elevated blood lactate as a marker of improved tissue perfusion.[20]

Fluid Therapy

Crystalloid fluids (such as 0.9% sodium chloride or lactated Ringer solutions) or colloids (albumin products) are used for resuscitation, and clinical studies comparing the fluids have found them to be equivalent.[28,31,32] Crystalloids require more fluid volume, which may lead to more edema (utilize caution in patients at risk for fluid overload, eg, congestive heart failure, renal failure, and ARDS); however, albumin is significantly more expensive. Hydroxyethyl starch (HES), another type of colloid, should not be used due to studies demonstrating increased morbidity and mortality.[33,34] A large, multicenter, randomized controlled trial comparing HES to Ringer's acetate in patients with severe sepsis showed an increased 90-day mortality rate and a higher need for renal replacement therapy in patients administered HES for fluid resuscitation.[33] For these reasons, crystalloids are preferred versus colloids for initial resuscitation, except in cases where large amounts of crystalloids are needed and hypervolemia may be harmful to the patient.[20]

After initial fluid administration, there remains clinical controversy surrounding the appropriate type of fluid for continued resuscitation. There are emerging data which suggest potential benefit of using balanced crystalloid solutions or a chloride-restrictive strategy. There are low-quality data that suggest the administration of large volumes of isotonic saline may be associated with increased incidences of AKI and renal replacement therapy secondary to hyperchloremic metabolic acidosis.[35,36]

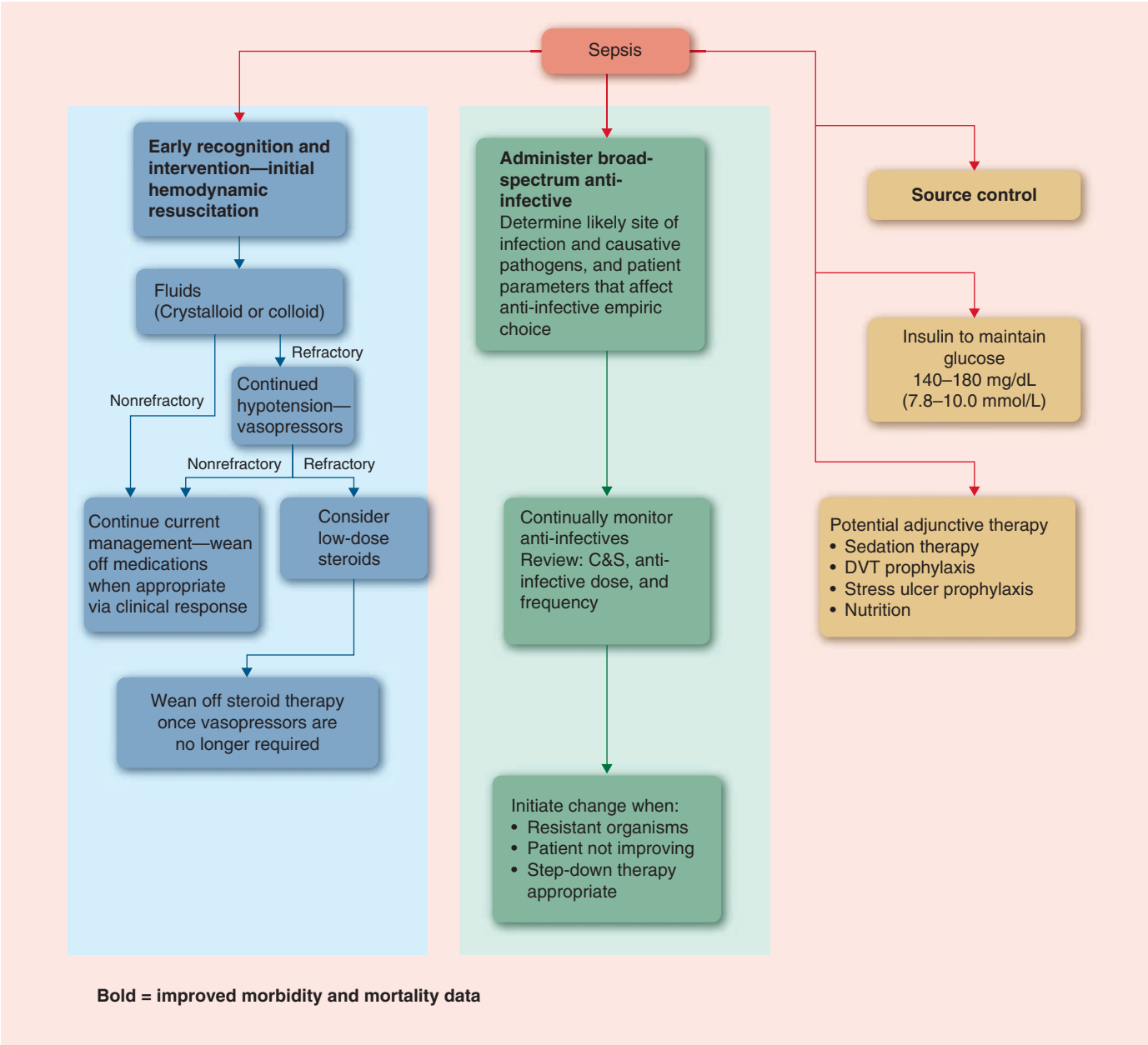

FIGURE 82–1. Therapeutic approach to sepsis. (C&S, cultures and susceptibilities.)

Anti-infective Therapy

KEY CONCEPT Appropriate empiric antimicrobial therapy decreases 28-day mortality compared with inappropriate empiric therapy (24% vs 39%).[18,19,37] Additionally, appropriate therapy administered within 1 hour of sepsis recognition also decreases complications and mortality.[18,19,37] Empiric antimicrobial therapy should include multiple agents for most cases, depending on the likely site of infection and causative pathogens. Anti-infective clinical trials in sepsis and septic shock patients are scarce and have not demonstrated differences among agents; therefore, factors that determine selection are:

- Site/source of infection.
- Causative pathogens.
- Community- or nosocomial-acquired infection.
- Immune status of patient.
- Antibiotic susceptibility and resistance profile for the institution and local community. Clinicians should be cognizant of growing prevalence of bacterial resistance in community and health care settings.
- Patient history (underlying disease, previous cultures or infections including any recent antibiotic therapy, and drug allergy/intolerance).
- Adverse reactions.
- Cost.

Anti-infective regimens should be broad-spectrum since delays in appropriate therapy result in increased mortality. In the subset of patients with septic shock, empiric therapy should include combination regimens with multiple antibiotics from different

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Hypertension, poorly controlled type 2 diabetes mellitus, end-stage renal disease on hemodialysis three times weekly

FH: Father died of heart attack at 71; mother has history of hypertension and diabetes mellitus

SH: Postal worker; previous smoker (10 pack-year history, quit at age 40); rare alcohol intake

Allergies: Penicillin (rash as child)

Meds: Lisinopril 20 mg by mouth once daily; insulin glargine 20 units subcutaneously at bedtime; insulin lispro 7 units subcutaneously before each meal and as needed per sliding scale; sevelamer 1600 mg by mouth three times daily with meals; Renal Caps (multivitamin) 1 tablet by mouth once daily

ROS: Unable to obtain; patient has become more confused

PE:

Within normal limits except as noted below

VS: BP 78/46 mm Hg, P 115 beats/min, RR 27 breaths/min, T 35.8°C (96.4°F)

Neurologic: Obtunded, oriented to person only

Skin: Cool, clammy

Labs: Serum creatinine 7.6 mg/dL (671.8 µmol/L); glucose 201 mg/dL (11.2 mmol/L); white blood cells: leukocytosis (18,300/mm^3 [18.3 × 10^9/L]) with left shift; lactic acid 7.2 mEq/L (7.2 mmol/L)

Cultures: Blood and urine cultures pending

Radiology: Chest x-ray unremarkable

According to the patient's parameters, what is her most likely diagnosis (ie, systemic inflammatory response syndrome, sepsis, or septic shock)?

What are the goals of treatment?

Formulate an initial plan for therapy.

mechanistic classes (eg, two anti-pseudomonal antimicrobials in patients with known risk factors to ensure appropriate coverage of multidrug resistant organisms or clindamycin with β-lactam antibiotics for streptococcal toxic shock to decrease toxin production).

Monitoring and Treatment Strategies to Maximize Efficacy and Minimize Toxicity for Antimicrobials

- Administer broad-spectrum antimicrobials for initial therapy as early as possible and within the first hour of recognition of sepsis.
- Appropriate cultures should be obtained before initiating antibiotic therapy, but should not prevent prompt administration.
- Administer antibiotics that concentrate at the site of infection.
- Monitor patient parameters to ensure adequate dosing.
- Abnormal renal and hepatic function will increase drug concentration and predispose the patient to toxicity.
- Ensure antibiotic dosing is changed to normal doses once renal dysfunction has resolved to limit the development of treatment failure, antimicrobial resistance, or both.
- Septic patients may have increased volume of distribution due to initial large volume resuscitation.

Patient Encounter Part 3: Treatment and Outcome Evaluation

The patient has been intubated due to altered mental status and concern for inability to protect her airway. She remains hypotensive despite previous intervention. Her serum creatinine remains elevated at 8.8 mg/dL (777.9 µmol/L) and her serum potassium has risen to 5.9 mEq/L (5.9 mmol/L).

What additional therapies will you consider adding to this patient?

- Reevaluate the initial dosing regimen daily to optimize activity, prevent development of resistance, reduce toxicity, and decrease costs.
- Initiate step-down therapy based on microbiologic cultures to prevent resistance, reduce toxicity, including *Clostridium difficile* infection, and minimize cost.
- Monotherapy is equivalent to combination therapy once a causative pathogen has been identified in the vast majority of cases.

Duration of Anti-infective Therapy

Average duration of antimicrobial therapy for septic patients is 7 to 10 days. However, durations vary depending on the site of infection and response to therapy. Step-down therapy from IV to oral antimicrobials is recommended in certain targeted patients who are hemodynamically stable, afebrile for 48 to 72 hours, have a normalized WBC, have an organism susceptible to oral therapies, and are able to take oral medications.

Source Control

Evaluate septic patients for the presence of a localized infection amenable to **source control** measures. Common source control measures include drainage and debridement, device removal, and prevention.[20-22] Implementation of source control methods should be instituted as soon as possible following initial fluid resuscitation. The selection of optimal source control methods must weigh benefits and risks of the intervention. Source control measures may cause complications (bleeding, fistulas, and organ injury); therefore, the method with the least risk should be employed.[20]

HEMODYNAMIC SUPPORT

Vasopressors and Inotropic Therapy

LO 8

KEY CONCEPT When fluid resuscitation does not provide adequate arterial pressure and organ perfusion, vasopressors and/or inotropic agents should be initiated. Vasopressors are recommended in patients with a systolic blood pressure less than 90 mm Hg or MAP lower than 60 to 65 mm Hg (8.0–8.6 kPa), after failed treatment with crystalloids.[20,23,24] Vasopressors and

inotropes are effective in treating life-threatening hypotension and improving cardiac index, but complications such as tachycardia and myocardial ischemia require slow titration of the adrenergic agents to restore MAP without impairing stroke volume. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when fluid resuscitation is in progress and hypovolemia has not yet been corrected. Agents commonly considered for vasopressor or inotropic support include norepinephrine, epinephrine, dopamine, phenylephrine, vasopressin, and dobutamine. Norepinephrine is the first-line vasopressor to correct hypotension in septic shock.[20]

Norepinephrine is a potent α-adrenergic agent with less pronounced β-adrenergic activity. Doses of 0.01 to 3 mcg/kg/min can reliably increase blood pressure through vasoconstriction with small changes in heart rate or cardiac index. Norepinephrine is a more potent agent than dopamine in refractory septic shock.[20,23,24] Norepinephrine induces less arrhythmias compared with dopamine.[38]

Dopamine is an α- and β-adrenergic agent with dopaminergic activity. Low doses of dopamine (1–5 mcg/kg/min) maintain renal perfusion; higher doses (> 5 mcg/kg/min) exhibit α- and β-adrenergic activity and are frequently utilized to support blood pressure and to improve cardiac function, mainly through increasing stroke volume and heart rate. Because of the effects on heart rate, dopamine causes more tachycardia and thus increases potential for arrhythmias versus norepinephrine. Based on these data, dopamine should not be used routinely in the management of septic shock.[20,38] Low doses of dopamine should not be used for renal protection as part of the treatment of sepsis.[20,23,24]

Epinephrine is a nonspecific α- and β-adrenergic agonist that can increase cardiac index and produce significant peripheral vasoconstriction. Some human and animal studies suggest it can also increase lactate levels and impair blood flow to the splanchnic system; however, studies comparing norepinephrine to epinephrine show no difference in mortality rates. Epinephrine may be added to norepinephrine in patients with persistent hypotension.[20,23,24]

Phenylephrine is a fast-acting, short-acting pure α_1-agonist. Phenylephrine is the least likely vasopressor to cause tachycardia, but may decrease stroke volume. Phenylephrine should be reserved for use in patients with high cardiac output in whom tachycardia or ischemia limits the use of other vasopressors or as salvage therapy.[20,23,24]

Vasopressin levels are increased during hypotension to maintain blood pressure by vasoconstriction. However, there is a vasopressin deficiency in septic shock. Low, fixed doses of vasopressin increase MAP, leading to the discontinuation of vasopressors. However, routine use of vasopressin with norepinephrine is not recommended because of no difference in mortality compared with norepinephrine monotherapy.[39] Vasopressin is a direct vasoconstrictor without inotropic or chronotropic effects and may result in decreased cardiac output and hepatosplanchnic flow. The addition of vasopressin to other vasopressor agents may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose vasopressors.[20,23,24]

Dobutamine is recommended as the first-line inotropic agent. Dobutamine is a β-adrenergic inotropic agent that can be utilized for improvement of cardiac output and oxygen delivery. Doses of 2 to 20 mcg/kg/min increase cardiac index; however, heart rate increases significantly. Dobutamine should be considered in septic patients with adequate filling pressure and blood pressure, but low cardiac index. If used in hypotensive patients, dobutamine should be combined with vasopressor therapy.[20,23,24]

Patient Encounter Part 4

Three days later, the patient's blood pressure begins to respond to therapy with a MAP remaining greater than 65 mm Hg (8.6 kPa) on minimal vasopressor support.

What changes to the patient's medication regimen do you recommend?

Corticosteroids

LO 8

Stress-induced adrenal insufficiency complicates 9% to 24% of septic patients and is associated with increased mortality. The role of steroid use in septic shock remains unclear. Previous studies have demonstrated a mortality benefit or quicker reversal of shock in patients with sepsis-induced adrenal insufficiency treated with hydrocortisone.[40] However, a large, multicenter, randomized controlled trial (CORTICUS) showed no difference in mortality rates in septic shock patients treated with hydrocortisone.[41] KEY CONCEPT For these reasons, the use of IV hydrocortisone at a dose of 200 mg/day should be reserved for patients who remain hemodynamically unstable despite fluid and vasopressor therapy.[20] Patients should be weaned from steroid therapy when vasopressors are no longer required.

Glucose Control

The optimal blood glucose range in septic patients is unknown. Tight glycemic control (80–110 mg/dL [4.4–6.1 mmol/L]) improved survival in postoperative surgical patients, but did not show a benefit in medical critically ill patients.[42,43] More recent studies, including the large NICE-SUGAR trial, do not demonstrate a mortality benefit in favor of tight glycemic control, but actually a higher incidence of severe hypoglycemia and increased mortality rates.[44] KEY CONCEPT Following initial stabilization of septic patients, current guidelines recommend initiating insulin therapy when two consecutive blood glucose measurements are greater than 180 mg/dL (10.0 mmol/L) and then maintaining a blood glucose of less than or equal to 180 mg/dL (10.0 mmol/L). Blood glucose levels should be monitored frequently, every 1 to 2 hours, until glucose values and insulin infusion rates are stable, then every 4 hours thereafter.[20]

Adjunctive Therapies

▶ *Blood Product Administration*

There are no trials showing the optimal hemoglobin concentration in patients with sepsis. However, based on other studies which included subgroups of septic patients, with the exception of myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, it is recommended to target a hemoglobin concentration of 7 to 9 g/dL (70–90 g/L; 4.34–5.59 mmol/L) and red blood cell transfusion should occur when the hemoglobin concentration is less than 7 g/dL (70 g/L; 4.34 mmol/L).[20,45] Erythropoietin-stimulating agents, fresh frozen plasma, and antithrombin should not be administered, unless other compelling indications exist, to treat sepsis-induced abnormalities.[20]

▶ *Sedation, Analgesia, and Neuromuscular Blockade*

It is common for sepsis patients to require mechanical ventilation during their course of therapy. These patients may require analgesic or sedative agents to facilitate mechanical ventilation. Historically, concerns for patient safety and posttraumatic stress

disorder emphasized the need for sedation in these patients. However, there continue to be ample data indicating that, while sedation may be necessary, limiting exposure to certain sedative medications, specifically benzodiazepines, may improve morbidity and mortality rates. When sedation is needed, a standardized protocol targeting specific endpoints should be utilized.[20,46]

Neuromuscular blockade usually is reserved for patients in whom sedation alone does not improve the effectiveness of mechanical ventilation. Neuromuscular blockers may lead to prolonged skeletal muscle weakness and should be avoided if possible especially if receiving concomitant corticosteroid therapy, which can increase the risk of critical illness polyneuropathy. Patients requiring neuromuscular blockade should be monitored, and intermittent bolus doses or continuous infusion should be utilized. Monitor depth of neuromuscular blockade with either train-of-four stimulation or other forms of clinical assessment when using continuous infusion. Patients with early, sepsis-induced ARDS with a PaO_2/FiO_2 less than 150 mm Hg (20.0 kPa) may benefit from a short course of a neuromuscular blocking agent not to exceed 48 hours.[20]

Renal Replacement Therapy

Patients who develop AKI as a manifestation of sepsis may require some type of renal replacement therapy. There are no data currently that suggest superiority for either continuous or intermittent modalities of hemodialysis as both have demonstrated similar mortality rates. In patients who are hemodynamically unstable, continuous renal replacement therapy may be more beneficial due to less overall hypotension during therapy.

Deep Vein Thrombosis Prophylaxis

Combination pharmacologic and mechanical prophylaxis against venous thromboembolism is recommended for septic patients when possible. Low-dose unfractionated heparin, low-molecular-weight heparin (eg, enoxaparin or dalteparin), or pentasaccharide therapy (eg, fondaparinux) may be utilized. Graduated compression stockings or an intermittent compression device is recommended for patients with a contraindication to heparin products (thrombocytopenia, severe coagulopathy, active bleeding, or recent intracerebral hemorrhage).[20]

Stress Ulcer Prophylaxis

Patients with severe sepsis are at increased risk for developing a stress ulcer bleeding event. Stress ulcer prophylaxis using either a histamine-receptor antagonist (H-2 blocker) or proton pump inhibitor (PPI) is recommended in septic patients. Patients at greatest risk for stress ulcers include those who are coagulopathic, mechanically ventilated (> 48 hours), or hypotensive. Histamine-2 receptor antagonists (eg, ranitidine)

Patient Care Process

LO 8

Collect Information:

- Retrieve available diagnostic and laboratory data, especially CBC with differential, CMP, ABG, and lactic acid.
- Measure vital signs, including temperature, heart rate, respiratory rate, and blood pressure.
- Speak with patient/family and review records to identify previous antimicrobial history, microbiologic cultures, and medication allergies.

Assess the Information:

- Based on physical examination and review of systems, determine whether the patient meets criteria for sepsis.
- Assess for a potential source of infection.
- Identify comorbidities, concomitant medications, and/or laboratory findings that may impact antimicrobial choices.
- Understand which parameters indicate effective/ineffective resuscitation. Plan for additional resuscitation therapy if the patient remains hypotensive.

Develop a Care Plan:

- Formulate an appropriate plan for antimicrobial therapy, which should include starting broad spectrum agents that cover the most likely pathogens within 1 hour of suspecting sepsis.
- Make recommendations to control the source of infection.
- Develop a strategy to optimize hemodynamics. Crystalloid fluids should be used first, followed by vasopressors and/or inotropes. Corticosteroids may be utilized in patients who remain hemodynamically unstable.
- Formulate appropriate dosing regimens for medications involved in therapy and revise as needed.
- Consider the need for adjunctive therapies such as analgesics, sedatives, insulin, neuromuscular blockers, blood product administration, renal replacement therapy, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, and nutrition.

Implement the Care Plan:

- Patient parameters may change frequently, thus requiring modifications of therapy. Reassess vital signs and laboratory values often and adjust medications and dosing regimens as needed.
- Involve the patient and family members in each step of the care plan.

Follow-up: Monitor and Evaluate:

- Continually monitor patient parameters to ensure optimal therapy to minimize morbidity and mortality.
- Continue antimicrobial therapy on average for a total of 7 to 10 days, depending on the site of infection and response to therapy. Monitor for ongoing signs and symptoms of infection, including leukocytosis, fever, hypotension, and tachycardia.
- Step-down therapy from IV to oral antimicrobials when the patient is hemodynamically stable, afebrile, has a normalized WBC, has a pathogen susceptible to oral therapy, and is able to take oral medications.
- Escalate or de-escalate antimicrobial therapy based on culture and susceptibility results, which should be assessed daily.

are more efficacious than sucralfate. There is ongoing debate to determine if PPIs (eg, omeprazole) are more efficacious than H-2 blockers with low-quality data showing conflicting outcomes.[20,47] Both, however, demonstrate equivalence in the ability to increase gastric pH.[20] The benefit of prophylaxis must be weighed against the potential effect of increased stomach pH and development of infectious complications, such as hospital-acquired pneumonia and/or *Clostridium difficile* infection.

Nutrition

Meeting the nutritional needs of septic patients can be challenging, especially in patients who are hemodynamically unstable. When possible, early initiation of enteral nutrition should be considered to maintain gut mucosa and potentially decrease the risk of bacterial translocation leading to infection. Patients who are hemodynamically unstable may not tolerate enteral nutrition and are at risk for gut ischemia. Parenteral nutrition alone or in conjunction with enteral nutrition should not be initiated in the first 7 days as this has not been shown to improve outcomes.[20]

Prognosis

There are various factors that influence outcome. Gram-negative bacteria are more likely to produce septic shock than gram-positive bacteria (50% vs 25%) and have a higher mortality rate than other pathogens. This may be related to the severity of the underlying condition. Patients with rapidly fatal conditions, such as leukemia, aplastic anemia, and burns, have a worse prognosis than patients with nonfatal underlying conditions, such as diabetes mellitus or chronic renal insufficiency. Other factors that worsen the prognosis of septic patients include advanced age, malnutrition, resistant bacteria, utilization of medical devices, and immunosuppression. Data for long-term mortality are lacking (it is estimated that the mortality for sepsis survivors within the first year is 20%).[12] Patients may have prolonged physical disability related to muscle weakness and posttraumatic stress.

Abbreviations Introduced in This Chapter

ABG	Arterial blood gas
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
CBC	Complete blood count
CMP	Comprehensive metabolic panel
CVP	Central venous pressure
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EGDT	Early goal directed therapy
FiO_2	Fraction of inspired oxygen
HES	Hydroxyethyl starch
IV	Intravenous
MAP	Mean arterial pressure
MDR	Multidrug-resistant
PaO_2	Partial pressure of oxygen
PPI	Proton pump inhibitor
SOFA	Sequential [Sepsis-related] organ failure assessment

REFERENCES

1. Russell JA. Management of sepsis. N Engl J Med. 2006;355:1699–1713.
2. Angus D, van der Poll T. Severe sepsis and septic shock. N Engl J Med. 2013;369:840–851.
3. Singer M, Deutschman C, Seymour C, et al. The third international consensus defintions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–810.
4. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003;348:138–150.
5. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546–1554.
6. Hoste E, Lameire NH, Vanholder RC, et al. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol. 2003;14:1022–1030.
7. Poutsiaka DD, Davidson LE, Kahn KL, et al. Risk factors for death after sepsis in patients immunosuppressed before the onset of sepsis. Scand J Infect Dis. 2009;41(6–7):469–479.
8. Wafaisade A, Lefering R, Bouillon B, et al. Epidemiology and risk factors of sepsis after multiple trauma: an analysis of 29,829 patients from the trauma registry of the German society for trauma surgery. Crit Care Med. 2011;39(4):621–628.
9. Lin MT, Albertson TE. Genomic polymorphisms in sepsis. Crit Care Med. 2004;32:569–579.
10. Bodey GP, Mardani M, Hanna HA, et al. The epidemiology of Candida glabrata and Candida albicans fungemia in immunocompromised patients with cancer. Am J Med. 2002;112:380–385.
11. Costa SF, Marino I, Araujo EA, et al. Nosocomial fungemia: a 2-year prospective study. J Hosp Infect. 2000:45:69–72.
12. Cartin-Ceba R, Kojicic M, Li G, et al. Epidemiology of critical care syndromes, organ failures, and life-support interventions in a suburban US community. Chest. 2011;140(6):1447–1455.
13. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29:1303–1310.
14. Marie C, Muret J, Fitting C, et al. Interleukin-1 receptor antagonist production during infectious and noninfectious systemic inflammatory response syndrome. Crit Care Med. 2000;28:2277–2282.
15. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis. 2005;41:S504–S512.
16. Kim PK, Deutschman CS. Inflammatory responses and mediators. Surg Clin North Am. 2000;80:885–894.
17. van der Poll T, van Deventer SJH. Cytokines and anticytokines in the pathogenesis of sepsis. Infect Dis Clin North Am. 1999;13:413–426.
18. Harbarth S, Garbino J, Pugin J, et al. Inappropriate initial antimicrobial therapy and its effects on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med. 2003;115:529–535.
19. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, et al. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med. 2003;31:2742–2751.
20. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486–552.
21. Jimenez MF, Marshall JC. Source control in the management of sepsis. Intensive Care Med. 2001;27:S49–S62.
22. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR. 2002;51:1–29.
23. Rivers E, Nguyen B, Havstad S, et al; Early Goal-directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345:1368–1377.
24. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med. 2004;32:1928–1948.

25. Yealy D, Kellum J, Huang D, et al; The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683–1693.
26. Peake S, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371: 1496–1506.
27. Mouncey P, Osborn T, Power S, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372:1301–1311.
28. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350:2247–2256.
29. Ferrada P, Anand R, Whelan J, et al. Qualitative assessment of the inferior vena cava: useful tool for the evaluation of fluid status in critically ill patients. Am Surg. 2012;78:468–470.
30. Schefold J, Storm C, Bercker S, et al. Inferior vena cava diameter correlates with invasive hemodynamic measures in mechanically ventilated intensive care unit patients with sepsis. J Emerg Med. 2010;38:632–637.
31. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014; 370:1412–1421.
32. Patel A, Laffan M, Waheed U, et al. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trail sequential analysis of all-cause mortality. BMJ. 2014;349:g4561.
33. Perner A, Haase N, Guttormsen AB, et al; 6S Trial Group. Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367:124–134.
34. Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators. Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367:1901–1911.
35. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308:1566–1572.
36. Rochwerg B, Alhazzani W, Sindi A, et al. Fluids in sepsis and septic shock group: fluid resuscitation in sepsis: a systematic review and network meta-analysis. Ann Intern Med. 2014;161:347–355.
37. MacArthur RD, Miller M, Albertson T, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis. 2004;38:284–288.
38. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–789.
39. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med. 2008;358:877–887.
40. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002;288:862–871.
41. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med. 2008;358:111–124.
42. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449–461.
43. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patient. N Engl J Med. 2001;345:1359–1367.
44. Finfer S, Chittock D, Yu-Shuo S, et al; The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–1297.
45. Hebert PC, Wells G, Blajchman MA, et al; Transfusion Requirements in Critical Care Investigators. A multicenter, randomized, controlled clinical trial or transfusion requirements in critical care. N Engl J Med. 1999;340:409–417.
46. Barr J, Fraser G, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41:263–306.
47. MacLaren R, Reynolds P, Allen R. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. JAMA. 2014;174:564–574.

83 Superficial Fungal Infections

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LEARNING OBJECTIVES

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

1. Explain the underlying pathophysiology of vulvovaginal candidiasis (VVC), oropharyngeal candidiasis (OPC), esophageal candidiasis, and fungal skin infections.
2. Identify symptoms of VVC, OPC, esophageal candidiasis, and fungal skin infections.
3. Identify the desired therapeutic outcomes for patients with uncomplicated and complicated VVC, OPC, esophageal candidiasis, and fungal skin infections.
4. Recommend appropriate lifestyle modifications and pharmacotherapy interventions for patients with VVC, OPC, esophageal candidiasis, and fungal skin infections.
5. Recognize when long-term suppressive therapy is indicated for a patient with VVC.
6. Recognize when topical versus oral treatment is indicated for a patient with OPC, esophageal candidiasis, VVC, and fungal skin infections.
7. Educate patients about the disease state, appropriate lifestyle modifications, and medication therapy required for effective treatment of VVC, OPC, esophageal candidiasis, and fungal skin infections.

INTRODUCTION

Superficial fungal infections, also referred to as mycoses, are common and treatable conditions seen in everyday practice. Treatment largely depends on the use of azole and allylamine antifungal agents, either topically or orally, depending on the site, severity, and immune status of the patient.

VULVOVAGINAL CANDIDIASIS

Vulvovaginal candidiasis (VVC), whether symptomatic or asymptomatic, refers to infections in women whose vaginal cultures are positive for *Candida* species.

EPIDEMIOLOGY AND ETIOLOGY

VVC, also known as moniliasis, is a common form of vaginitis, accounting for 20% to 25% of vaginitis cases. Although VVC is uncommon prior to **menarche**, an estimated 75% of women will have at least one occurrence of VVC.[1]

According to the treatment guidelines of the Centers for Disease Control and Prevention (CDC),[1] VVC can be classified as uncomplicated or complicated. Uncomplicated infections occur sporadically, cause mild to moderate symptoms, and occur in nonimmunocompromised women. Uncomplicated infections, most often caused by *Candida albicans*, often have no identifiable precipitating cause. Complicated infections, including recurrent, severe infections, and those in women with uncontrolled diabetes, debilitation, or immunosuppression, may be caused by nonalbicans or azole-resistant fungal organisms. Recurrent VVC, defined as four or more infections per year, occurs in less than 5% of women, and is distinguishable from a persistent infection by the presence of a symptom-free interval between infections.[1]

LO 1

KEY CONCEPT *C. albicans* is the primary pathogen responsible for VVC, accounting for 66% of cases.[2] Other cases are caused by nonalbicans species, including *Candida glabrata, Candida tropicalis, Candida krusei*, and *Candida parapsilosis*.[2]

PATHOPHYSIOLOGY

The normal vaginal environment protects women against vaginal infections. Under the influence of estrogen, vaginal epithelium cornifies to reduce the risk of infection. Vaginal discharge, composed of exfoliated cells, cervical mucus, and colonized bacteria, cleans the vagina. The normal pH of vaginal secretions, near 4.0, is toxic to many pathogens and is maintained by *Lactobacillus acidophilus*, diphtheroids, and *Staphylococcus epidermidis*. Alterations in the vaginal environment, including pH changes, allow for overgrowth of organisms that are normally suppressed, increasing the risk of vulvovaginitis.

RISK FACTORS

LO 2

KEY CONCEPT Although no risk factors are consistently associated with conversion to symptomatic infection, a variety of factors may increase the risk of developing symptomatic VVC in certain women (Table 83–1).

TREATMENT

The goals of treatment of VVC are as follows:

- Relief of symptoms
- Eradication of infection
- Reestablishment of normal vaginal flora
- Prevention of recurrent infections in complicated infections

Clinical Presentation and Diagnosis of VVC

Patients with VVC may present with vulvar and/or vaginal symptoms. Symptoms often develop the week before menses and resolve with the onset of menses.

Symptoms

- Vaginal itching
- Vaginal soreness
- Vaginal burning
- Irritation
- External dysuria
- Dyspareunia

Signs

- Nonodorous vaginal discharge (may vary from watery to curd-like)
- Yellow or yellowish green discharge
- Erythema and edema of the labia and vulva
- Fissures
- Pustulopapular lesions
- Normal cervix

Diagnostic Testing

- Microscopic investigation for the presence of blastospores or pseudohyphae; saline wet mount has a sensitivity of 40% to 50%, whereas a potassium hydroxide (KOH) preparation has a sensitivity of 50% to 70%.[7] Asymptomatic vaginal colonization of *C. albicans* is not diagnostic of VVC since 10% to 20% of women are asymptomatic carriers of *Candida* species. Asymptomatic vaginal colonization does not require treatment; therefore, the presence alone of *Candida* should not determine care.
- Vaginal pH less than or equal to 4.5; pH should remain normal in cases of fungal infection, whereas an elevated pH suggests bacterial infection.
- *Candida* cultures should be obtained only if signs and microscopy are inconclusive or in cases of recurrent VVC.

Table 83–1

Possible Risk Factors Associated with VVC

Risk Factor	Proposed Mechanism
Broad-spectrum antibiotic use	Altered vaginal flora allowing overgrowth of *Candida* organisms; risk increases with duration of antibiotic use
Systemic corticosteroid or immunosuppressant use	Reduced vaginal protection by immunoglobulins
Sexual activity	VVC is often associated with the onset of sexual activity; partners may have penile or oral colonization; use of vaginal irritants or devices, including diaphragms and intrauterine systems, can irritate vaginal mucosa
Tight-fitting and nonabsorbent clothing	Promotes warm, moist environment for fungus growth
Elevated estrogen levels, hormonal contraceptives, and pregnancy	Estrogen enhances *Candida* adherence to vaginal epithelial cells and yeast-mycelial transformation; this is supported by the fact that infection rates are lower before menarche and after menopause (except in women taking hormone replacement therapy), whereas rates are higher during pregnancy
Vaginal pH	Changes in glycogen and lactic acid levels
Gastrointestinal reservoir of *Candida* organisms	Transfer of organism from rectum to vagina; irritation of the vulvovaginal area during sexual intercourse may enhance invasion of organisms
Diabetes	Enhanced binding of *Candida* to epithelial cells due to hyperglycemia; asymptomatic colonization is more common in patients with diabetes; elevated sugar levels may cause conversion to symptomatic infection

VVC, vulvovaginal candidiasis.

Nonpharmacologic Treatments

In combination with pharmacologic treatment, the practitioner should recommend basic nonpharmacologic approaches to treatment and prevention of VVC:

- Keep the genital area clean and dry.
- Avoid prolonged use of hot tubs.
- Avoid constrictive clothing.
- Avoid vaginal douching.
- Wear underwear made of breathable materials, such as cotton.
- Avoid soaps and perfumes in the genital area.
- Although study results are conflicting, possibly due to the strain or concentration studied, the daily consumption of active *Lactobacillus* may reduce recurrence. Newer studies have found ingestion of *Lactobacillus rhamnosus* and *Lactobacillus reuteri* suppressed metabolic activity and killed *C. albicans*,[3] whereas older studies found no difference in infection rates in women who ingested yogurt.[4]

Patient Encounter 1

A 29-year-old woman presents to your clinic complaining of itching in her vaginal area and a white discharge. After questioning the woman, you determine that she has vaginal burning, soreness, and itching, accompanied by a curd-like discharge. Upon further questions, you determine that the woman is currently training for a marathon despite the summer heat. She reports having had a vaginal infection once before. The woman is concerned that she has either developed another vaginal infection or is allergic to her running shorts. On examination, she has erythema of the labia and a nonodorous discharge.

What information is suggestive of VVC?

What additional information do you need to know before creating a treatment plan for this patient?

Pharmacologic Treatment of Uncomplicated VVC

For most cases of uncomplicated VVC, the CDC guidelines recommend a short course of therapy (1–3 days) with an oral or vaginal antifungal agent, either prescription or nonprescription.[1] Nonprescription azole antifungal products are available as 1-night, 3-night, and 7-night regimens in a variety of formulations, including cream, suppository, and vaginal tablets (Table 83–2). Oral fluconazole offers the option of treatment with one dose administered without regard to time of day. Due to the risk of severe hepatotoxicity, the use of oral ketoconazole should be reserved for severe fungal infections resistant to other antifungal options.

Inability to resolve an infection may indicate a mixed infection, infection owing to a nonalbicans strain, an infection that is not fungal, or indicative of serious underlying conditions, such as diabetes or human immunodeficiency virus (HIV) infection. For these reasons, if infection does not resolve with a single antifungal course or if symptoms return within 2 months, practitioners should check cultures and further evaluate the patient's health status.

LO 3

KEY CONCEPT Due to the numerous treatment options available, a variety of factors can influence product selection, with patient preference playing a significant role. To improve adherence with therapy, the practitioner should discuss with the patient what options are available and what her preferences are.

Adherence rates are greater with oral treatment than with vaginal therapy, possibly due to ease of administration, short duration, and administration flexibility. Vaginal creams provide rapid relief of itching and burning, while symptom resolution may take 1 to 2 days with oral treatment. The practitioner may wish to recommend applying a vaginal cream externally to reduce itching and burning when using an oral agent, although this increases the cost of therapy. Most over-the-counter (OTC) products cost $10 to $20 per course of therapy. The cost of prescription products can vary based on insurance coverage. If the patient does not have prescription coverage, nonprescription products may prove less expensive than even one or two fluconazole tablets.

▶ *Risk of Adverse Effects and Interactions*

Systemic adverse effects associated with vaginally administered azoles are less frequent than with oral products. With topical products, local discomfort such as burning, itching, stinging, and redness may occur, particularly with the first application. In contrast, common adverse effects associated with fluconazole include headache, diarrhea, nausea, dizziness, abdominal pain, and taste alterations. Around 15% of patients experience gastrointestinal side effects with orally administered fluconazole.[5]

Oral azoles are associated with significant drug interactions, particularly due to potent inhibition of cytochrome P-450 (CYP) 2C9 and moderate inhibition of CYP 3A4. For patients receiving only one dose of oral fluconazole, these interactions may not pose a significant risk but may pose a risk with long-term suppressive therapy for recurrent infections.

TREATMENT OF RECURRENT VVC

The goal of treating recurrent VVC is control of the infection, rather than cure. First, any acute episodes are treated, followed by maintenance therapy. Although acute episodes of recurrent VVC will respond to azole therapy, some patients may require prolonged therapy to achieve remission. To achieve remission, 14 days of topical azole therapy or a second dose of oral fluconazole 150 mg repeated 3 days after the first dose can be used. The practitioner should consider that nonalbicans infections are more common in recurrent VVC; therefore, fluconazole and itraconazole resistance may make these agents less effective.

LO 4

KEY CONCEPT After achieving remission, recurrent VVC requires long-term suppressive therapy for 6 months (Table 83–3). Per CDC guidelines, oral fluconazole 100-, 150-, or 200-mg weekly for 6 months is first-line treatment.[1] Cessation of suppressive therapy is associated with resurgence of symptomatic infection in 30% to 50% of women.[1]

TREATMENT OF NONALBICANS INFECTIONS

Treatment response rates are lower for nonalbicans infections (eg, *C. glabrata* and *C. krusei*). Although an optimal regimen is unknown, use of nonfluconazole azole therapy for 7 to 14 days is recommended.[1] For second-line therapy, boric acid

Table 83–2

Treatment Options for Uncomplicated VVC

1-Day Therapies
Butoconazole 2% sustained-release cream, 5 g intravaginally as a single application
Fluconazole 150 mg, one tablet orally as a single dose
Tioconazole 6.5% ointment, 5 g intravaginally as a single application
3-Day Therapies
Butoconazole 2% cream, 5 g intravaginally for 3 nights
Clotrimazole 100-mg vaginal tablet, two tablets for 3 nights
Miconazole 200-mg vaginal suppository, one suppository for 3 nights
Terconazole 0.8% cream, 5 g intravaginally for 3 nights
Terconazole 80-mg vaginal suppository, one suppository for 3 nights
7- to 14-Day Therapies
Boric acid 600-mg vaginal suppository, one suppository intravaginally twice daily for 14 days
Clotrimazole 1% cream, 5 g intravaginally for 7–14 nights
Clotrimazole 100-mg vaginal tablet, one tablet for 7 nights
Miconazole 2% cream, 5 g intravaginally for 7 nights
Miconazole 100-mg vaginal suppository, one suppository for 7 nights
Nystatin 100,000-unit vaginal tablet, one tablet for 14 nights
Terconazole 0.4% cream, 5 g intravaginally for 7 nights

VVC, vulvovaginal candidiasis.

Table 83–3

Treatment Options for Maintenance Therapy

Daily
Boric acid 600 mg in gelatin capsule vaginally daily during menses (5 days)
Itraconazole 100 mg orally once daily
Ketoconazole 100 mg orally once daily
Weekly
Clotrimazole 500 mg vaginal suppository once weekly
Fluconazole 100 or 150 mg orally once weekly
Terconazole 0.8% cream 5 g vaginally once weekly
Monthly
Fluconazole 150 mg orally once monthly
Itraconazole 400 mg orally once monthly

600 mg in a gelatin capsule administered vaginally daily for 2 weeks is recommended.[1] This regimen provides mycologic cure rates of 40% to 100%,[6] although local irritation often limits its use. Oral itraconazole 200-mg twice daily 1 day per month for 6 months is also effective.[7] Other topical options include nystatin intravaginal suppositories, 100,000 units/day for 2 weeks. Topical 4% flucytosine is also effective, but use should be limited due to the potential for resistance.

VVC DURING PREGNANCY

During pregnancy, VVC may prove difficult to treat due to elevated estrogen levels, lower response rates, and frequent recurrences, accompanied by concern for the fetus. Vaginal antifungals remain the preferred treatment during pregnancy, although therapy should continue for 1 to 2 weeks to ensure effectiveness.[8] Most topical antifungals are classified as risk category C, whereas clotrimazole is classified as risk category B. Fluconazole's risk category classification for the single 150-mg dose is risk category C but category D for all other doses due to case studies of congenital limb deformities with doses of 400 to 800 mg daily during the first trimester.[9] Therefore, topical intravaginal application of clotrimazole or miconazole is generally preferred over oral antifungal therapy with fluconazole in pregnant patients.

Cultural Awareness During Treatment of VVC

As with all gynecologic issues, the practitioner is faced with cultural perceptions of female genitalia. In particular, practitioners are treating an increased number of patients who have undergone female genital mutilation. Female genital mutilation, formerly known as female circumcision, describes the intentional alteration or injury of female genitalia. More than 100 million women and girls, particularly in Africa and the Middle East, have undergone such procedures for cultural and religious reasons.[10] Some authorities suggest using the term "genital cutting" when dealing with patients to avoid appearing judgmental.[11] Women who have undergone this procedure suffer acute and chronic complications. Patients with female genital mutilation may suffer from recurrent VVC due to inadequate drainage of vaginal fluids. Regardless of the practitioner's opinion on female genital mutilation, the practitioner must be sensitive to the patient's feeling and cultural values.

OUTCOME EVALUATION

Whether using a topical or an oral agent, patients should notice relief of itching and discomfort within 1 to 2 days. The volume of discharge should also begin to decrease within a few days. The entire course of therapy should be continued even if symptoms have resolved. If the condition recurs within 4 weeks or more than four times per year, the patient should be further evaluated for possible non-*Candida* infections, resistant organism, or other complicating factors, along with assessment of need for long-term suppressive therapy.

OROPHARYNGEAL AND ESOPHAGEAL CANDIDIASIS

Oropharyngeal candidiasis (OPC) is a common fungal infection, often associated with immune suppression (ie, HIV infection, diabetes, and malignancies). If left untreated, it will progress to more serious oral disease, such as esophageal candidiasis.

Patient Care Process: VVC

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. If patient has experienced previous VVC, determine what medications were utilized and were effective previously.
- Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substances that could interact with prescribed medications.
- Based on the medical history and lifestyle factors, determine whether the patient has compelling risk factors for VVC.
- Based on physical examination, determine whether the patient's signs and symptoms are consistent with VVC or another vaginal infection, such as a sexually transmitted infection.
- Review relevant laboratory tests, if any available, such as A1C.
- Assess the efficacy, safety, and patient adherence of current and planned pharmacotherapy.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- Select lifestyle modifications and antifungal therapy that are likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.

Implement the Care Plan:

- Educate the patient about lifestyle modifications, medication therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about VVC and its management.
- Discuss importance of medication adherence and lifestyle modifications to cure VVC and prevent recurrence.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the formulary.

Follow-up: Monitor and Evaluate:

- No monitoring and evaluation is necessary unless unresolved.
- If unresolved, review medication and lifestyle modification adherence, review physical examination, and consider diagnostic laboratory to evaluate for other types of infection.

EPIDEMIOLOGY AND ETIOLOGY

LO 4

KEY CONCEPT The occurrence of oropharyngeal and esophageal candidiasis is an indicator of immune suppression, often developing in infants, the elderly, and the immunocompromised. One-third to one-half of geriatric inpatients develop OPC. Denture stomatitis is present in approximately 40% of denture wearers,[12] more commonly in women than men. Oral candidiasis is the most commonly reported adverse drug event reported by patients receiving inhaled corticosteroids,[13] with the prevalence of esophageal candidiasis reaching 37% among patients treated with inhaled corticosteroids.[14] The incidence of esophageal candidiasis is highest among patients receiving high doses of corticosteroids or with diabetes.

The prevalence of HIV infection plays a significant role in the incidence of oropharyngeal and esophageal candidiasis. In the 1980s, the incidence of OPC increased fivefold, in association with the spread of HIV infections.[15] Although HIV infection remains a risk factor for candidiasis, the introduction of highly active antiretroviral therapy precipitated a decline in the incidence of oral candidiasis to 45.9% to 79.1%, varying by geographic location, race, and therapy.[16]

OPC remains the most common opportunistic infection in patients with HIV. For the majority of patients, it is the first manifestation of HIV infection.[28] The incidence of oropharyngeal infection increases with decreasing CD4+ lymphocyte counts, and most often observed when CD4+ counts are less than 200 cells/mm^3 (350 × 106/L). An incidence of 59% is observed in patients with a CD4+ count less than 350 cells/mm^3 (350 × 106/L).[17]

Esophageal candidiasis usually occurs in patients with lower CD4+ counts than those that develop OPC.[21] Although esophageal candidiasis represents the first manifestation of HIV infection in less than 10% of cases, it is the most common acquired immunodeficiency syndrome (AIDS)–defining disease.[18] The CDC classifies esophageal candidiasis as a Stage 3-defining opportunistic infection in HIV.[19] As with OPC, the incidence of esophageal candidiasis increases with decreasing CD4+ counts, and therefore is a measure of declining CD4+ count or treatment failure.

C. albicans accounts for 80% of cases of OPC and esophageal candidiasis. Over the last 20 years, an increasing incidence of *C. albicans* resistance has been accompanied by an increased incidence of nonalbicans species infections, including *C. glabrata, C. tropicalis, C. krusei*, and *C. parapsilosis*. In patients with cancer and HIV, the prevalence of *C. glabrata* infections or mixed *C. albicans* and *C. glabrata* infection has been increasing.[20] Such infections tend to be more severe and require larger doses of antifungal agents for treatment.

PATHOPHYSIOLOGY

Similar to VVC, the development of OPC occurs when the normal environment is altered. *Candida* organisms frequently colonize the oropharynx and mucous membranes. These organisms do not become pathogenic until the environmental balance is disturbed. This occurs in the setting of broad-spectrum antibiotic use, tissue damage (due to chemotherapy, catheter tubing, trauma, or smoking), hyposalivation, or immune deficiency.

RISK FACTORS

Risk factors for OPC can be found in Table 83–4.

CLINICAL PRESENTATION AND DIAGNOSIS

See text boxes for clinical presentation and diagnosis of OPC and esophageal candidiasis.

Table 83–4

Risk Factors for Oropharyngeal and Esophageal Candidiasis

Factor	Proposed Mechanism
Extremes of age	Immature immunity in infants and reduced immunity in the elderly
Impaired mucosal integrity	Breaks in the protective barrier allows fungal invasion; often due to radiation, surgery, or mucositis
Dentures	Adherence of fungus to dentures, along with reduced salivary flow under dentures; ill-fitting dentures may impair mucosal integrity
Xerostomia	Reduced cleansing and defense factors of saliva
Use of antibiotics	Altered flora of mucosa allowing fungal overgrowth
Use of steroids	Suppression of immunity
Use of immunosuppressant	Suppression of immunity
HIV infection	Decreased CD4 T lymphocytes
Diabetes mellitus	Elevated glucose levels and defense factors in saliva
Nutritional deficiencies	Altered defense mechanisms, impaired mucosal integrity, or enhanced pathogenic potential of fungus

HIV, human immunodeficiency virus.

TREATMENT

Along with selecting an effective treatment, selection of an appropriate antifungal agent requires consideration of location and severity of infection, medication adherence, potential drug interactions, concomitant medical conditions, and presence of sucrose or dextrose. Topical agents require frequent dosing and prolonged contact time with oral mucosa. Rough surfaces of tablets and troches may irritate sensitive mucosa. Patients with xerostomia may have inadequate saliva to dissolve troches. Topical agents containing sucrose or dextrose may increase the risk of caries or cause elevated blood sugar in patients with diabetes. Along with being expensive, oral azoles exhibit an increased risk of toxicity and drug interactions due to inhibition of CYP-450.

Because oropharyngeal and esophageal candidiasis are signs of immunocompromise, the immune status of the patient should be considered in the therapeutic care plan. For HIV-infected patients, this should also include an evaluation of the patient's antiretroviral therapy because fungal infections may represent immune status deterioration.

LO 5

KEY CONCEPT For low-risk patients, topical agents are first-line therapy for OPC, although systemic agents may be used for severe or unresponsive cases. Infectious Disease Society of America (IDSA) guidelines recommend clotrimazole troches, 10 mg five times per day, or miconazole mucoadhesive buccal 50 mg tablet for 7 to 14 days for mild infections. Alternatives for mild infections include nystatin suspension or pastilles four times daily.[21] Once-daily oral fluconazole 100 to 200 mg for 7 to 14 days is reserved for moderate-to-severe cases.[21] Two weeks of oral itraconazole 200-mg or posaconazole 400-mg daily, voriconazole 200-mg twice daily, or amphotericin-B suspension four times daily are alternatives, typically reserved for refractory cases. For refractory cases additional therapy options include intravenous echinocandin or intravenous amphotericin-B deoxycholate but

Clinical Presentation and Diagnosis of Oropharyngeal Candidiasis

OPC is often a presumptive diagnosis based on signs and symptoms, along with the resolution of them after treatment with antifungal agents.

Symptoms

- Sore, painful mouth and tongue
- Burning tongue
- Dysphagia
- Metallic taste/loss of taste

Signs

Signs vary depending on the type of oropharyngeal candidiasis.

- Diffuse erythema on the surface of buccal mucosa, throat, tongue, and gums
- White patches on tongue, palate, gums, or buccal mucosa; removal of patches reveals erythematous and bloody tissue; ability to remove patches distinguishes OPC from oral hairy leukoplakia
- Angular cheilitis presents with small cracking lesions, erythema, and soreness at the corners of the mouth; associated with vitamin and iron deficiency
- Denture stomatitis presents with flat, red lesions on mucosa beneath dentures; signs of chronic erythema and edema on mucosa
- Hyperplastic OPC presents with discrete, transparent raised lesions on the inner mucosa of the cheek; typically found in men who smoke
- Pseudomembranous OPC presents with yellow-white plaques that may be small and discrete or confluent; most common form found in HIV patients

Diagnostic Testing

Diagnosis is primarily based on identification of characteristic lesions and confirmed by scraping of lesions to perform a gram-stain. Although rarely necessary, diagnostic testing is possible if a definitive diagnosis is required.

- Cytology, although presence of *Candida* is not diagnostic because colonization is common
- Culture to identify species of yeast or presence of resistance
- Biopsy

are considered second-line due to lack of concentration of drug at the site of infection.

For non–HIV-infected patients who have suppressed immune systems, the practitioner must consider the patient's risk of dissemination. Patients with cell-mediated immune deficiency but near-normal granulocyte function, such as patients with diabetes, solid organ transplant, or solid tumors, are at low risk for dissemination. The risk of dissemination is higher in patients who develop neutropenia, including patients with leukemia or bone marrow transplant. These patients should be treated aggressively to prevent invasive fungal infection.

For the treatment of OPC in HIV-infected individuals, initial episodes can be adequately controlled with topical agents, such as clotrimazole troches, so long as symptoms are not severe and no esophageal involvement is suspected.

LO 6

KEY CONCEPT Representing a severe extension of OPC, esophageal candidiasis requires systemic antifungal therapy. The significant morbidity associated with esophageal candidiasis warrants aggressive treatment.

Unlike OPC, which can be treated with topical agents, esophageal candidiasis requires systemic antifungal therapy for effective treatment.[18] The IDSA recommends oral fluconazole for 7–14 days in patients with esophageal candidiasis and moderate to severe disease, with an echinocandin or amphotericin-B as alternatives in patients unable to tolerate oral therapy, or with resistant or refractory disease.[21] Itraconazole 200-mg daily, posaconazole 400-mg twice daily, voriconazole 200-mg twice daily, and intravenous fluconazole are considered second-line therapy. If immunocompromised patients experience frequent or severe recurrences, particularly of esophageal candidiasis,

Clinical Presentation and Diagnosis of Esophageal Candidiasis

Symptoms

- Fever
- Odynophagia
- Dysphagia
- Retrosternal pain

Signs

- Fever
- Hyperemic or edematous white plaques
- Ulceration of esophagus
- Increased mucosal friability
- Narrowing of lumen

Diagnostic Testing

Unlike OPC, diagnosis of esophageal candidiasis is not based solely on clinical presentation, instead requiring endoscopic visualization of lesions and culture confirmation. Due to the invasive nature of these procedures, most practitioners opt to treat the infection presumptively, reserving endoscopic evaluation for patients who fail therapy.

- Cytology and culture to identify species of yeast or presence of resistance
- Barium esophagogram
- Endoscopy revealing whitish plaques with progression to superficial ulceration of the esophageal mucosa
- Mucosal biopsy

Patient Care Process: Oropharyngeal Candidiasis

Collect Information:

- Assess the patient's symptoms to determine whether symptoms are consistent with oropharyngeal or esophageal candidiasis.
- Review any available diagnostic data, including cultures.
- Evaluate for risk factors, such as immunocompromise.
- Review the medical history. Does the patient have compelling indications or contraindications for specific antifungal treatment?
- Review available laboratory tests, especially liver function.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use. Is the patient taking any medications that may contribute to candidiasis? Is the patient taking any medications that may interfere with treatment?
- Determine if the patient has any allergies.

Assess the Information:

- If the patient has had oropharyngeal or esophageal candidiasis previously, determine what treatments were helpful to the patient in the past.
- If the patient has had oropharyngeal or esophageal candidiasis previously, determine whether the patient has risk factors for recurrent infection.
- Determine whether long-term suppressive therapy is necessary.
- Evaluate the patient for the potential of adverse drug reactions, drug allergies, or drug interactions.

Develop a Care Plan:

- Select antifungal therapy that is likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.
- Discuss warning signs to report, include recurrence or worsening symptoms.

Implement the Care Plan:

- Stress the importance of adherence with the antifungal regimen until complete.
- Provide patient education pertaining to oropharyngeal or esophageal candidiasis and antifungal therapy, including causes, risk factors, medication administration, potential adverse effects, and potential medication interactions.
- Discuss warning signs to report, include recurrence or worsening symptoms.

Follow-up: Monitor and Evaluate:

- Follow-up if symptoms do not resolve within 7 days or if symptoms worsen.
- Follow up on any identifiable precipitating cause, such as immunocompromise.

chronic maintenance therapy with fluconazole 100 to 200 mg daily should be considered.

OUTCOME EVALUATION

Patients should notice symptomatic relief within 2 to 3 days of initiating therapy. Complete resolution typically occurs within 7 to 10 days. The entire course of therapy should be continued even if symptoms have resolved. If the condition does not resolve or worsens, the patient should be referred to a specialist for aggressive therapy.

Patient Encounter 2, Part 1

A 40-year-old man presents to your clinic stating that he noticed "this funny white stuff" in his mouth, along with "burning and soreness in my mouth." He also mentions that he has a metallic taste in his mouth.

On initial examination, he has white patches on his tongue, gums, and buccal mucosa. These patches are easily removed, revealing erythematous tissue underneath.

Although he has visited the clinic before, his medical records are incomplete. He denies any current or recent medication use or being HIV-positive.

What additional information do you need to know before creating a treatment plan for this patient?

What underlying medical conditions might make him susceptible to fungal infections?

Short courses of oral azoles are associated with gastrointestinal upset, whereas courses lasting longer than 7 to 10 days are associated with increased risk of hepatotoxicity and CYP-450 drug interactions. In patients receiving prolonged therapy lasting more than 3 weeks, periodic monitoring of liver function tests should be considered.

Immunocompetent patients generally do not require reassessment after treatment. Patients with neutropenia exhibit an increased risk of dissemination of infection and therefore should be monitored for signs of systemic fungal infection. Due to an increased risk of recurrence, HIV-positive patients should routinely be evaluated for recurrence at each visit.

MYCOTIC INFECTIONS OF THE SKIN, HAIR, AND NAILS

Tinea infections are superficial fungal infections in which the pathogen remains within the keratinous layers of the skin or nails (Table 83–5). Typically these infections are named for the affected body part, such as tinea pedis (feet), tinea cruris (groin), and tinea

Patient Encounter 2, Part 2

How is the treatment care plan altered if the patient has a history of frequent and severe OPC? If the patient is HIV-positive? If the patient is neutropenic?

Table 83–5

Signs, Symptoms, and Risk Factors of Superficial Fungal Infections

Infection	Symptoms, Signs, and Risk Factors
Tinea pedis	• Involves plantar surface and interdigital spaces of foot • Interdigital infections produce itching; presents as fissures, scaling, or macerated skin; can occur between any toes but most often between fourth and fifth toes; may cause foul smell due to superinfection with *Pseudomonas* or diphtheroids • Hyperkeratotic infections present with slivery white scales on a thickened, red base; usually covers entire foot; occasionally may also affect hand • Vesiculobullous tinea pedis presents as pustules or vesicles on soles of feet; associated with maceration, itching, and thickening of sole; may cause lymphangitis and cellulitis; most common during summer months • Ulcerative tinea pedis presents as macerated, denuded, and weeping ulcers on soles; may produce extreme pain and erosion of interdigital spaces; typically complicated by opportunistic gram-negative infections • Risk factors include occlusive footwear, foot trauma, and use of public showers
Tinea manuum	• Infection of the interdigital and palmar surfaces • Presents as white scales in palmar folds; may also develop scales on remainder of palm; may present as singular plaque • More commonly affecting only one hand • Presents with hyperkeratotic skin
Tinea cruris	• Presents with follicular papules and pustules on the medial thigh and inguinal folds • Ringed lesions may extend from inguinal fold over adjacent inner thigh • Lesions usually spare the penis and scrotum, in contrast to candidiasis • Frequency increases during summer • Primarily develops in young men • Risk factors include tight-fitting clothing, excessive sweating, poor hygiene, increased humidity and temperatures • Commonly referred to as "jock itch"
Tinea corporis	• Presents with circular, scaly patch with enlarged border • Lesions may have red papules or plaque in center that clears, leaving hypopigmentation or hyperpigmentation • Itching may be present • Commonly referred to as ringworm of the body • Risk factors include animal to human contact
Tinea versicolor	• Characterized by skin depigmentation but can present as hyperpigmentation, particularly in dark-skinned patients • Typically occurs in areas with sebaceous glands, including neck, trunk, and arms • Depigmentation may persist for years • Primarily develops in young and middle-aged adults • Risk factors include application of oil, greasy skin, high ambient temperature, high relative humidity, tight-fitting clothing, immunodeficiency, malnutrition, hereditary predisposition
Tinea barbae	• Infection of beard area
Tinea capitis	• Infection of the head and scalp • May be asymptomatic initially, then progresses to inflammatory alopecia • "Black dot" alopecia may develop due to breakage of hair at the root • May form kerions (nodular swellings) • Scaling or favus may develop on scalp • Cervical lymphadenopathy is common • Primarily found in infants, children, and young adolescents, often in African American and Hispanic populations • Can be spread from person to person or animal to person
Onychomycosis (tinea unguium)	• Infection of nail plate and bed • Nail becomes opaque, thick, rough, yellow or brownish, and friable; nail may separate from bed • Toenails affected more frequently than fingernails • Prevalence increases with advanced age

corporis (body). Tinea infections are commonly referred to as ringworm due to the characteristic circular lesions. In actuality, tinea lesions can vary from rings to scales and single or multiple lesions.

EPIDEMIOLOGY AND ETIOLOGY

Tinea infections are second only to acne in frequency of reported skin disease. The common tinea infections are tinea pedis, tinea corporis, and tinea cruris. Tinea pedis, the most prevalent cutaneous fungal infection, afflicts more than 25 million people annually in the United States.

Fungal skin infections are primarily caused by **dermatophytes** such as *Trichophyton*, *Microsporum*, and *Epidermophyton*. *Trichophyton rubrum* accounts for more than 75% of all cases in the United States.[22] To a lesser extent, *Candida* and other fungal species cause skin infections. With tinea infections, the causative dermatophyte typically invades the stratum corneum without penetration into the living tissues, leading to a localized infection.

PATHOPHYSIOLOGY

The primary mode of transmission of tinea infections is direct contact with other persons or surface reservoirs. Upon contact, the dermatophytes attach to the keratinized cells, leading to thickening of the cells. Although infection remains localized, bacterial superinfections may develop.

Clinical Presentation and Diagnosis of Mycotic Infections

Symptoms and Signs

See Table 83–5.

Diagnostic Testing

- KOH prep
- Wood's ultraviolet lamp
- Microscopic examination
- Fungal cultures
- Periodic acid-Schiff (PAS) staining of nail

Treatment of Skin and Hair Infections

The goals of treatment include the following:

- Providing symptomatic relief
- Resolution of infection
- Preventing spread of infection

The pathophysiology of onychomycosis depends on the clinical type. With the most common form of onychomycosis, distal lateral subungual, the fungus spreads from the plantar skin. The fungus invades the underside of the nail through the distal lateral nail bed, leading to inflammation of the area. In cases of white superficial onychomycosis, the fungus invades the surface of the nail plate directly. With white superficial onychomycosis, the nail bed and hyponychium are infected secondarily. Proximal subungual onychomycosis infections begin in the cuticle and the proximal nail fold, then penetrate the dorsum of the nail plate.

RISK FACTORS

- Prolonged exposure to sweaty clothing
- Excessive skin folds
- Sedentary lifestyle
- Warm, humid climate
- Use of public pools
- Walking barefoot in public areas
- Skin trauma
- Poor nutrition
- Diabetes mellitus
- Immunocompromise
- Impaired circulation

TREATMENT

Nonpharmacologic Therapy

- Because fungi thrive in warm, moist environments, the practitioner should encourage patients to wear loose-fitting clothing and socks, preferably garments made of cotton or other fabrics that wick moisture away from the body. Avoid clothing made with synthetic fibers or wool.
- Sweaty or wet clothing should be removed as soon as possible.
- Clean the infected area daily with soap and water.
- The infected area should be dried completely prior to dressing, paying particular attention to skin folds.
- To allow circulation of air, the infected area should not be bandaged.
- For foot infections, cotton socks are recommended, although these should be changed two to three times a day to reduce moisture.
- To prevent spread, towels, clothing, and footwear should not be shared with other persons.
- Wear protective footwear in public showers and pool areas.

Pharmacologic Therapy of Tinea Infections

LO 7

KEY CONCEPT Since dermatophyte hyphae seldom penetrate into the living layers of the skin, instead remaining in the stratum corneum, most infections can be treated with topical antifungals. Infections covering large areas of the body, infections involving nails or hair, chronic infections, or infections not responding to topical therapy may require systemic therapy. Treatment is typically initiated based on symptoms, rather than on microscopic evaluation. For infections accompanied by inflammation, combination therapy with a topical steroid can be considered (Tables 83–6, 83–7, and 83–8).

Typically, tinea pedis requires treatment one to two times daily for 4 weeks, whereas tinea corporis and tinea cruris require topical treatment one to two times daily for 2 weeks. When applying treatment, the medication should be applied at least 1 inch beyond the affected area. Treatment of infection should continue at least 1 week after resolution of symptoms. Many practitioners opt to initiate therapy with nonprescription clotrimazole, tolnaftate, miconazole, or terbinafine, reserving prescription topical agents, such as naftifine, ciclopirox, and butenafine, for second-line therapy or refractory cases and systemic therapy for refractory cases.

When recommending topical therapy, the selection of vehicle is based on the type of lesion and location of the infection. Solutions and lotions are recommended for hairy areas and oozing lesions, whereas creams and ointments should be avoided in these areas. Creams are better for moderately scaling and nonoozing lesions. For hyperkeratotic lesions, ointments can be considered. The selected formulation should be applied to the affected area after it is cleaned and dried. The medication should be rubbed into the infected area for improved penetration. Because most patients do not rub in sprays and powders, penetration of the epidermis is minimal, making them less effective than other formulations. Sprays and powders should be considered as adjuvant therapy with a cream or lotion or as prophylactic therapy to prevent recurrence.[7] For OTC medications, in addition to formulation, it is important to identify the active ingredient desired. Even products with the same brand name may contain different active ingredients. Due to the severity of infection and inflammation, tinea capitis does not adequately respond to topical agents; therefore, oral agents for 6 to 8 weeks are recommended. Griseofulvin has long been considered the treatment of choice due to its ability to achieve high levels within the stratum corneum.[23] Terbinafine and itraconazole have also demonstrated effectiveness.[23] Due to its lipophilicity, itraconazole achieves high dermal concentrations that are maintained for 4 weeks after discontinuation of therapy.[24]

Table 83–6

Available Topical Antifungal Agents

Medication	Rx/OTC	Cream/Ointment	Gel	Lotion	Spray/Solution	Powder
Butenafine	OTC	X				
Ciclopirox	Rx	X		X	Lacquer and shampoo	
Clotrimazole	OTC	X		X	X	X
Econazole	Rx	X				
Efinaconazole	Rx				X	
Haloprogin	Rx	X			X	
Ketoconazole	Rx/OTC	X			Shampoo	
Miconazole	OTC	X		X	X	X
Naftifine	Rx	X	X			
Nystatin	Rx	X		X		X
Oxiconazole	Rx	X		X		
Sertaconazole	Rx	X				
Sulconazole	Rx	X				
Tavaborole	Rx				X	
Terbinafine	OTC	X	X		X	
Tolnaftate	OTC	X		X	X	

Treatment of Onychomycosis

For onychomycosis, a chronic infection that rarely remits spontaneously, adequate treatment is essential to prevent spread to other sites, secondary bacterial infections, cellulitis, or gangrene. LO 8 KEY CONCEPT Due to the chronic nature and impenetrability of nails, topical agents have low efficacy rates for treating onychomycosis. Oral agents that can penetrate the nail matrix and nail base, such as itraconazole and terbinafine, are more effective than ciclopirox lacquer, efinaconazole solution, or tavaborole solution. Itraconazole (200 mg twice daily for 1 week per month or 200 mg daily for 12 weeks) and terbinafine (250 mg daily for 12 weeks) demonstrate mycological cure rates of 71% and 77%, respectively, whereas the cure rate range from 29% to 36% for ciclopirox, approximately 55% for efinaconazole, and 35% for tavaborole.[25] For patients with liver disease or who are unable to use oral agents, ciclopirox lacquer, efinaconazole solution, and tavaborole solution remain reasonable alternatives, despite requiring 48 weeks of therapy. Due to low efficacy, griseofulvin should only be considered as second-line therapy with therapy continued for 4 months for fingernail infections or 6 months for toenail infections.

There is a small but real risk of developing congestive heart failure with itraconazole therapy due to its negative inotropic effects.[26] Itraconazole should not be administered to patients with ventricular dysfunction such as congestive heart failure. The Food and Drug Administration (FDA) also released warnings that itraconazole and terbinafine are associated with serious hepatic toxicity, including liver failure and death. Liver failure associated with these medications has occurred in patients with no preexisting living disease or serious underlying medical conditions. Treatment with itraconazole or terbinafine for prolonged periods requires laboratory monitoring of liver function tests before initiation of therapy and at monthly intervals.

Table 83–7

Dosing of Topical Agents for Tinea Infections and Onychomycosis

Agents	Topical Dosing Frequency
Butenafine	Once daily
Ciclopirox	Twice daily; at bedtime (lacquer)
Clotrimazole	Twice daily
Econazole	Once daily
Efinaconazole	Once daily (nail solution)
Haloprogin	Twice daily
Ketoconazole	Once daily
Miconazole	Twice daily
Naftifine	Once daily (cream); twice daily (gel)
Oxiconazole	Twice daily
Sertaconazole	Twice daily
Sulconazole	Twice daily
Tavaborole	Once daily (nail solution)
Terbinafine	Twice daily
Tolnaftate	Two to three times daily

Cultural Awareness When Treating Mycotic Infections

Awareness of cultural beliefs related to feet and hands is essential when treating patients with fungal infections. In Arab countries, showing the bottom of the foot is a grave insult. The foot is considered the dirtiest part of the body. As such, patients from these countries may be hesitant to show their feet to the practitioner. In other countries, the open palm "high five" gesture is considered insulting. When treating patients with infections on the hand, the practitioner should refrain from making this gesture while discussing the patient's hand infection.

Table 83–8

Dosing of Systemic Therapy for Tinea Infections

Medication	Adult Dosing	Pediatric Dosing
Fluconazole	150 mg/week	6 mg/kg/week
Griseofulvin	0.5–1 g/day	10–20 mg/kg/day
Itraconazole	200 mg twice daily	Not studied
Ketoconazole	200–400 mg/day	3.3–6.6 mg/kg/day
Terbinafine	250 mg/day	< 25 kg: 125 mg/day; 25–35 kg: 187.5 mg/day; > 35 kg: 250 mg/day

Patient Care Process: Mycotic Infections—1

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. If patient has experienced previous tinea infections, determine the location of that infection and what medications were utilized and were effective previously.
- Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substances that could interact with prescribed medications.
- Based on the medical history and lifestyle factors, determine whether the patient has compelling risk factors for tinea infections.
- Based on physical examination of affected area, determine whether the patient's signs and symptoms are consistent with a superficial fungal infection.
- Review relevant laboratory tests, if any available.
- Assess the efficacy, safety, and patient adherence of current and planned pharmacotherapy.
- Identify any significant adverse drug effects or interactions.

Develop a Care Plan:

- Select lifestyle modifications and antifungal therapy that are likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.

Implement the Care Plan:

- Educate the patient about lifestyle modifications, medication therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about the tinea infection and its management.
- Discuss importance of medication adherence and lifestyle modifications to cure tinea pedis, cruris, or corporis and prevent fungal infection recurrence.
- Determine whether the patient has insurance coverage or whether recommended agents are included on the formulary.

Follow-up: Monitor and Evaluate:

- No monitoring and evaluation is necessary for short course therapy unless unresolved. For courses lasting longer than 6 weeks in children, baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measurements are recommended, along with complete blood count (CBC) at 6 weeks.
- If unresolved, review medication and lifestyle modification adherence, review physical examination, and consider diagnostic laboratory to evaluate for other types of infection.

OUTCOME EVALUATION

For infections of the skin, patients should notice relief of symptoms, including pruritus, scales, and inflammation, within 1 to 2 weeks. Therapy should be continued at least 1 week after complete resolution of symptoms. If the condition worsens on topical therapy, the patient should be treated with oral therapy.

For onychomycosis, relief of symptoms is slow. The infected nail will need months to grow out. The practitioner should advise the patient not to become frustrated by the slow resolution. Despite the slow progress, the antifungal agent is curing the infection. The practitioner should also advise the patient that even after the infection is cured, the nail may not look "normal."

Patient Care Process: Mycotic Infections—2

Collect Information:

- Assess the patient's symptoms to determine whether self-treatment with OTC antifungal therapy is appropriate. Exclusions for self-treatment include infection of nails or hair, unsuccessful initial treatment, worsening condition, signs of secondary bacterial or systemic infection, large infected areas, or chronic medical conditions such as diabetes, immunosuppression, or impaired circulation.
- Review any available diagnostic data, including cultures and KOH preps.
- Obtain a thorough history of prescription, nonprescription, and natural drug product use.
- Any allergies?

Assess the Information:

- If the patient has had a mycotic infection previously, determine what treatments were helpful to the patient in the past.
- Determine whether long-term prophylactic therapy is necessary to prevent recurrence.
- Determine whether the patient has prescription coverage.

Develop a Care Plan:

- Evaluate the patient for the potential for adverse drug reactions, drug allergies, and drug interactions.
- Select lifestyle modifications and antifungal therapy that are likely to be effective and safe.
- Choose medications, doses, and dosage forms that are optimal for the patient.

(*Continued*)

Patient Care Process: Mycotic Infections—2 (*Continued*)

Implement the Care Plan:

- Educate the patient on lifestyle modifications that will prevent recurrence, including keeping the area dry, wearing shower shoes, washing clothing in hot water, using drying powders, avoiding sharing towels or clothing, and wearing loose-fitting clothing.
- Provide the patient education pertaining to mycotic infections and antifungal therapy, including causes, medication application or administration, length of therapy, how to avoid spread of infection or recurrence, and potential adverse effects.
- Discuss dietary modifications that are necessary with oral agents.
- Discuss medications that may interact with antifungal therapy, particularly with oral agents used for nail infections.
- Discuss warning signs to report such as recurrent or difficult-to-cure infections, infections with malodorous discharge or bleeding.
- Stress the importance of adherence with the antifungal regimen.

Follow-up: Monitor and Evaluate:

- Follow-up if unresolved or worsens with treatment.

Abbreviations Introduced in This Chapter

AIDS	Acquired immunodeficiency syndrome
CDC	Centers for Disease Control and Prevention
HIV	Human immunodeficiency virus
KOH	Potassium hydroxide
OPC	Oropharyngeal candidiasis
OTC	Over-the-counter
PAS	Periodic acid-Schiff test
VVC	Vulvovaginal candidiasis

REFERENCES

1. Center for Disease Control and Prevention. Diseases characterized by vaginal discharge. In: Sexually Transmitted Diseases Treatment Guidelines, 2010. MMWR Recomm Rep. 2010;59(RR-12):56–63.
2. Vijaya D, Dhanalakshmi A, Kulkarni. Changing trends of vulvovaginal candidiasis. J Lab Physicians. 2014;6(1):28–30.
3. Kohler GA, Asseja S, Reid G. Probiotic interference of Lactobacillus rhamnosus GR-1 and Lactobacillus reuteri RC-14 with the opportunistic fungal pathogen Candida albicans. Infect Dis Ob Gyn. 2012;636474.
4. Pirotta M, Chondros, P, Grover S, et al. Effect of lactobacillus in preventing post-antibiotic vulvovaginal candidiasis: a randomized controlled trial. BMJ. 2004;329:548.
5. Pfizer, Incorporated. Diflucan package insert. New York, NY: Pfizer, Incorporated; 2014 .
6. Iavazzo C, Gkegkes ID, Zarkada IM, Falagas ME. Boric acid for recurrent vulvovaginal candidiasis: the clinical evidence. J Women's Hlth. 2011;20(8):1245–1255.
7. Davis JD, Harper AL. Treatment of recurrent vulvovaginal candidiasis. Am Fam Physician. 2011;83(12):1482–1484.
8. National guideline on the management of vulvovaginal candidiasis. British Association for Sexual Health and HIV. Available from: www.bashh.org/documents/50/50.pdf. Accessed July 5, 2018.
9. Pursley TJ, Blomquist IK, Abraham J, et al. Fluconazole-induced congenital anomalies in three infants. Clin Infect Dis. 1996;22:336–340.
10. Female genital mutilation. World Health Organization. Available from: http://www.who.int/mediacentre/factsheets/fs241/en/. Accessed July 5, 2018.
11. Braddy CM, Files JA. Female genital mutilation: cultural awareness and clinical considerations. J Midwifery Womens Health. 2007;52:159–163.
12. Kossioni A. The prevalence of denture stomatitis and its predisposing conditions in an older Greek population. Gerodontology. 2011;28:85–90.
13. Aun MV, Ribeiro MR, Garcia CLC, Agondi RC, Kalil J, Giavina-Bianchi P. Esophageal candidiasis—an adverse effect of inhaled corticosteroids therapy. J Asthma. 2009;46:399–401.
14. Kanda N, Yasuba H, Takahashi T, et al. Prevalence of esophageal candidiasis among patients treated with inhaled fluticasone propionate. Am J Gastroenterol. 2003;98:2146–2148.
15. Fotos PG, Lilly JP. Clinical management of oral and perioral candidosis. Dermatol Clin. 1996;14:273–280.
16. Gaitan-Cepeda LA, Sanchez-Vargas O, Castillo N. Prevalence of oral candidiasis in HIV/AIDS children in highly active antiretroviral therapy-era. A literature analysis. Int J STD AIDS 2014 Aug 25: pii 0956462414548906. [Epub ahead of print.]
17. Petruzzi MNMR, Cherubini K, Salum FG, Zancanaro de Figueiredo MA. Risk factors of HIV-related oral lesions in adults. Rev Saude Publica. 2013;47(1):52–59.
18. Masur H, Brooks JT, Benson CA, et al. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: updated guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014 May;58(9):1308–1311.
19. Center for Disease Control and Prevention. Revised surveillance case definition for HIV infection. MMWR 2014;63(RR-03):1–10.
20. Redding SW. Dahiya MC, Kirkpatrick WM, Coco BJ, et al. Candida glabrata is an emerging cause of oropharyngeal candidiasis in patients receiving radiation for head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol Endo. 2004;97:47–52.
21. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Feb 15;62(4):e1–e50.
22. Kemna ME, Elewski BE. A U.S. epidemiologic survey of superficial fungal diseases. J Am Acad Dermatol. 1996;35:539–542.
23. Higgins EM, Fuller LC, Smith CH. Guidelines for the management of tinea capitis. Brit J Dermatol. 2000;143:53–58.
24. Leyden J. Pharmacokinetics and pharmacology of terbinafine and itraconazole. J Am Acad Dermatol. 1198;38(5):S42–S47.
25. Del Rosso JQ. The role of topical antifungal therapy for onychomycosis and the emergency of new agents. J Clin Aesthetic Derm 2014;7(7):10–18.
26. Ahmad SR, Singer SJ, Leissa BG. Congestive heart failure associated with itraconazole. The Lancet. 2001;357(9270):1766–1767.

84 Invasive Fungal Disease

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LEARNING OBJECTIVES

LO

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

1. Differentiate epidemiologic differences and host risk factors for acquisition of primary and opportunistic invasive fungal diseases.
2. Recommend appropriate empiric or targeted antifungal therapy for the treatment of invasive fungal diseases.
3. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for invasive fungal disease.
4. Evaluate the role of antifungal prophylaxis in the prevention of opportunistic fungal diseases.

INTRODUCTION

Invasive fungal disease or invasive mycoses are general terms for diseases caused by invasion of living tissue by fungi. In contrast to superficial mycoses (see Chapter 83), invasive fungal diseases are less common, but are of greater medical concern because of their disproportionately higher severity and mortality. Approximately 1.5 million people die each year from the 10 most common invasive fungal diseases, which is higher than World Health Organization mortality estimates for tuberculosis (1.4 million) or malaria (1.2 million).[1] However, these numbers likely underestimate the actual mortality burden of invasive fungal disease considering that the four most common infections (cryptococcosis, invasive candidiasis, invasive aspergillosis (IA), and *Pneumocystis jiroveci* pneumonia) are often underdiagnosed and not reportable diseases to public health agencies (Table 84–1).

Invasive fungal diseases are broadly categorized as either primary or opportunistic mycoses. KEY CONCEPT Primary invasive fungal diseases develop following exposure to fungal spores or conidia in the soil that, when disturbed, can become aerosolized and inhaled leading to infection, even in an immunocompetent patient exposed to a sufficient inoculum. Because these fungi are in specific soil types in select geographic areas, they are also referred to as endemic fungi. In the United States, three species (*Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides immitis/Coccidioides posadasii*) account for most of these infections (see Table 84–1).

KEY CONCEPT In contrast, opportunistic fungal diseases are most frequently encountered in the setting of compromised host immune defenses, and are caused by a wider spectrum of less virulent fungal species that rarely cause infection in healthy patients (see Table 84–1). Hence, the spectrum, severity, and outcome of opportunistic fungal diseases are strongly influenced by the degree, type, and severity of host immunosuppression. As a rule, opportunistic fungal diseases are difficult to diagnose, but often fatal if not diagnosed early and treated aggressively.

Occasionally, opportunistic fungal diseases may be associated with outbreaks in non-immunocompromised patients if fungi are inadvertently inoculated into patients from contaminated drug solutions or medical devices. In 2012, an outbreak of fungal meningitis and joint infections (n = 751 cases) in 20 states was eventually traced by the Centers for Disease Control and state health departments to contaminated preservative-free methylprednisolone solution compounded by a pharmacy that was distributed to multiple doctors' offices. These contaminated steroid solutions were administered as epidural and **articular** injections in patients with chronic back or joint pain. The **dematiaceous** mold eventually linked to the fungal meningitis

Table 84–1

Invasive Mycoses

Primary (Endemic) Invasive Fungi
Histoplasma capsulatum[a]
Coccidioides immitis/Coccidioides posadasii[a]
Blastomyces dermatitidis[a]
Opportunistic Invasive Fungi
Yeast
Candida species (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei*, and others)[a]
Cryptococcus neoformans[a]
Trichosporon spp. and others
Mold
Hyalohyphomycoses (non-dematiaceous)
Aspergillus fumigatus, *Aspergillus terreus*, *Aspergillus flavus*, and other species[a]
Fusarium solani and *Fusarium oxysporum*
Mucorales (formally *zygomycosis*) (*Mucor, Absidia, Rhizopus, Cunninghamella*, and *Rhizomucor*)
Penicillium species
Phaeohyphomycoses (dematiaceous)
Pseudallescheria boydii (*Scedosporium* spp.)
Bipolaris
Alternaria
Exserohilum rostratum
Other
Pneumocystis jiroveci (formerly *P. carinii*)[a]

[a]Most common.

cases, *Exserohilum rostratum*, had rarely been described as a human pathogen prior to the outbreak.[2]

PRIMARY (ENDEMIC) MYCOSES

EPIDEMIOLOGY AND ETIOLOGY

Endemic mycoses are capable of infecting otherwise healthy individuals. In immunocompromised patients, endemic fungal infections present with more severe manifestations or can reactivate with life-threatening consequences. Because initial symptoms of an endemic fungal infection are nonspecific and produce symptoms indistinguishable from other slowly progressing infections (tuberculosis), a careful patient history concerning travel and activities that may have resulted in exposure to endemic fungi are essential for early diagnosis.

LO 1

Two of the most common endemic fungal infections (histoplasmosis and North American blastomycosis) are found in overlapping regions in the eastern and central river basins of the United States (Figure 84–1). *H. capsulatum* var. *capsulatum*, the causative fungus of histoplasmosis, grows heavily in soil contaminated with bird or bat excreta, which serve to enhance sporulation of the fungus.[3,4] Infections have been associated with activities that disturb soil contaminated with this excreta, including cave exploration (spelunking), working in or demolishing chicken coops or older buildings, or work in campsites in heavily wooded areas. For blastomycosis, decaying organic matter, warm humid conditions, and proximity to water or frequent rainfall support growth of this fungus. Outbreaks of blastomycosis have been most frequently associated with occupational or recreational activities around the major waterways such as the Great Lakes region, where soil concentrations of *B. dermatitidis* are elevated.[4]

Coccidioidomycosis differs from histoplasmosis and blastomycosis, as the fungus is associated with arid to semiarid climates, hot summers, low altitude, alkaline soil, and sparse flora. Hence the fungus is found in the Southwestern region of the United States stretching from Western Texas to Southern California (see Figure 84–1).[5] Epidemics of coccidioidomycosis have been reported in California following dust storms and earthquakes, including cycles of intense drought and rain, which favor the growth of the fungus and dispersal of its spores, called arthroconidia.

Patient Encounter 1, Part 1: Endemic Fungal Infection

A 42-year-old Filipino woman from Phoenix, Arizona presents with headache, fever, and new skin lesions 3 months following a liver transplant for autoimmune hepatitis. The patient has had persistent fever for 3 weeks despite a recent 2-week course of amoxicillin/clavulanate. The skin lesions were tender and warm to palpation but lacked erythema, pallor, or fluctuance. Lymphadenopathy was not appreciated on physical examination. Her medications included an immunosuppressant tacrolimus. Chest computed tomography (CT) found multiple pulmonary nodules.

What information is suggestive that this patient may have an endemic fungal infection?

What is the most likely endemic fungal pathogen based on this patient's area of residence?

PATHOPHYSIOLOGY

Endemic fungi share several characteristics that contribute to their pathogenicity in humans. All endemic fungi exhibit temperature-dependent dimorphism, meaning they can propagate as either

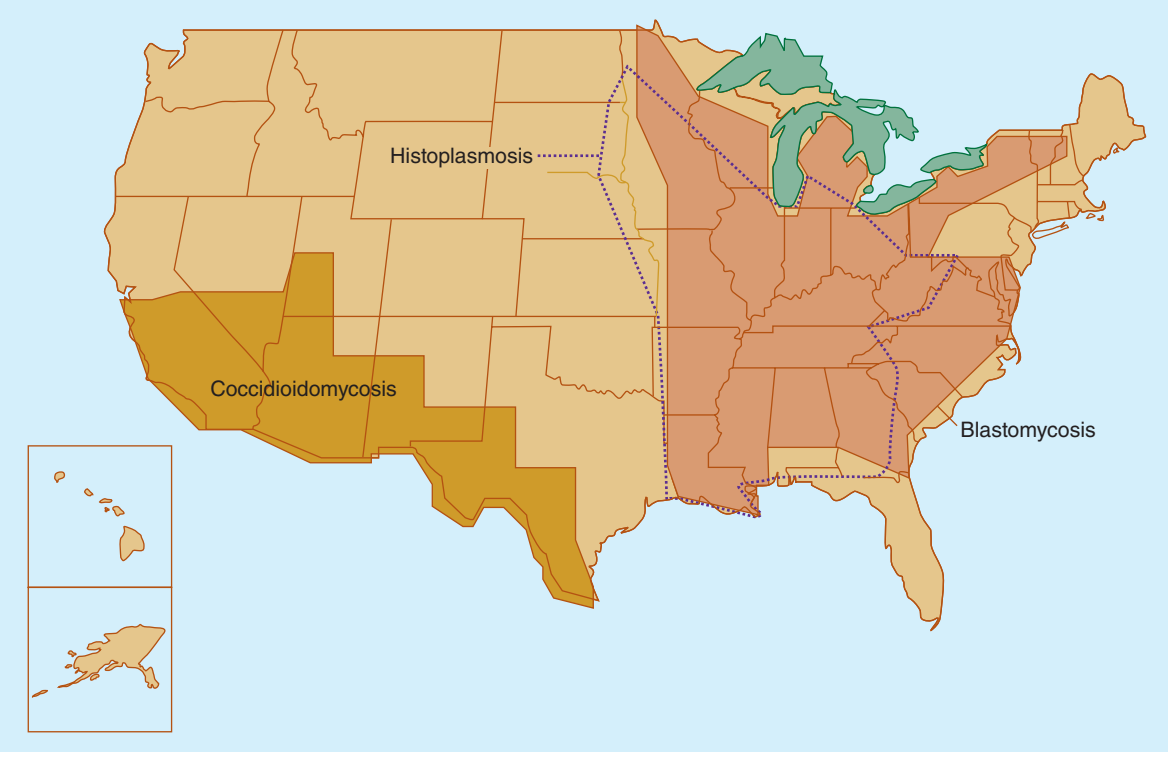

FIGURE 84–1. Geographic localization of primary (endemic) fungi in the United States.

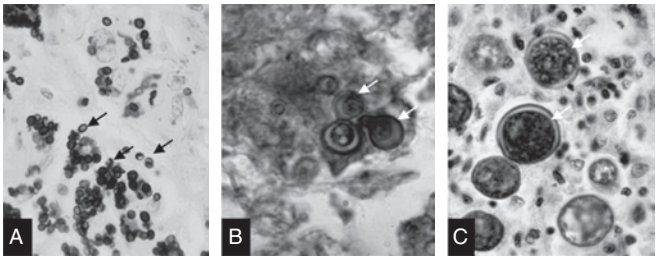

FIGURE 84–2. Histopathology of endemic mycoses in tissue. **(A)** Histoplasmosis (yeast). **(B)** Blastomycoses (broad-based budding yeast). **(C)** Coccidioidomycoses (spherules with endospores).

yeast (single cells that reproduce by budding into daughter cells) or molds (multicellular filamentous fungi that reproduce through production of conidia or spores). At environmental temperatures (25–30°C [77–86°F]), *H. capsulatum*, *B. dermatitidis*, and *C. immitis* grow in the mold form, producing 2- to 10-µm round- to oval-shaped (*Histoplasma* and *Blastomyces*) or barrel-shaped **conidia** (*Coccidioides*) that are dispersed throughout the environment and in air currents. At physiologic temperatures, the conidia germinate into yeast (*Histoplasma* and *Blastomyces*) or in specialized cell forms called spherules (*Coccidioides*) that are resistant to killing by alveolar macrophages and neutrophils in the lung.

Control of infection by the host requires the development of antigen-specific T-lymphocyte response that enhances macrophage fungicidal activity and formation of a **granuloma** to contain the fungus.[6] Not surprisingly, patients with T-cell–mediated immune deficiency (eg, acquired immunodeficiency syndrome [AIDS] patients and transplant recipients requiring immunosuppressive therapy) or suppressed cellular immunity due to drug therapy (eg, chemotherapy, high-dose corticosteroids, or tumor necrosis-α blockers such as infliximab) are at higher risk for reactivation of fungal disease.

The most common route of infection for endemic fungi is the respiratory tract, where conidia aerosolized from contaminated soil are inhaled into the lung. Once in the lung, conidia are phagocytosed but not destroyed by macrophages and neutrophils in the alveoli and bronchioles. Within 2 to 3 days, conidia germinate into yeast resistant to phagocytosis and killing by macrophages and neutrophils (**Figure 84–2A** and **B**). For *C. immitis*, germination of the arthroconidia results in the formation of a sac-like structure called a spherule filled with endospores (**Figure 84–2C**). Spherules then rupture to release large numbers of endospores, which are the propagating form of the infection. Control of infection in the lungs requires the formation of a granuloma to contain the fungus. However, in patients exposed to an overwhelming inoculum, or a lower-inoculum exposure in the setting of suppressed T-cell–mediated immunity can result in a potentially fatal infection that disseminates outside the lung to the skin and oral mucosa, adrenal glands, bone, spleen, thyroid, gastrointestinal (GI) tract, heart, and central nervous system (CNS).

CLINICAL PRESENTATION AND DIAGNOSIS

Histoplasmosis and coccidioidomycosis frequently present with mild self-limiting, influenza-like or mild lower-respiratory tractlike illness 1 to 3 weeks after inhalation of conidia. The clinical presentation of blastomycosis can range from asymptomatic infection, to acute or chronic pneumonia that develops weeks after exposure, to full-blown disseminated disease.

Severe endemic fungal disease often presents with a clinical history of persistent pneumonia despite multiple courses of antibiotic therapy that is accompanied by fever, chills, cough, arthralgia, night sweats, and weight loss. This clinical presentation is often indistinguishable from other chronic infections such as pulmonary tuberculosis. Therefore, the diagnosis of endemic fungal infection is often prompted by a patient history of prolonged infectious symptoms, travel or residence in an endemic area, and/or participation in activities that result in exposures to soil contaminated by endemic fungi.

LO 1

Radiological findings

- Chest radiographs often reveal either diffuse or nodular infiltrates in the lung, accompanied by enlargement of the hilar and/or mediastinal lymph nodes.
- Fulminant pneumonia may be seen with high inoculum exposures, resulting in diffuse lung infiltrates that progress to **acute respiratory distress syndrome** (ARDS) and respiratory failure.

Signs and Symptoms

- Rheumatologic symptoms such as severe arthritis, **pericarditis**, and **erythema nodosum** may be seen in 10% to 30% of patients with endemic fungi.[3–5]
- Dissemination outside the lung is common in patients with suppressed cellular immunity and frequently produces signs of progressing infection.
- Ulcerative oral and cutaneous lesions may also arise with any endemic fungal infection.
- Verrucose (wart-like) skin lesions on sun-exposed areas on the face are particularly suggestive of progressing blastomycosis and are frequently mistaken for skin cancer.
- Dissemination of the fungi to bone marrow may result in anemia or thrombocytopenia.
- Hepatomegaly, splenomegaly, and adrenal insufficiency can also occur with dissemination of the endemic fungi to these internal organs.
- Seizures, meningeal signs, and **hydrocephalus** may occur with dissemination of the infection to the CNS and signify a poor prognosis.

Definitive diagnosis of an endemic fungal infection requires growth of the fungus from body fluids or tissue, or evidence of cellular or tissue invasion in clinical samples by histopathology. However, cultures may only be positive in the setting of high inoculum exposures, pneumonia, or disseminated disease. Serologic detection of antibodies is helpful in the diagnosis and management of patients with histoplasmosis or coccidioidomycosis, but lacks specificity for diagnosis of *B. dermatitidis*.[4] In general, a fourfold rise in antibody or complement fixation titers of *Histoplasma* or *Coccidioides*, or any titer greater than 1:16, suggests active infection. However, many clinicians still consider titers as low as 1:8 as evidence of active disease because undetectable titers may be present in one-third of all active infections. Enzyme-linked immunosorbent assays (ELISAs) have been developed for direct detection of *Histoplasma* antigens in serum and urine. Serial antigen testing can also provide a means for assessing response of histoplasmosis to antifungal therapy and detection of relapsing disease.[3]

TREATMENT

LO 2

KEY CONCEPT The approach to antifungal therapy in patients with endemic fungal infections is determined by the severity of clinical presentation, the patient's underlying immunosuppression, and potential toxicities and drug interactions associated with antifungal treatment. Immunocompetent patients with mild disease following exposure to *H. capsulatum* or *C. immitis* often experience a benign course of infection that does not require antifungal therapy. Persons of Filipino or African descent have a higher risk for dissemination with *C. immitis*, and this may also be taken to consideration for more aggressive treatment.[5] Approximately 9% of patients exposed to coccidioidomycosis (defined by positive IgM or IgG serology) develop pneumonia requiring hospitalization, and 1% may develop infections of the CNS, which are difficult to treat if not incurable.[5]

Current guidelines suggest that patients with mild histoplasmosis or coccidioidomycosis may be initially followed in the outpatient setting with serial antigen or serologic studies to confirm resolving infection. Patients without clinical improvement within the first month can be treated with oral itraconazole for 6 to 12 weeks (Table 84–2).[3,5] Broader-spectrum triazoles such as voriconazole and posaconazole, and possibly isavuconazole, appear to have clinically useful activity against endemic fungi; but have limited data to recommend their routine first-line use. Fluconazole treatment (6–12 mg/kg/day; 400–800 mg/day) is associated with somewhat higher relapse rates than itraconazole but has fewer GI adverse effects and drug interactions compared to itraconazole. Echinocandins and flucytosine are not clinically useful agents for the treatment of endemic mycoses.

LO 2

Patients with symptoms persisting longer than 2 weeks, greater than 10% weight loss, extensive pneumonia, or serologic titers greater than 1:8 of histoplasmosis or coccidioidomycosis are candidates for immediate antifungal therapy. Any patient with underlying immunosuppression should also receive immediate antifungal therapy. The following signs and symptoms are indicators of severe disease that require

Table 84–2

Common Treatment Regimens for Endemic Fungal Infections

Mycosis	Recommended Treatment Regimens	Comments
Histoplasmosis		
Mild to moderate	Observation or itraconazole 200 mg three times daily for 3 days, then two times daily for 6–12 weeks. Fluconazole 12 mg/kg/day PO for 6–12 weeks adjusted for renal function.[a]	Fluconazole has a higher rate of relapse than itraconazole but is better tolerated by many patients than itraconazole. Echinocandins are not clinically effective against endemic mycoses.
Severe including CNS disease or immunocompromised host	Amphotericin B 0.7 mg/kg/day IV or liposomal AMB. Amphotericin B 3–5 mg/kg/day for 12 weeks or until clinically stable.	Liposomal amphotericin B better tolerated than conventional formulations, especially for CNS disease. Patients initially treated with amphotericin B–based regimens are transitioned to itraconazole or fluconazole once they are clinically stable. Corticosteroid therapy should be considered in hypoxic patients with acute pulmonary infection. Itraconazole is less effective for CNS infections.
Blastomycosis		
Mild to moderate	Itraconazole 200 mg three times daily for 3 days, then two times daily for 6–12 months.	
Severe including CNS disease or immunocompromised host	Amphotericin B 0.7 mg/kg/day IV until patient is clinically stable, then itraconazole (non-CNS) or fluconazole 12 mg/kg/day orally adjusted for renal function.[a]	
Coccidioidomycosis		
Mild to moderate including non-complicated pneumonia	Observation or itraconazole 200 mg three times daily for 3 days, then two times daily for 3–6 months. OR Fluconazole 6–12 mg/kg/day (400–800 mg daily) daily adjusted for renal function[a] for 3–6 months.	Itraconazole demonstrated trend toward superiority over fluconazole in a randomized-controlled trial for progressive, nonmeningeal coccidioidomycosis; however, fluconazole is better tolerated than itraconazole.
Diffuse pneumonia or disseminated infection	Amphotericin B 1–1.5 mg/kg/day with dose and frequency decreased as improvement occurs. Patient then transitioned to triazole therapy. OR Liposomal amphotericin B formulation 3–5 mg/kg/day. Patient then transitioned to triazole therapy.	Fluconazole 800–1000 mg/day adjusted for renal function[a] is often recommended after initial AMB therapy for meningitis.

[a]CrCl > 50–90 mL/min (0.83–1.50 mL/s), 100% of dose; CrCl 10–50 mL/min (0.17–0.83 mL/s), 50% of dose; CrCl < 10 mL/min (0.17 mL/s) 50%.
CNS, central nervous system; IV, intravenous; PO, oral.

hospitalization and initial treatment with systemic amphotericin B (see Table 84–2).

- Hypoxia indicated by a partial pressure of oxygen less than 80 mm Hg (10.6 kPa)
- Hypotension (systolic blood pressure < 90 mm Hg)
- Impaired mental status
- Anemia (hemoglobin < 10 g/dL [100 g/L or 6.2 mmol/L])
- Leukopenia (< $1 \times 10^3/mm^3$ [$1 \times 10^9/L$])
- Elevated hepatic transaminases (> 5 times upper limit of normal) or bilirubin (> 2.5 times upper limit of normal)
- Coagulopathy (impaired clotting ability)
- Evidence of dissemination, including cutaneous manifestations
- Meningitis

All patients with blastomycosis require antifungal treatment, even though patients with mild disease can be managed as outpatients with oral itraconazole.[7] Patients with evidence of severe pulmonary disease or dissemination require initial treatment in the hospital with amphotericin B–based regimens until they are clinically stable, whereupon they can complete a 6- to 12-month treatment course as outpatients with oral triazoles.[4] Methylprednisolone (0.5–1 mg/kg daily IV) may be administered during the first 1 to 2 weeks of antifungal therapy if the patient develops hypoxemia or significant respiratory distress.

OUTCOME EVALUATION

Response to antifungal therapy may be slow in patients with a prolonged history of infection or severe manifestations. However, gradual improvements in symptoms and reduction in fever are indicators of response to treatment. For histoplasmosis and coccidioidomycosis, decreasing antigen titers or serology are indicative of response to antifungal therapy.[3,5]

LO 3

Antifungals used for the treatment of endemic mycoses can be associated with many clinically significant drug interactions and toxicities, especially with the prolonged treatment courses required for endemic mycoses. Itraconazole is available as a capsule formulation that should be taken with food and as a cyclodextrin-solubilized solution taken without food. The liquid formulation of itraconazole has several advantages over the capsule: It has a better oral bioavailability and does not require the low gastric pH that is required for dissolution and absorption of the capsule. However, the oral solution is somewhat dilute, has an unpalatable aftertaste (an issue when taking months of therapy), and has a much higher rate of GI intolerance. Therefore, the capsule formulation is often preferred provided patients are not on acid-suppression therapy (ie, proton pump inhibitors, histamine antagonists, or antacids). Acidic beverages, such as orange or apple juice, or cola can improve the absorption of itraconazole capsules.

Fluconazole is available in both IV and oral formualtions that have good bioavailability. Posaconazole is formulated as a micronized suspension that is best absorbed when taken with high-fat meals and when taken in divided doses up to 800 mg/day. A delayed-release tablet formulation of posaconazole with improved bioavailability and fewer gastric pH-associated drug interactions is also available, and is probably the preferred oral treatment formulation of posaconazole in most patients unless the patient cannot swallow the tablet.[8] An IV formulation of posaconazole is also available for patients who cannot take oral formulations. Absorption of voriconazole is not affected by gastric pH, but is generally administered 1 hour prior to or 2 hours after eating. Isavuconazole is available in both an IV and oral pro-drug formulation that is not affected by gastric pH or food.[9]

Drug interactions are an important concern in patients taking long-term triazole therapy. Itraconazole, voriconazole, and isavuconazole are substrates of the cytochrome P450 (CYP) 3A4 enzyme. Coadministration of itraconazole, voriconazole, and to lesser extent fluconazole, posaconazole, and isavuconazole with inducers of this CYP 3A4 enzyme (eg, rifampin, phenytoin, and phenobarbital) increase drug clearance resulting in ineffective plasma and tissue concentrations of the drug.[10] In general, coadministration of the broader-spectrum triazoles (itraconazole, voriconazole, posaconazole, and isavuconazole) with these inducers should be avoided. Itraconazole, voriconazole, posaconazole, and, to a lesser extent, isavuconazole are also potent inhibitors of CYP 3A4, which predisposes these agents to a large number (estimated > 2000) of clinically significant pharmacokinetic drug–drug interactions.[10]

LO 3

All patients should have their medication profile carefully reviewed prior to initiating and stopping triazole antifungals, preferably with the aid of a computerized drug-interactions database. Even in the absence of drug interactions, serum drug levels of triazoles can be unpredictable.[11] Serum drug concentration monitoring or therapeutic drug monitoring (TDM) has been recommended in patients receiving itraconazole, voriconazole, and posaconazole suspension for documented infections, or when inadequate serum concentrations are suspected because of altered absorption, drug interactions.[11] Suspected toxicities, especially CNS adverse effects during voriconazole therapy,[12] may also be indicative of excessive drug levels that can be detected with TDM (Table 84–3).

LO 3

All azole antifungals carry the potential for rash, photosensitivity, and hepatotoxicity. In general, hepatotoxicity is mild and reversible, presenting as asymptomatic increases in liver transaminases, and less frequently increases in total bilirubin. Fulminant hepatic failure is less common and typically mediated by immunologic mechanisms. Therefore, serial monitoring of liver function is recommended in all patients receiving triazole antifungals. Long-term therapy with itraconazole has also been associated with reversible adrenal suppression and cardiomyopathy due to negative inotropic effects of the drug. Long-term therapy with voriconazole can be associated with severe phototoxic reactions and cutaneous erythema in sun-exposed skin, which may not be preventable with sunscreen alone. This phototoxic reaction has been linked to a high risk for developing squamous cell carcinoma or melanoma.[13] Patients should be instructed to avoid sun exposure while on voriconazole therapy and have frequent skin examinations by a dermatologist. Long-term voriconazole therapy may also predispose patients to perisotitis, or inflammation of tissue surrounding bone due to

Patient Encounter 1, Part 2: Endemic Fungal Infection

Patient Management

The patient's serum titer for coccidioidomycosis returns as greater than 1:8. Based on the information presented, select an appropriate treatment plan for the patient's infection.

Should the patient receive antifungal therapy now? What factors need to be considered?

Table 84–3

Recommendations for Antifungal Therapeutic Drug Monitoring

Drug	Indication for Monitoring	Time of First Measurement	Target Conc. for Efficacy (mcg/mL or mg/L)	Target Conc. for Safety (mcg/mL or mg/L)
Flucytosine	Routine during first week of therapy, renal insufficiency, or poor clinical response	3–5 days	Peak > 20 (155 µmol/L)	Peak < 50 (387 µmol/L) to reduce risk of marrow toxicity
Itraconazole	Routine during first week of therapy, GI dysfunction, suspected drug interactions	4–7 days	Prophylaxis > 0.5 (0.7 µmol/L); therapy trough > 1–2 (1.4–2.8 µmol/L)	Some evidence to suggest trough > 4 (5.7 µmol/L) increased adverse effects
Voriconazole	Lacking response, GI dysfunction, suspected drug interactions, pediatrics,[a] IV to oral switch, unexplained neurological changes	4–7 days	Prophylaxis trough > 0.5 (0.7 µmol/L); therapy trough 1–2 (2.9–5.7 µmol/L)	Trough < 6 (17.2 µmol/L) to reduce risk of CNS toxicities
Posaconazole	Lacking response, GI dysfunction, potent acid suppression therapy (ie, proton pump inhibitor) therapy, suspected drug interactions	4–7 days	Prophylaxis trough > 0.5 (0.7 µmol/L); therapy trough 0.5–1.5 (0.7–2.1 µmol/L)	Not established Delayed-release tablet formulation preferred for most patients because fewer pH drug interactions and improved bioavailability. IV formulation is available for patients who cannot take oral therapy
Isavuconazole	Lacking response, suspected drug interactions, mucormycosis	4–7 days	Not established, in clinical trials media trough concentration surpassed 2 (5.7 µmol/L)	Not established, in clinical trials the average trough concentration surpassed 2 (5.7 µmol/L)

[a]Pediatric patients display accelerated linear clearance of voriconazole. Therefore, higher daily voriconazole dosing (7 mg/kg every 12 hours) are recommended to achieve similar exposures to adults. Some children may require doses as high as 12 mg/kg every 12 hours to achieve similar serum drug exposures to adults. Therefore, therapeutic drug monitoring is recommended.

GI, gastrointestinal; IV, intravenous.

fluoride toxicity from chronic voriconazole exposure, (fluoride toxicity) that present with nonspecific joint, shoulder, and limb pain that can be diagnosed by x-ray and serum analysis of fluoride levels.[14] Alopecia, chapped lips and brittle nails, and cognitive difficulties have also been reported with longer-term voriconazole therapy, especially at higher doses.[15] Peripheral neuropathy may develop in 3% to 17% of patients on long-term triazole therapy, and is most frequently reported with itraconazole and voriconazole.[16]

Amphotericin B remains the mainstay of treatment of patients with severe endemic fungal infections. The conventional deoxycholate formulation of the drug can be associated with substantial infusion-related adverse effects (chills, fever, nausea, rigors, and in rare cases hypotension, flushing, respiratory difficulty, and arrhythmias). As-needed premedication with low doses of acetaminophen and diphenhydramine, and less frequently nonsteroidal anti-inflammatory agents hydrocortisone or meperidine (if rigors are present) are used to reduce acute infusion-related reactions. Venous irritation associated with the drug can also lead to thrombophlebitis; hence, central venous catheters are the preferred route of administration in patients receiving more than a week of therapy.

LO 3

The most severe adverse effect associated with amphotericin B therapy is nephrotoxicity, which occurs through direct effects on glomerular filtration (constriction of the afferent arterioles in the kidney tubule) and damage of the distal tubular membrane.[17] Generally, nephrotoxicity with amphotericin B is reversible provided the drug is stopped. However, treatment interruptions can be problematic in patients with severe infections. Precipitous decreases in glomerular filtration may occur in patients with marked dehydration or during aggressive diuresis. Infusion of normal saline before and after amphotericin B, a practice known as "sodium loading," can blunt precipitous decreases in renal perfusion pressure and slow the rate of decline in the glomerular filtration rate, but may not be tolerated in patients with poor cardiac function. Administration of amphotericin B by continuous infusion reduces the glomerular but not distal tubular toxicity, and is generally not advocated because of unproven efficacy. Amphotericin B–associated nephrotoxicity can be delayed by avoiding the use of other drugs with known tubular toxicity such as aminoglycosides, calcineurin inhibitors, cisplatin, or foscarnet. The initial manifestation of tubular toxicity manifests in patients with severe wasting of potassium and magnesium in the urine. Therefore, patient electrolytes must be carefully monitored and potassium and magnesium supplementation is always necessary. Hypokalemia and hypomagnesaemia frequently precede decreases in glomerular filtration (increased serum creatinine), especially in patients who are adequately hydrated.[17] Continued tubular damage eventually results in decreases in renal blood flow and glomerular filtration through tubuloglomerular feedback mechanisms that further constrict the afferent arteriole.

During the 1990s, amphotericin B was reformulated into three different lipid-based formulations (Abelcet, AmBisome, and Amphotec) that have reduced rates of nephrotoxicity compared with the conventional deoxycholate formulation (Fungizone). Two of the formulations that are currently available (Abelcet and AmBisome) have lower rates of infusion-related reactions. Although these lipid formulations are generally considered to be as effective as conventional amphotericin B deoxycholate, they are not dosed equivalently to the standard formulation (see Table 84–2).

PROPHYLAXIS

LO 4 Primary **prophylaxis**, before development of infection, is generally not recommended for endemic fungi. Antifungal prophylaxis is generally recommended in specific situations, including the following:

1. Patients with HIV infection [and with $CD4^+$ cell counts less than 150 cells/mm^3 (150×10^6/L) (histoplasmosis)] living in regions with high endemic case rates (> 10 cases per 100 patient-years), or in any patient with positive IgM or IgG antibodies. The recommended regimen is itraconazole 200 mg daily.
2. Secondary prophylaxis or suppressive therapy with itraconazole 200 mg daily is recommended to prevent recurrence of blastomycosis in immunosuppressed patients if immunosuppression cannot be reversed.[4]
3. In patients with prior CNS disease, fluconazole or voriconazole are preferred over itraconazole and posaconazole due to the lower penetration of itraconazole and posaconazole into the CNS.[5]

OPPORTUNISTIC MYCOSES

LO 1 KEY CONCEPT Commensal or environmental fungi that are typically harmless can become invasive mycoses when the host immune defenses are impaired. Host immune suppression and risk for opportunistic mycoses can be broadly classified into three categories:

1. A reduction in the number or quality of neutrophils
2. Deficits in **cell-mediated immunity**
3. Disruption of the skin, gut and/or microbiologic barriers

A reduction in the number of neutrophils (neutropenia) resulting from neoplastic diseases, cytotoxic chemotherapy, marrow transplantation, or bone marrow aplasia are among the most common risk factors for opportunistic mycoses. Functional neutrophil defects may be seen in certain disease states (eg, advanced diabetes mellitus and chronic granulomatous disease) or with high-dose corticosteroid therapy. Deficits in T-cell–mediated immunity associated with HIV infection, high-dose corticosteroid therapy, calcineurin inhibitors, or other immunosuppressive drugs, chemotherapy, transplantation, bone marrow failure, and other immunodeficiencies are increasingly prevalent with the prolonged survival of transplant patients or other chronically immunosuppressed populations.

Immune deficits arising from disruption of the skin GI/genitourinary barriers can also predispose patients to fungal diseases. The most common types of barrier disruptions include surgery or infections/perforation of the abdominal viscus, use of central venous and urinary catheters, parenteral nutrition, and mucositis associated with cytotoxic chemotherapy and antibiotic therapy. Broad-spectrum antibacterial therapy, which is common in high-risk hematology patients and the critically-ill patient in the ICU, disrupts the protective microbiologic flora of the gut allowing overgrowth of *Candida* species that can translocate to the bloodstream and invade internal organs.

In general, opportunistic mycoses are difficult to diagnose and are frequently treated empirically before diagnosis is proven.

LO 1 KEY CONCEPT Deciding when to initiate antifungal therapy and what opportunistic pathogens to cover is a decision governed largely by the immune deficits of the host, local epidemiology and experience, or clinical or diagnostic clues suggestive of incipient infection.

INVASIVE CANDIDIASIS

EPIDEMIOLOGY AND ETIOLOGY

Candida species are the most common opportunistic fungal pathogens encountered in hospitals, ranking as the third to fourth most common cause of nosocomial bloodstream infections in **ICU**s in the United States and the eighth most common cause of bloodstream infections overall.[18] The incidence of nosocomial candidiasis has increased steadily since the early 1980s, with the widespread use of central venous catheters, broad-spectrum antimicrobials, and other advancements in the supportive care of critically ill patients. In the 1980s, *C. albicans* accounted for more than 80% of all bloodstream yeast isolates cultured from patients. By the late 2000s, this relative frequency of *C. albicans* had decreased to less than 50% in national surveys of bloodstream infections with increasing proportion of infections caused by non-*albicans* species.[19] Because of the inherent resistance (eg, *C. glabrata, C. krusei*, and more recently *C. auris*) of many of the non-*albicans* species, the introduction of fluconazole in the early 1990s is often cited as the key element driving the shift in the microbiology of invasive candidiasis.

LO 1 KEY CONCEPT Familiarity with the local epidemiology and frequency of non-albicans *Candida* species in the institution or intensive care unit (ICU) is essential before selecting **empiric** antifungal therapy for invasive candidiasis, as fluconazole is not recommended for the treatment of *C. glabrata* and *C. krusei* infections, and echinocandin-resistance among *C. glabrata* is increasing in some centers. *C. auris* is an emerging, multidrug-resistant fungal pathogen for which therapeutic options are limited.

CLINICAL PRESENTATION AND DIAGNOSIS

Invasive candidiasis encompasses several infectious syndromes broadly categorized as candidemia or deep-seated infections, which most frequently affect the kidney, eye, or bones but may also affect heart valves, the CNS, and other organs including the spleen and liver.[20] A major difficulty in the diagnosis of invasive candidiasis in high-risk patients is dinstinguishing colonization from true infection. *Candida* frequently colonizes the urine, sputum, and skin and wounds, especially in patients receiving broad-spectrum antibacterial therapy. However, isolation of *Candida* from these sites frequently does not indicate true infection. For example, *Candida* in the urine can be an indication of renal candidiasis or an obstructing fungus ball; however, it must be distinguished from more common benign colonization of the urinary tract, especially in patients with chronic indwelling urinary catheters. Similarly, *Candida* species isolated for respiratory samples (sputum, bronchoalveolar lavage) are nearly always indicative of colonization and not true *Candida* pneumonia, which is a rare clinical entity.

Approximately one-third of all patients with true invasive candidiasis fall within three groups at the time of diagnosis: (1) patients with uncomplicated candidemia in the absence of deep-seated candidiasis, most frequently arising from an infected catheter; (2) candidemia associated with deep-seated candidiasis, most frequently arising from the GI tract or secondary seeding from a separate infection site; and (3) deep-seated candidiasis without candidemia.[21]

Invasive candidiasis is most frequently diagnosed by growth of yeast in blood culture, which detects infection in most patients with candidemia alone, fewer patients with mixed of deep-seated disease and intermittent candidemia, and virtually no patients who have infection limited to deep tissues at the time of culture. As a result, it is estimated that half of all episodes of invasive candidiasis

are not detected by blood cultures alone. Therefore, a positive blood for *Candida* is always considered strong evidence of infection but a negative blood culture cannot rule out the possibility of invasive candidiasis, especially in patients with multiple underlying risk factors. The development of new diagnostic tools that do not exclusively rely on microbiological isolation of *Candida* has become a major research focus for improving diagnosis of the infection, especially deep-seated disease.[20]

Serodiagnostic tests have been developed for the detection of *Candida* cell wall antigens, or nucleic acids of *Candida* species, in the hope of improving the detection of invasive disease missed by blood cultures. Currently, the most frequently used test is the Fungitell (1→3)-β-D-glucan test, Associates of Cape Cod Inc. False-positive results may occur, however, in patients with gram-negative bacteremia, certain gauze dressing or dialysis membranes, or patients heavily colonized with *Candida* species. More recently the development and Food and Drug Administration (FDA) approval of the T2 Magnetic Resonance–based T2Candida Panel has made possible the rapid, direct, and culture-independent detection of *Candida* species, although this test is not available in all institutions.[22]

Laboratory identification of *Candida* in clinical samples must be performed to the species level whenever possible, as *Candida* species differ considerably in their susceptibility to antifungal agents (Figure 84–3A). Rapid discrimination of *C. albicans* from common non-albicans *Candida* species can be accomplished by the germ-tube test, which presumptively identifies *C. albicans* by the early formation (< 4 hours) of a hyphae-like structure when the yeast is incubated in serum at 37°C (98.6°F). Definitive species identification, however, may require an additional 48 to 72 hours after the organism is isolated on agar, but can be accelerated with fluorescent in situ hybridization (FISH) of *Candida* species–specific DNA sequences. Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) and magnetic resonance–based technologies have shown some promise in the early identification of *Candida* species in whole blood specimens in as little as 3 hours, which could shorten the time to earlier diagnosis.

C. albicans remains the most common cause of invasive candidiasis and is the most virulent of *Candida* species, but is

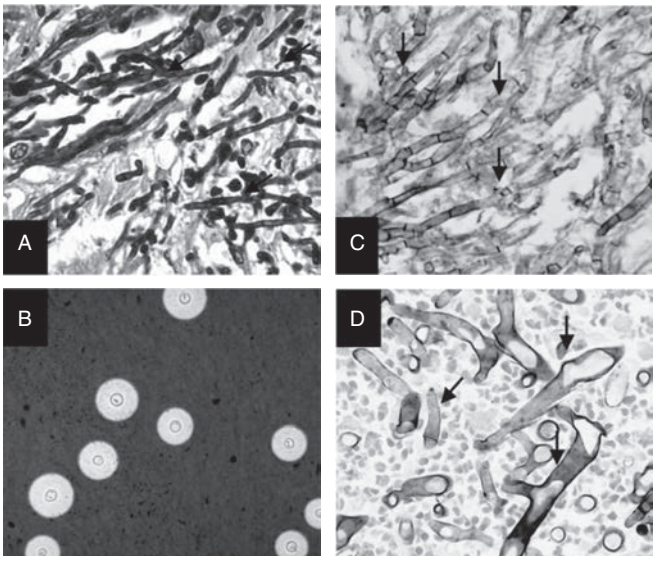

FIGURE 84–3. Opportunistic mycoses in clinical samples. **(A)** Candidiasis (tissue). **(B)** Cryptococcosis (India ink stain of CSF). **(C)** Aspergillosis (tissue). **(D)** Mucormycosis (tissue).

Patient Encounter 2, Part 1: Invasive Candidiasis

A 48-year-old man recovering in the surgical ICU following an abdominal gunshot wound and diffuse peritonitis develops fever while receiving broad-spectrum antibacterial therapy (meropenem 1 g every 8 hours and vancomycin 1 g every 12 hours). The patient has a central venous catheter and a Foley catheter. Blood cultures are negative at the time, but the patient has yeast growing in the sputum and urine. A serum (1→3)-β-D-glucan test is positive at 120 pg/mL (80 ng/L). Laboratory studies reveal a white blood cell count of 13,200 cells/mm^3 (13.2 × 10^9/L).

What are this patient's risk factors for developing an invasive fungal infection?

What evidence suggests this patient has an invasive fungal infection despite negative blood cultures?

If antifungal therapy is empirically started in this patient, what information should be considered?

the most susceptible to commonly used antifungals including fluconazole.[23] Like *C. albicans*, *C. tropicalis* is a relatively virulent species associated with the highest mortality rates, but has similar susceptibility profiles as *C. albicans*. *C. parapsilosis* is a less virulent species seen frequently in neonates and in adults with central venous catheters. However, many *C. parapsilosis* isolates form thick biofilms on prosthetic materials and catheters that make the organism difficult to eradicate. *C. parapsilosis* is generally susceptible to most antifungals, including fluconazole, although mean inhibitory concentrations (MICs) for echinocandins are higher than for other *Candida* species. *C. krusei* is uniformly resistant to fluconazole, although most isolates retain susceptibility to voriconazole and posaconazole. *C. auris* is an emerging highly virulent, multi-drug resistant pathogen that has been associated with infection outbreaks in hospitals and nursing homes.[24] A major problem with *C. auris* is frequent misidentification by automated systems used by many clinical microbiological laboratories, potentially resulting in the patient getting the wrong treatment. Therefore, specialized methods have been proposed for detection and identification of *C. auris* in health care facilities.[24]

C. glabrata may present as a breakthrough infection on fluconazole prophylaxis, and is becoming increasingly resistant to echinocandins.[18] Although *C. glabrata* is generally less virulent than other *C. albicans*, infections with this organism are typically seen in older patients with poor performance status, and therefore mortality remains high. The marginal susceptibility of *C. glabrata* to fluconazole and increasing echinocandin resistance[25,26] has fueled a growing clinical need for susceptibility testing of this species, as some isolates may demonstrate resistance to multiple antifungal classes. Generally, fluconazole-resistant strains of *C. glabrata* should be assumed to be cross-resistant to other triazoles.

TREATMENT

Seven antifungals (amphotericin B, fluconazole, voriconazole, isavuconazole, caspofungin, micafungin, and anidulafungin) have been studied as monotherapy in prospective, randomized comparative clinical trials for the treatment of invasive candidiasis. In a patient-level meta-analysis of several of these trials, increased patient age, elevated APACHE II score, use

of immunosuppressive therapy, and infection with *Candida tropicalis* were independent risk factors for mortality.[27] (See Table 84–4.) On the other hand, removal of central venous catheters in patients with candidemia and treatment with an echinocandin were variables associated with reduced patient mortality. It is also recommended that all patients with candidemia should undergo an eye examination to rule out *Candida* endophthalmitis, which can be sight threatening if not recognized early and may require direct installation of antifungal therapy for adequate treatment.[21] KEY CONCEPT Based on these findings and treatment guidelines endorsed by the Infectious Diseases Society of America, echinocandins are recommended as the preferred initial treatment for invasive bloodstream candidiasis, even less "critically-ill" patients.[21] Timely initiation of antifungal therapy for invasive candidiasis is critical, as any delay in the initiation of antifungal therapy once a patient has a positive blood culture increases the potential for metastatic seeding of organs and mortality. Clinically stable patients can

LO 2

Table 84–4

Therapeutic Approach to Opportunistic Invasive Fungal Infections

Mycoses	Recommended Treatment Regimens	Comments
Candidiasis		
Catheter-related and acute hematogenous	Fluconazole 12 mg/kg loading dose, then 6–12 mg/kg/day IV every 24 hours (400–800 mg/day) adjusted for renal function[a] OR Echinocandin[b] OR Voriconazole 6 mg/kg every 12 hours IV for 1 day, then 3 mg/kg every 12 hours IV *Second line:* Lipid amphotericin B formulation 3–5 mg/kg /day[c] OR Amphotericin B 0.7 mg/kg/day IV OR Amphotericin B + fluconazole	Treat for 14 days after the last positive blood culture and resolution of signs and symptoms; catheter should be removed whenever possible. Patients can be switched to oral fluconazole when clinically stable if isolate is susceptible. Echinocandins and amphotericin B are preferred agents for fluconazole-resistant species. Voriconazole appears to be effective against fluconazole-resistant *C. krusei*.
Empirical therapy in neutropenic patient	Fluconazole 6–12 mg/kg/day (low risk) adjusted for renal function[a] OR Liposomal amphotericin B 3 mg/kg every 24 hours OR Echinocandin OR Amphotericin B 0.7 mg/kg every 24 hours	Antifungals with coverage of *Aspergillus* spp. should be used in higher risk patients or prolonged neutropenia (ie, > 2 weeks).
Urinary candidiasis	Fluconazole 200 mg IV or orally for 7–14 days OR Amphotericin B 0.3 mg/kg/day IV for 1–7 days	Asymptomatic candiduria does not require therapy.
Cryptococcosis		
Pulmonary-Isolated	Fluconazole 6 mg/kg/day IV or PO for 6–12 months adjusted for renal function[a]	
Severe Pulmonary Infection and Meningitis	*Induction:* Amphotericin B 1 mg/kg/day + flucytosine 100 mg/kg/day orally divided every 6 hours for 2 weeks adjusted for renal function[c] *Consolidation:* Fluconazole 6–12 mg/kg/day for 10 weeks adjusted for renal function[a] *Second line:* Fluconazole + flucytosine for 2 weeks, then fluconazole for 10 weeks adjusted for renal function[a,c] OR Amphotericin + fluconazole for 2 weeks, then fluconazole for 10 weeks adjusted for renal function[a] OR Liposomal amphotericin B 5 mg/kg/day for 2 weeks, then fluconazole for 10 weeks adjusted for renal function[a]	Therapeutic drug monitoring is required for safe use of flucytosine, see Table 84–3. Echinocandins have no activity against cryptococci. Use of flucytosine-amphotericin B combination therapy was associated with faster CSF sterilization and improved survival. Similar benefits were not observed with combination fluconazole-amphotericin B regimens.

(*Continued*)

Table 84–4

Therapeutic Approach to Opportunistic Invasive Fungal Infections (*Continued*)

Mycoses	Recommended Treatment Regimens	Comments
Aspergillosis	Voriconazole 6 mg/kg IV every 12 hours × 2 doses, then 4 mg/kg IV every 12 hours Voriconazole 4 mg/kg oral every 12 hours OR Isavuconazole 300 mg (372 mg of isavuconazonium prodrug) every 8 hours for two days, then 300 (372 mg isavuconazonium prodrug) daily *ALTERNATIVES* Lipid formulations of amphotericin B OR Echinocandin[b] OR Posaconazole 300 mg every 12 hours IV day 1, then 300 mg IV daily Posaconazole delayed-release tablet 300 mg twice daily, day 1, then 300 mg daily Posaconazole suspension 200 mg by mouth four times daily for 14 days, then 400 mg PO twice daily OR Combination therapy, typically echinocandin plus triazole	Voriconazole can be administered as oral therapy in patients taking oral medications. However, patients with suspected aspergillosis should initially be stated on IV therapy. Therapeutic drug monitoring should be considered in patients receiving voriconazole (any formulation) or posaconazole suspension, see Table 84–3. Posaconazole tablets and IV formulations have less pharmacokinetic variability but some patients may still benefit from TDM. Combination therapy with triazole and echinocandin associated with improved survival in patients with galactomannan-diagnosed infection. *A. terreus* and *A. flavus* should be considered resistant to amphotericin B.

[a]Fluconazole renal dosing adjustments: CrCl > 50–90 mL/min (0.83–1.50 mL/s), 100% of dose; CrCl 10–50 mL/min (0.17–0.83 mL/s), 50% of dose; CrCl < 10 mL/min (0.17 mL/s) 50%.

[b]Anidulafungin 200 mg loading dose day 1, then 100 mg daily, caspofungin 70 mg loading dose day 1, then 50 mg daily; or micafungin 100 mg daily.

[c]Flucytosine renal dosing adjustments: CrCl > 50–90 mL/min (0.83–1.50 mL/s), 25 mg/kg every 12 hours; CrCl 10–50 mL/min (0.17–0.83 mL/s), 25 mg/kg every 12–24 hours; CrCl < 10 mL/min (0.17 mL/s) 25 mg/kg every 24 hours. Therapeutic drug monitoring is required for safe use of flucytosine (see Table 84–3).

CSF, cerebrospinal fluid; IV, intravenous; PO, oral; TDM, therapeutic drug monitoring.

be transitioned to oral fluconazole or other triazoles once the infecting isolate has been identified and susceptibility is known.[28]

The efficacy of echinocandins for deep-tissue candidiasis is less well established compared to bloodstream infections, and higher failure rates were reported for infections located in anatomical sites where echinocandin penetration is limited (ie, meninges, endophthalmitis, urine).[29] For other forms of deep tissue candidiasis, triazoles or lipid amphotericin B formulation may be preferable as initial therapy until diagnosis and culture results are available, depending on the suspected organs involved and the clinical severity of illness.[21] Frequently patients are transitioned to oral triazole therapy once stable because of the long-treatment courses that are often required (4–6 weeks minimum) for deep-seated infections.

An important caveat for echinocandin treatment is that cryptococcosis, endemic fungi, or other rare yeast (eg, *Trichosporon* species) occasionally produce fungemia in lymphopenic patients that may initially be mistakenly assumed to be *Candida*. Therefore, initial treatment with a lipid amphotericin B formulation may be judicious in profoundly lymphopenic patients (ie, $CD4^+ < 250/mm^3$ [250×10^6/L]) with yeast in blood cultures until fungal identification is confirmed, as echinocandins have poor activity against non-*Candida* yeast.

LO 2

Echinocandins (ie, caspofungin, micafungin, or anidulafungin); voriconazole; or lipid amphotericin B formulation are often administered as empiric treatment for *Candida* spp. in patients with prolonged neutropenia (ie, absolute neutrophil count < 500 PMN/mm^3 [500×10^6/L] for > 7 days) with fever.[21] (See Table 84–4.) Fluconazole may be an acceptable option in patients expected to have short duration of neutropenia (< 2 weeks) not receiving systemic antifungal prophylaxis with a triazole. Lipid amphotericin B formulations, an echinocandin, or voriconazole are preferred if the patient has or is expected to have prolonged neutropenia (ie, > 2 weeks) because of the increased risk for mold infections. If patients are receiving fluconazole prophylaxis, breakthrough infections with *C. glabrata*, and less frequently *C. krusei*, are possible and should be initially treatable with an echinocandin or amphotericin B.

Urinary candidiasis is a term for group of syndromes that can range from benign colonization (candiduria) in the bladder to invasive disease of the renal parenchyma. Isolation of *Candida* in the urine from nonneutropenic patients does not require antifungal therapy, as transient clearance of *Candida* from the urine has no demonstrable clinical benefit.[21] Patients should receive 7 to 14 days of antifungal therapy for urinary candidiasis if they are (a) symptomatic, (b) have clinical or laboratory evidence of infection, (c) are neutropenic, (d) are low-birth-weight infants; (e) will undergo urologic manipulations, or (f) have renal allografts. Removal of urinary tract instruments, including Foley catheters and stents, is essential to prevent relapse. The preferred therapy is fluconazole 200 mg daily, although IV amphotericin B deoxycholate 0.3 to 1 mg/kg/day is

Patient Encounter 2, Part 2: Invasive Candidiasis

The patient was started on fluconazole 400 mg/d, but 4 days later has persistent fever and develops hypotension and decreased urine output. Blood cultures are now growing a germ tube–negative yeast. Laboratory studies revealed a white blood cell count of 14,200/mm^3 (14.2 × 10^9/L), aspartate aminotransferase 68 IU/L (1.13 µkat/L), alanine aminotransferase 75 IU/L (1.25 µkat/L), alkaline phosphatase 168 IU/L (2.80 µkat/L), and normal bilirubin. Serum creatinine has increased from 1.2 to 1.8 mg/dL (106–159 µmol/L) over the last 3 days.

What factors suggest empiric antifungal therapy should be changed in this patient?

What other procedures should be recommended in this patient to improve management and response to antifungal therapy?

also effective. Other antifungal agents (except for flucytosine) do not achieve appreciable concentrations in the urine and therefore should not be considered first-line treatments for urinary candidiasis.[29] Irrigation with amphotericin B is not effective for infections above the bladder and should not be used in higher-risk patients except for its use as a diagnostic tool for confirming a localized infection of the bladder. *Candida* infections of the renal parenchyma secondary to metastatic seeding from the bloodstream are treated in a similar fashion to candidemia.

Oral candidiasis (thrush) is not an invasive disease and can be treated with topical azoles (clotrimazole troches), oral fluconazole, or oral polyenes (such as nystatin or oral amphotericin B). Orally administered and absorbed azoles (fluconazole, voriconazole, or itraconazole solution), amphotericin B suspension, IV echinocandins, or IV amphotericin B are recommended for refractory or recurrent infections.

Although more severe than mucocutaneous candidiasis, esophageal candidiasis typically does not evolve into a life-threatening infection unless the esophagus is ruptured. However, topical therapy is ineffective. Triazole antifungals (fluconazole, itraconazole solution, or voriconazole), echinocandins, or IV amphotericin B (in cases of unresponsive infections because of antifungal resistance, most commonly to fluconzole) are effective treatment options. Parenteral therapy should be used in patients who are unable to take oral medications.

OUTCOME EVALUATION

The outcome of invasive candidiasis is influenced by the timely administration of appropriately dosed antifungal therapy appropriate for the *Candida* species isolated, as well as early source control (eg, removal of infected catheters) which reduces the risk of progression to sepsis. To ensure appropriate and cost-effective use of diagnostics and treatments for invasive candidiasis, some institutions have devised "*Candida* treatment bundles" to ensure logical evidence-based interventions in the management of invasive candidiasis and support antifungal stewardship. Examples of elements of treatment bundles for invasive candidiasis are highlighted at the end of the chapter (see Patient Care Process section).

PROPHYLAXIS

Prophylaxis for invasive candida infections has been evaluated in high-risk populations such as those with neutropenia, hematopoietic stem cell transplant, or non-neutropenic patients requiring hospitalization in an intensive care unit. Fluconazole (400 mg/day) has been studied as a prophylactic regimen to prevent invasive candidiasis in patients with prolonged (> 2 weeks) neutropenia.[21] Placebo-controlled, prospective randomized trials performed in the 1990s demonstrated that fluconazole was effective in reducing the frequency, morbidity, and, in some trials, mortality due to invasive candidiasis in neutropenic patients if administered until marrow recovery. However, the major limitation with fluconazole is its lack of mold coverage needed for high-risk patients with prolonged (ie, > 3 weeks) neutropenia. Itraconazole, voriconazole, posaconazole, and the echinocandin micafungin have demonstrated a benefit in reducing the incidence of invasive candidiasis when used for prophylaxis in hematopoietic cell transplant recipients until engraftment; however, all of the drugs have limitations with respect to prolonged administration in high-risk patients. Therefore, the approach toward antifungal prophylaxis is often institution-specific depending on the patient population, epidemiology of invasive fungal infections, and options for outpatient IV drug therapy.

LO 4

Use of antifungal prophylaxis for invasive candidiasis in non-neutropenic patients remains an area of controversy. Fluconazole prophylaxis has been shown to reduce the incidence but not necessarily mortality associated with invasive candidiasis in select high-risk transplant populations (eg, liver, pancreatic, or small-bowel transplantation) or subsets of ICU patients at high risk for infection (ie, neonatal intensive care).[21] Because prophylaxis can result in excessive antifungal use in lower-risk patients, many experts have advocated **preemptive** (ie, starting therapy based on biomarkers of infection such as serum β-glucan) or empirical (symptoms of infection) treatment approaches in this population instead of routine prophylaxis.

LO 2

A multiinstitutional prospective randomized trial of administering empirical fluconazole (800 mg/day versus placebo) in ICU patients with persistent fever failed to demonstrate significant benefits in reducing the incidence or mortality associated with invasive candidiasis.[30] Similarly, a recent multiinstitutional studies that focused on ICU patients identified as "high risk" for invasive candidiasis that administered either caspofungin[31] or micafungin[32] failed to demonstrate any mortality benefit. Therefore, many questions persist regarding the optimal approach for preventing or preemptive treating invasive candidiasis in non-neutropenic ICU patients.

CRYPTOCOCCOSIS

EPIDEMIOLOGY

Cryptococcus neoformans is an encapsulated yeast that can infect normal hosts but has historically been associated with severe infections in immunocompromised patients. *C. neoformans* is divided into two varieties based on serotype: *C. neoformans* var. *neoformans* (serotypes a and d) that is associated with infections in immunocompromised patients, and *C. neoformans* var. *gattii* (serotypes b and c) that is associated with infections in healthy hosts. *C. neoformans* var. *gattii* is found predominantly in tropical and subtropical climates with eucalyptus trees, and has been linked to infectious outbreaks around Vancouver Island and the US Pacific Northwest. *C. neoformans* var. *neoformans* is found

worldwide and is associated with pigeon droppings and other avian excreta. Before the AIDS pandemic, cryptococcosis was a relatively uncommon disease, but became a leading cause of meningitis among HIV-infected patients. Although the incidence of cryptococcal meningitis has declined in developed countries with the widespread use of highly active antiretroviral therapy (HAART), *C. neoformans* remains an important pathogen in the developing regions with high rates of AIDS and in immunocompromised patients, including transplant and cancer patients, who may present with initially indolent pulmonary forms of the infection.

LO 1

CLINICAL PRESENTATION AND DIAGNOSIS

C. neoformans is acquired primarily through inhalation of the desiccated yeast particles found in the environment. Inhaled cells reach distal alveolar spaces where they gradually rehydrate and form a polysaccharide capsule that is resistant to phagocytosis. Defects in cellular immunity allow reconstitution of the protective capsule and multiplication of yeast in the lungs. Although alveolar macrophages phagocytose the yeast, containment and killing require a coordinated response between innate and adaptive humoral (complement and anti-cryptococcal antibodies) and T-cell–mediated host responses.[6] Deficiencies in host cell-mediated immunity allow the yeast to survive as a **facultative** intracellular pathogen in macrophages as they migrate from the lung to draining lymph nodes, leading to dissemination via the bloodstream to the meninges.

Unlike most opportunistic fungi, true virulence factors have been identified for *C. neoformans*. The capsules, including the soluble polysaccharides released from the yeast cells during infection, impair phagocytosis and binding of anti-cryptococcal antibodies. Primary cryptococcal infection begins in the lung, presenting as a mildly symptomatic or asymptomatic infection that resolves spontaneously or undergoes encapsulation in noncalcified lung nodules. These isolated nodules may be detected on chest x-rays during routine workup and aspirated or removed because of concerns for lung cancer.

In the immunocompromised host, infection of the lung may present with more diffuse, bilateral, and interstitial disease that mimics the presentation of *P. jiroveci (carinii)* pneumonia (PCP). Dissemination to other organs, particularly the CNS, eye, and possibly the skin, is more likely to occur in patients with severe deficits in cell-mediated immunity. Fever, cough, dyspnea, and pleural pain are common at presentation, with accompanying hypoxemia that can rapidly evolve to acute respiratory failure. Because the features of diffuse pulmonary cryptococcosis overlap with other opportunistic pathogens, early diagnosis requires bronchoalveolar lavage or transbronchial biopsy, which can effectively diagnose 80% to 100% of cases.[33] The clinical course of diffuse cryptococcal pneumonia can be as severe as PCP, with mortality rates approaching 100% in untreated patients by 48 hours.

C. neoformans readily disseminates from the lung to the CNS, specifically the leptomeninges, and occasionally the parenchyma of the brain. The clinical characteristics of cryptococcal meningitis differ somewhat, however, between patients with and without underlying AIDS. In patients without AIDS, disease presentation is more insidious, and symptoms such as dizziness, irritability, decreased comprehension, and unstable gait may present many weeks to months before the diagnosis is established. Patients with AIDS generally present much later in the course of disease with severe meningoencephalitis.[33] The most common signs and symptoms on presentation are fever, headache, **meningismus**, photophobia, mental status changes, and seizures. CT or more tissue-sensitive imaging techniques such as magnetic resonance imaging (MRI) may reveal cerebral edema, multiple areas of enhanced nodules, or a single mass lesion (cryptococcoma). Examination of the cerebrospinal fluid (CSF) often reveals increased opening pressure upon lumbar puncture, but glucose, protein, and leukocyte levels can be normal.[33]

LABORATORY DIAGNOSIS

Clinical diagnosis is confirmed by cultures from the blood, CSF, or other clinically relevant fluids or tissue. *C. neoformans* can be directly visualized in the CSF when stained with India Ink, which is excluded by the yeast capsule (**Figure 84–3B**). However, infection is most frequently diagnosed by detection of cryptococcal antigen in either serum or CSF, which has high sensitivity and specificity (> 95%) and correlates with fungal burden.[33] A positive serum antigen test of greater than 1:4 strongly suggests cryptococcal infection, and greater than or equal to 1:8 is indicative of active disease. Antigen titers in serum are positive in 99% of patients with cryptococcal meningitis and often exceed 1:2048 in patients with AIDS.[33] However, the time course of cryptococcal antigen elimination is unknown, and a positive test result can persist for many years. Changes in the CSF cryptococcal antigen titers have limited value in the monitoring of drug therapy for cryptococcal meningitis, although it is expected that a decrease should be seen after 2 or more weeks of antifungal therapy.[33]

TREATMENT

Cryptococcal meningitis is fatal if left untreated. Because pneumonia frequently precedes dissemination of disease and subsequent meningitis, all patients with culture-, histopathology-, or serology-proven disease should receive antifungal therapy. In patients with isolated pulmonary cryptococcosis, fluconazole is generally considered to be the therapy of choice (see Table 84–2).[33] Alternatively, itraconazole, voriconazole, or combination therapy (fluconazole plus flucytosine) has also been used with some success, but these regimens are generally considered inferior to amphotericin B and are recommended only for persons unable to tolerate or unresponsive to standard treatment. Echinocandins do not have activity against *C. neoformans*.

Disseminated or CNS cryptococcosis requires a more aggressive treatment approach. Pretreatment predictors of a poor prognosis include:

- Progressive underlying disease or immune dysfunction
- Abnormal mental status at the time of presentation
- Increased opening pressure on lumbar puncture (> 260 mm H_2O [2.55 kPa])
- High fungal burden as reflected by a CSF antigen titer (in AIDS patients) of greater than 1:2048

LO 2

Clinical trials performed by the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group defined the standard treatment regimen for cryptococcal meningitis consisting of 2 weeks of induction antifungal therapy with combination amphotericin B (0.7 mg/kg/day) plus flucytosine (100 mg/kg/day) for cryptococcal meningitis, followed by consolidation therapy with fluconazole (400 mg daily) for 8 weeks (see Table 84–2).[33] However, other combinations of either fluconazole plus flucytosine, or fluconazole plus amphotericin B were sometimes recommended due to difficulties in obtaining flucytosine (especially in developing countries) and toxicity (see Table 84–2).

KEY CONCEPT In a landmark study addressing which combination is best for cryptococcal meningitis, significantly fewer deaths were

observed in patients receiving amphotericin B plus flucytosine compared to patients receiving amphotericin B alone, or a combination of amphotericin B plus fluconazole.[34] Notably, the amphotericin B–flucytosine combination was associated with more rapid clearance of yeast from the CSF versus other regimens.

PROPHYLAXIS

LO 4

Fluconazole (200 mg/day) is recommended as maintenance therapy for life in patients with persistent underlying immune dysfunction to prevent recurrent cryptococcal meningitis.[33] Available data suggest it is safe to discontinue maintenance therapy in AIDS patients who have had a sustained immunologic response on effective antiretroviral therapy (ie, $CD4^+$ count greater than 100 cells/microliter [100×10^6/L] with undetectable or very low viral RNA) if they have received at least 12 months of antifungal therapy.[33] Occasionally, initiation of HAART can result in the reactivation of a subclinical, immunologic manifestation of cryptococcal infection (or other opportunistic infections). Manifestations of this **immune reconstitution inflammatory syndrome (IRIS)** may include exacerbations of meningitis or necrotizing pneumonia. Antifungal therapy plus a nonsteroidal anti-inflammatory agent or prednisone has been used successfully in patients with cryptococcal-associated IRIS.[35] However, there are few studies that have evaluated treatment options for control of IRIS.

INVASIVE ASPERGILLOSIS

EPIDEMIOLOGY

KEY CONCEPT Invasive molds, most frequently due to *Aspergillus* species but occasionally caused by *Fusarium* spp, or Mucorales may cause infection in patients undergoing intensive cancer chemotherapy required for hematologic malignancies, and prolonged immunosuppression following hematopoietic and solid organ transplantation.[36] The four most common *Aspergillus* species that cause invasive infection in humans are: *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*. Of these four species, *A. fumigatus* accounts for most infections. However, identification of *Aspergillus* mold in culture to the species level when cultures are available is still important because *Aspergillus terreus* and *Aspergillus flavus* display relatively higher MICs (resistance) to amphotericin B. Additionally, less common mold infections such as fusariosis and mucormycosis often present with similar clinical and radiographic features as aspergillosis, but require different treatment approaches due to their inherent resistance to many antifungal agents. Early and accurate diagnosis of IA improves the outcome of infection, reducing mortality rates by 30% to 50% with the timely administration of effective antifungal therapy.[36]

CLINICAL PRESENTATION AND DIAGNOSIS

The pathogenesis of IA is defined largely by the underlying immune dysfunction of the host. The most common route of acquisition for *Aspergillus* is through the respiratory tract. Conidia dispersed in air currents are continuously inhaled through the sinuses and mouth and penetrate down to distal alveolar spaces (see **Figure 84–4**). Most conidia are rapidly phagocytosed and removed by resident macrophages and neutrophils in the upper and lower respiratory tract.[6] However, macrophage function may be suppressed following transplantation, cytotoxic chemotherapy, or in patients who have received high-dose corticosteroid therapy. Conidia that escape phagocytosis begin to germinate into hyphal forms that invade blood vessels or contiguous tissues or bone (in sinuses), resulting in hemorrhage and/or infarction and coagulative

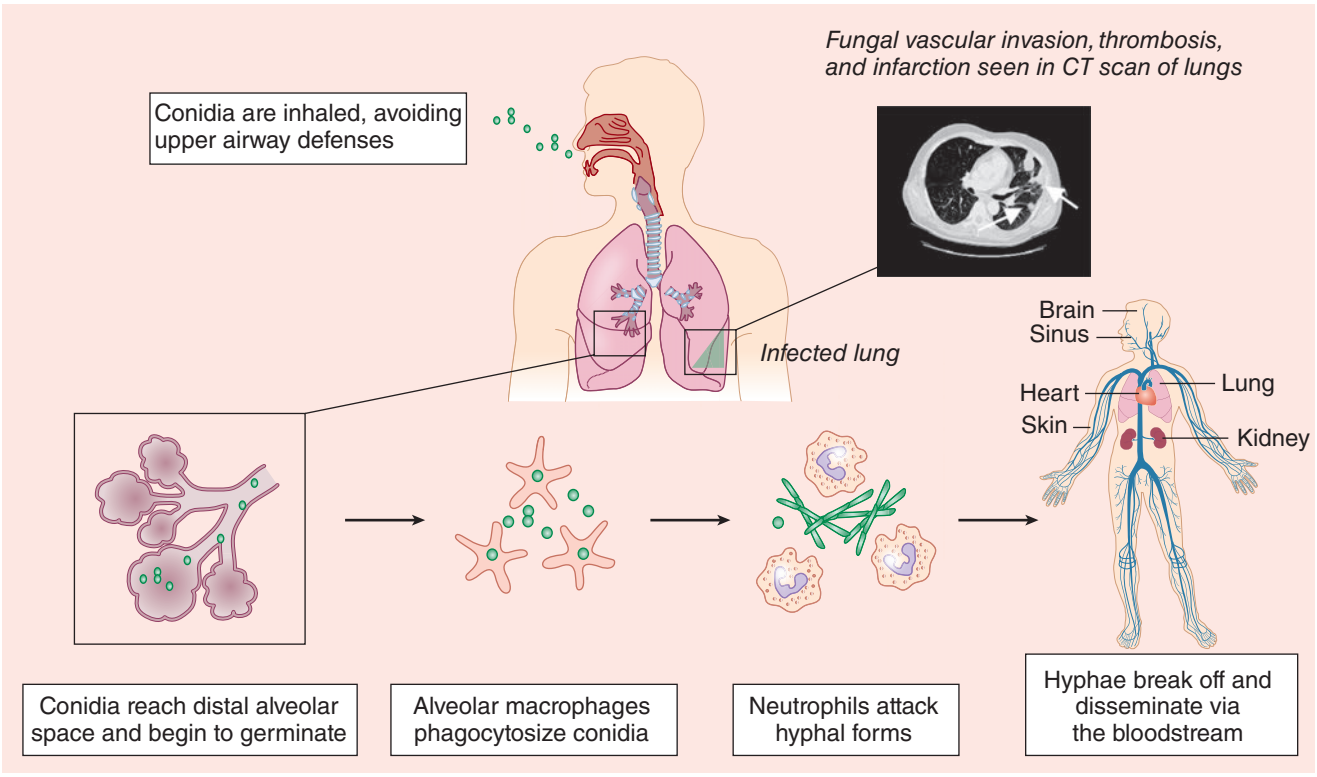

FIGURE 84–4. Pathogenesis of invasive aspergillosis (IA).

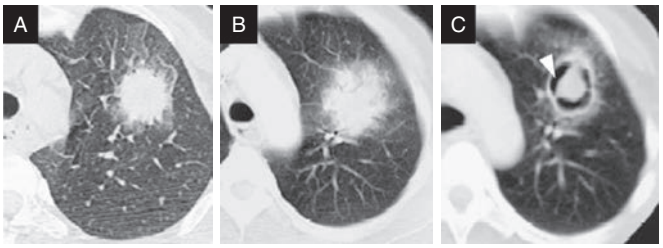

FIGURE 84–5. Radiographic evolution of invasive pulmonary aspergillosis in a neutropenic patient. **(A)** Early halo sign of ground glass opacity surrounding nodular lesions. **(B)** Nonspecific infiltrate of increased diameter. **(C)** Air crescent sign observed with neutrophil recovery, cavitation of infected lung in walled off cavity with air (*arrowhead*).

necrosis. Once in the bloodstream, viable hyphal fragments can break off and disseminate to distal organs including the brain. Control of the infection at this stage requires development of an adaptive T-helper cell type 1 (TH1) or type 17 (TH17) response to enhance the fungicidal activity of neutrophils against hyphal elements.[6] Patients with dysregulated, suppressed T-cell–mediated immunity, or prolonged neutropenia are unable to control fungal growth and are at high risk for dissemination of the infection to other organs including the brain. Without early diagnosis and antifungal therapy, IA in persistently immunosuppressed patients is uniformly fatal.

Signs and symptoms of IA are often subtle in the immunocompromised host. Fever is common but nonspecific for infection and may be accompanied by pleuritic chest pain, cough, hemoptysis, and/or friction rub.[36] Neurologic signs, including seizures, hemiparesis, and stupor, may be present in patients with dissemination to the brain. Cutaneous plaques or papules characterized by a central necrotic ulcer or eschar occur in up to 10% of patients with disseminated disease; however, concomitant blood cultures are often negative. Chest radiographs cannot detect early forms of disease and may remain negative in up to 10% of patients within 1 week of death. Nodular lesions detected by high-resolution computed tomography (HRCT), along with fever, are often the first indication of invasive pulmonary aspergillosis in severely immunocompromised patients. CT images of the lung often reveal wedge-shaped or nodular lesions, surrounded by intermediate attenuation called the "halo sign" (Figure 84–5). These early lesions on CT scans represent hemorrhage and edema surrounding an infarcted blood vessel. Despite "effective" antifungal therapy, lesions on CT scan may continue to increase in size in neutropenic patients until neutrophil counts recover, at which time they begin to cavitate, forming the "air-crescent sign" on chest radiographs, indicative of resolving infection. Immunocompromised patients on fluconazole with progressive sinus or pulmonary disease by radiography should be considered to have a possible mold infection and receive antifungal therapy directed (at minimum) against *Aspergillus* species.

LABORATORY DIAGNOSIS

Like other invasive mycoses, definitive diagnosis of aspergillosis requires histopathologic evidence of hyphal invasion in tissue (see Figure 84–3C and D). However, procedures needed to establish a definitive diagnosis by sampling of suspicious lesions (eg, fine-needle aspiration or open-lung thoracoscopic biopsy) are not feasible in many patients with underlying thrombocytopenia secondary to hematologic malignancies or chemotherapy. Even if **hyphae** are observed in tissue, histopathology alone cannot distinguish *Aspergillus* from other angioinvasive septate molds, such as *Fusarium*, which have different patterns of antifungal susceptibility (see Table 84–1). Therefore, respiratory and/or wound cultures (if cutaneous or sinus/hard palate lesions are present) are important factors in the modification of empiric antifungal therapy.

Respiratory cultures, including sputum, bronchial washings, or bronchoalveolar lavage, have a low sensitivity for diagnosis of IA but a higher positive predictive value in severely immunocompromised patients. Therefore, a negative bronchoalveolar lavage culture does not rule out invasive pulmonary aspergillosis, but a positive culture in a high-risk patient (eg, allogeneic hematopoietic cell transplant patients) indicates pulmonary aspergillosis in at least 60% to 80% of such patients. Blood cultures have little diagnostic value for IA, but may reflect true disease with *A. terreus.* Patients with limited lung involvement or on prophylactic or empiric antifungal therapy may continue to be culture-negative for *Aspergillus* species, despite the appearance of progressing disease. Therefore, negative cultures are never the sole indication for stopping antifungal therapy in patients with suspected or proven aspergillosis.

In the past, antifungal susceptibility testing was not routinely recommended for *Aspergillus* spp. in treatment guidelines because of limited data to support the recommendation. *Aspergillus terreus* and *A. flavus* were the major concerns because of their intrinsic resistance to amphotericin B. However, more recently multi-triazole-resistant *Aspergillus fumigatus* spp. have been reported in China, Canada, the United States, and several European countries, with especially high levels in the Netherlands and

Patient Encounter 3: Invasive Aspergillosis

A 52-year-old man with acute myeloid leukemia who received a matched-allogeneic donor hematopoietic stem-cell transplantation presents to the clinic 70 days after transplant with complaints of fever. On laboratory examination, he is noted to have an alanine aminotransferase of 119 IU/L (1.98 µkat/L), aspartate aminotransferase 107 IU/L (1.78 µkat/L), and total bilirubin of 1.8 mg/dL (31 µmol/L). The patient has an absolute neutrophil count of 970 (970×10^6/L). His current medications include tacrolimus 5 mg twice daily (most recent level: 9 ng/mL [9 mcg/L; 11 nmol/L]), prednisone 10 mg daily, levofloxacin 500 mg daily, fluconazole 200 mg/d, valacyclovir 500 mg twice daily. A CT scan of the chest reveals a single dense pleural-based lung nodule in the left lung. A serum galactomannan test is reported to be negative (index 0.4, positive when > 0.5). The primary service wishes to start voriconazole.

What are the patient's risk factors and signs that suggest he has an invasive fungal infection?

What problems need to be anticipated in this patient if voriconazole is started?

If the patient's infection appears to resolve and he continues to take voriconazole for months while tapering immunosuppression, what are some of the toxicities potentially associated with prolonged voriconazole therapy?

United Kingdom.[37] These trends suggest that MIC testing (when isolates can be grown from patient) may be increasingly necessary to confirm susceptibility to first-line antifungal treatments.

Considerable effort has been focused in the last decade to develop non–culture-based laboratory methods (antigen detection, polymerase chain reaction [PCR]) for the diagnosis of IA. The hope is that these surrogate tests could detect early evidence of *Aspergillus* infection before significant target organ damage eventually detected by CT scans occurs. Currently, most centers use an ELISA-based assay for the detection of a polysaccharide component of the *Aspergillus* cell wall called galactomannan. Although several large prospective studies have found that the sensitivity and specificity of the assay approaches 90% in neutropenic patients with hematologic malignancies, the median time span between galactomannan detection and clinical signs and symptoms of IA averages less than 6 days. The sensitivity of the galactomannan may be enhanced if the test is performed on bronchial lavage fluid collected during bronchoscopy. Other factors such as patient immune status (higher sensitivity in neutropenic vs. non-neutropenic patients) antibacterial therapy, antifungal prophylaxis, and diet may affect the sensitivity and specificity of the galactomannan test.[36] For example, false-positive results are reported more frequently in pediatrics, following the ingestion of certain cereals, pastas, nutritional supplements, or soy sauce. Piperacillin-tazobactam therapy was also associated with false-positive galactomannan tests in the past, but more recent studies have suggested that galactomannan-contamination of the antibiotic is now uncommon.[38]

Increasing galactomannan levels are a harbinger of breakthrough infection, and declining galactomannan concentrations are an early indicator of response to treatment. However, antifungal therapy is rarely stopped in patients once the serum galactomannan becomes negative, especially in persistently immunosuppressed patients. Hence, the galactomannan test and other non–culture-based strategies, such as serum β-glucan, which can also be detected during *Aspergillus* infection, serve as complementary methods to confirm results from microbiologic, histopathologic, and radiographic investigations directed toward diagnosing IA.[39]

TREATMENT

LO 2

Four comparative randomized controlled clinical trials have evaluated antifungal therapies for the treatment of diagnosis-proven IA. Voriconazole or isavuconazole are considered in consensus treatment guidelines to be the first-line antifungal for IA (see Table 84–2).[35] However, patients who are intolerant to triazoles, have ongoing hepatotoxicity issues, or have received voriconazole or posaconazole prophylaxis in the recent past may initially be treated with a liposomal amphotericin B formulation. Lipid amphotericin B formulations are recommended over echinocandins because of their better coverage of Mucorales molds which sometimes breakthrough on *Aspergillus*-active therapy because of their intrinsically higher resistance to voriconazole and other antifungals. Echinocandins are not typically recommended as a frontline monotherapy regimen for invasive aspergillosis due to poorer responses rates in nonrandomized trials compared to triazoles.[40] Once the infection has stabilized and diagnosis is clarified, patients can be transitioned back to an intravenous or oral triazole for the completion of therapy.

Isavuconazole is a newer triazole unique from other agents because it is administered as a prodrug, isavuconazonium, which is rapidly cleaved in vivo to the active drug (isavuconazole) and an inactive prodrug cleavage product (BAL8728). In a phase 3 trial, patients with proven or probable aspergillosis treated with isavuconazole achieved similar clinical response rates as a standard voriconazole regimen, but with significantly fewer hepatic, skin, and visual adverse effects.[9] Isavuconazole has also been reported to be as effective and amphotericin B–based treatment for mucormycosis. Therefore, isavuconazole appears to be a promising alternative to voriconazole for the treatment of IA.

Multiple studies in vitro and in animal models, as well as small clinical studies have suggested that administration of an echinocandin with a triazole such as voriconazole may be synergistic and improve survival in IA over monotherapy, but prospective clinical studies, until recently, have been lacking. A multicenter, randomized clinical trial comparing voriconazole-anidulafungin combination therapy to voriconazole monotherapy for proven or probable aspergillosis reported a trend in improved 6-week survival for patients randomized to combination therapy, that was significant among a post-hoc analyzed group of patients whose disease was diagnosed with galactomannan antigen but not culture (reflecting patients with earlier-diagnosed disease).[38] Nevertheless, the failure of the study to meet its primary endpoint objective raises lingering questions about the efficacy of combination therapy, and many clinicians reserve the use of combination regimens for patients with extensive disease (ie, multifocal or bilateral pneumonia, disseminated infection) or in cases of suspected breakthrough infection.

PROPHYLAXIS

LO 4

Primary antifungal prophylaxis against *Aspergillus* is recommended in guidelines for some groups of patients with baseline risk of IA that approaches or exceeds 10%. These subgroups typically include patients with acute myeloid leukemia undergoing remission induction chemotherapy, or allogeneic hematopoietic stem cell transplants with graft versus host disease. Depending on the institution and local epidemiology, other groups of patients may also be considered candidates for prophylaxis. KEY CONCEPT Posaconazole was shown in two prospective randomized trials to reduce Aspergillus-associated death in patients with acute high-risk leukemia and reduce mold infections in patients with graft-versus-host disease following hematopoietic stem cell transplantation. Similar data are available for voriconazole, for HSCT, but no significant advantage was observed compared to standard fluconazole prophylaxis plus intensive galactomannan monitoring in the hematopoietic stem cell transplant patients.[41]

OUTCOME EVALUATION

LO 3

Response to antifungal therapy in invasive molds is slow and difficult to judge by clinical signs alone. Resolution of fever and eventual clearing of CT scans (in the case of lung infections) are indications of response to antifungal therapy. Toxicity associated with antifungal therapy is similar in these patients as in those described earlier. Patients who develop breakthrough infections on voriconazole should also undergo a careful clinical workup for other invasive mold pathogens such as mucormycosis (see Table 84–1), which are not susceptible to voriconazole. In most cases, antifungal therapy may be continued until immunosuppression has resolved.

Patient Care Process

Collect Information:

- Review the medical history, physical assessment findings, and recent laboratory results of the patient to assess current immunological status and organ function.
- Perform a medication history for use of prescription and nonprescription medications. Identify allergies to medications and other substances.

Assess the Information:

- Analyze patient's medication profile for potential drug interactions with triazole antifungals using an updated computerized drug interaction database.
- Confirm prescribed antifungal therapy is the appropriate spectrum for likely fungal pathogen(s).
- Review whether modifiable risk factors affecting treatment outcome (eg, timely administration of antifungal therapy, catheter removal in patients with invasive candidiasis) have been addressed.
- Ensure prescribed antifungal dose is appropriate for patient age, weight, renal, and/or hepatic function.

Develop a Care Plan:

- Confirm prescribed antifungal therapy is the appropriate spectrum for likely fungal pathogen(s).
- Ensure prescribed antifungal dose is appropriate for patient age, weight, renal, and/or hepatic function.
- Prepare a strategy for therapeutic drug monitoring (TDM) for antifungals with unpredictable pharmacokinetics (eg, itraconazole, voriconazole, and posaconazole suspension).
- Anticipate how antifungal therapy can be modified when culture results become available, intolerance to the drug of first choice, or if there is consideration of switching from IV to oral therapy.

Implement the Care Plan:

- Educate the patient about potential for medication adverse effects, importance of taking medications correctly, and potential for drug interactions.
- Review TDM results, microbiology and susceptibility information if available, and treatment response parameters to ensure patient is on correct antifungal at the best dose.
- Streamline antifungal therapy if possible and/or switch to oral therapy if patient is clinically stable.

Follow-up: Monitor and Evaluate:

- Monitor patient clinical, laboratory, and radiographic parameters to assess effectiveness and safety of therapy.
- Reevaluate potential for serious drug interactions.
- Consider TDM if patient has changes to medication profile, change in clinical status, or new-onset toxicity.

Abbreviations Introduced in This Chapter

AIDS	Acquired immunodeficiency syndrome
ARDS	Acute respiratory distress syndrome
CNS	Central nervous system
CrCl	Estimated creatinine clearance
CSF	Cerebrospinal fluid
CT	Computed tomography
CYP	Cytochrome P-450 isoenzyme
ELISA	Enzyme-linked immunosorbent assay
FISH	Fluorescent in situ hybridization
HAART	Highly active antiretroviral therapy
HRCT	High-resolution computed tomography
IA	Invasive aspergillosis
ICU	Intensive care unit
IRIS	Immune reconstitution inflammatory syndrome
IV	Intravenous
MALDI-TOF	Matrix-assisted laser desorption/ionization time of flight
MIC	Minimum inhibitory concentration
NIAID	National Institute of Allergy and Infectious Diseases
PCP	*Pneumocystis jiroveci (carinii)* pneumonia
PCR	Polymerase chain reaction
PMN	Polymorphonuclear cell
TDM	Therapeutic drug monitoring

REFERENCES

1. Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med. 2012;4:165rv13.
2. Kainer MA, Reagan DR, Nguyen DB, et al.; Tennessee Fungal Meningitis Investigation T. Fungal infections associated with contaminated methylprednisolone in Tennessee. N Engl J Med. 2012;367:2194–2203.
3. Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, Mckinsey DS, Loyd JE, Kauffman CA; Infectious Diseases Society of A. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45:807–825.
4. Chapman SW, Dismukes WE, Proia LA, et al; Infectious Diseases Society of America. Clinical practice guidelines for the management of blastomycosis: 2008 update by the infectious diseases society of america. Clin Infect Dis. 2008;46: 1801–1812.
5. Galgiani JN, Ampel NM, Blair JE, et al. Executive summary: 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. Clin Infect Dis. 2016;63:717–722.
6. Romani L. Immunity to fungal infections. Nat Rev Immunol. 2011;11:275–288.
7. Chapman SW, Bradsher RW, Campbell GD, Pappas PG, Kauffman CA. Practice guidelines for the management of patients with blastomycosis. Clin Infect Dis. 2000;30:679–683.

8. Duarte RF, Lopez-Jimnez J, Cornely OA, et al. Phase 1b study of new posaconazole tablet for the prevention of invasive fungal infections in high-risk patients with neutropenia. Antimicrob Agents Chemother. 2014;58:5758–5765.
9. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by aspergillus and other filamentous fungi (secure): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387:760–769.
10. Brüggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis. 2009;48:1441–1458.
11. Stott KE, Hope WW. Therapeutic drug monitoring for invasive mould infections and disease: pharmacokinetic and pharmacodynamic considerations. J Antimicrob Chemother. 2017;72:i12–i18.
12. Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis. 2012;55:381–390.
13. Epaulard O, Villier C, Ravaud P, et al. A multistep voriconazole-related phototoxic pathway may lead to skin carcinoma: results from a french nationwide study. Clin Infect Dis. 2013;57:e182–e188.
14. Wermers RA, Cooper K, Razonable RR, et al. Fluoride excess and periostitis in transplant patients receiving long-term voriconazole therapy. Clin Infect Dis. 2011;52:604–611.
15. Malani AN, Kerr L, Obear J, Singal B, Kauffman CA. Alopecia and nail changes associated with voriconazole therapy. Clin Infect Dis. 2014;59(3):e61–e65.
16. Baxter CG, Marshall A, Roberts M, Felton TW, Denning DW. Peripheral neuropathy in patients on long-term triazole antifungal therapy. J Antimicrob Chemother. 2011;66:2136–2139.
17. Saliba F, Dupont B. Renal impairment and amphotericin b formulations in patients with invasive fungal infections. Med Mycol. 2008;46:97–112.
18. Kullberg BJ, Arendrup MC. Invasive candidiasis. N Engl J Med. 2015;373:1445–1456.
19. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. Clin Microbiol Rev. 2007;20:133–163.
20. Clancy CJ, Nguyen MH. Finding the missing 50% of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis. 2013;56:1284–1292.
21. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of america. Clin Infect Dis. 2016;62:e1–e50.
22. Mylonakis E, Clancy CJ, Ostrosky-Zeichner L, et al. T2 magnetic resonance assay for the rapid diagnosis of candidemia in whole blood: A clinical trial. Clin Infect Dis. 2015;60:892–899.
23. Pfaller MA, Diekema DJ. The epidemiology of invasive candidiasis. Candida and Candidiasis, Second Edition. 2012.
24. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous emergence of multidrug-resistant candida auris on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis. 2017;64:134–140.
25. Alexander BD, Johnson MD, Pfeiffer CD, et al. Increasing echinocandin resistance in candida glabrata: clinical failure correlates with presence of FKS mutations and elevated minimum inhibitory concentrations. Clin Infect Dis. 2013;56:1724–1732.
26. Beyda ND, John J, Kilic A, et al. FKS mutant candida glabrata; risk factors and outcomes in patients with candidemia. Clin Infect Dis. 2014;59(6):819–825.
27. Andes DR, Safdar N, Baddley JW, et al.; Mycoses Study G. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis. 2012;54:1110–1122.
28. Vazquez J, Reboli AC, Pappas PG, et al. Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial. BMC Infect Dis. 2014;14:97.
29. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev. 2014;27:68–88.
30. Schuster MG, Edwards JE, Sobel JD, Others. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. Ann Intern Med. 2008;149(2):83–90.
31. Ostrosky-Zeichner L, Shoham S, et al. Msg-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk. Clin Infect Dis. 2014;58(9):1219–1226.
32. Timsit JF, Azoulay E, Schwebel C, et al. Empirical Micafungin treatment and survival without invasive fungal infection in adults with ICU-acquired sepsis, candida colonization, and multiple organ failure: the EMPIRICUS randomized clinical trial. JAMA. 2016;316(15):1555–1564.
33. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:291–322.
34. Day JN, Chau TTH, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med. 2013;368:1291–1302.
35. Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis. 2007;7: 395–401.
36. Patterson TF, Thompson GR, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1–e60.
37. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole resistance in aspergillus fumigatus: can we retain the clinical use of mold-active antifungal azoles. Clin Infect Dis. 2016;62:362–368.
38. Demiraslan H, Atalay MA, Eren E, Demir K, Kaynar L, Koc AN, Doganay M. Assessing the risk of false positive serum galactomannan among patients receiving piperacillin/tazobactam for febrile neutropenia. Med Mycol. 2017;55(5):535–540.
39. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al.; Vital AFMI. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16:828–837.
40. Viscoli C, Herbrecht R, Akan H, et al; Infectious Disease Group of the EORTC. An EORTC phase II study of caspofungin as first-line therapy of invasive aspergillosis in haematological patients. J Antimicrob Chemother. 2009;64:1274–1281.
41. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010;116:5111–5118.

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85 Antimicrobial Prophylaxis in Surgery

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LEARNING OBJECTIVES

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

1. Describe the impact of surgical site infections (SSIs) on patient outcomes and health care costs.
2. Name and differentiate the four different types of wound classifications.
3. Recognize at least three risk factors for postoperative SSIs.
4. Identify likely pathogens associated with different surgical operations.
5. Compare and contrast antimicrobials used for surgical prophylaxis and identify potential advantages and disadvantages for each antimicrobial.
6. Discuss the importance of β-lactam allergy screening and how this could impact resistance and health care costs.
7. Identify nonantimicrobial methods that can reduce the risk of postoperative infection.
8. Discuss the importance of antimicrobial timing, duration, and redosing in relation to antimicrobial prophylaxis in surgery.
9. Recommend appropriate prophylactic antimicrobial(s) given in a surgical operation.

INTRODUCTION

KEY CONCEPT

Surgical site infections (SSIs) are a significant cause of morbidity and mortality. Data from the National Healthcare Safety Network (NHSN) showed an SSI rate of 1.9% for surgical procedures performed in the United States.[1–3] Rates may be higher than this percentage as half of SSIs are diagnosed after discharge.[1–3]

SSIs negatively affect patient outcomes and increase health care costs. Patients who develop SSIs are five times more likely to be readmitted to the hospital and have twice the mortality of patients who do not develop an SSI.[2] A patient with an SSI is also 60% more likely to be admitted to an ICU.[2] SSIs lengthen hospital stays and increase costs.[1,2,4,5] Deep SSIs, involving organs or spaces, result in longer durations of hospital stay and higher costs compared with incisional SSIs.[6] Additionally, since 2008, Medicare and Medicaid Services no longer reimburse hospitals for any cost incurred from treating certain hospital-acquired infections, including SSIs.[7]

LO 1

SSIs are defined and reported according to Centers for Disease Control and Prevention (CDC) criteria.[8] SSIs are classified as either incisional or organ/space. Incisional SSIs are further divided into superficial incisional SSI (skin or subcutaneous tissue) and deep incisional SSI (deeper soft tissues of the incision). Organ/space SSIs involve any anatomic site other than the incised areas (eg, meningitis after brain tumor removal). An infection is considered an SSI if any of the above criteria is met and the infection occurs within 30 days or 90 days depending on the site of operation and type of infection.[8]

LO 2

EPIDEMIOLOGY AND ETIOLOGY

LO 3

Risk factors for SSIs can be divided into two categories: patient and operative characteristics.[6,9,10] Patient risk factors for SSI include age, comorbid disease states (especially chronic lung disease and diabetes), malnutrition, immunosuppression, nicotine or steroid use, and colonization of the nares with *Staphylococcus aureus*. Modifying risk factors prior to planned operations may decrease the threat of SSI.

Operative characteristics are based on the actions of both the patient and the operating staff. Shaving of the surgical site prior to operating can produce microscopic lacerations and increase the chance of SSI and is, therefore, not accepted as a method of hair removal.[6] Maintaining aseptic technique and proper sterilization of medical equipment is effective in preventing SSI. Surgical staff should wash their hands thoroughly. In clean operations, most bacterial inoculums introduced postoperatively are generally small. However, subsequent patient contact between contaminated areas (such as the nares or rectum) and the surgical site can lead to SSI. Finally, the appropriate use of antimicrobial prophylaxis can have a significant impact on decreasing SSIs.

PATHOPHYSIOLOGY

Prophylaxis Versus Treatment

Antimicrobial prophylaxis begins with the premise that no infection exists but that during the operation there can be a low-level inoculum of bacteria introduced into the body. However, if sufficient antimicrobial concentrations are present, bacteria can be controlled without infection developing. This is the case when surgery is done

under controlled conditions, there are no major breaks in sterile technique or spillage of gastrointestinal (GI) contents, and perforation or damage to the surgical site is absent. An example would be an elective hysterectomy done with optimal surgical technique.

If an infection is already present, or presumed to be present, then antimicrobial use is for treatment, not prophylaxis, and the goal is to resolve the infection. This is the case when there is spillage of GI contents, gross damage or perforation is already present, or the tissue being operated on is actively infected (pus is present and cultures are positive). An example would be a patient undergoing surgery for a ruptured appendix with diffuse peritonitis.

KEY CONCEPT The distinction between prophylaxis and treatment influences the choice of antimicrobial and duration of therapy. Appropriate antimicrobial selection, dosing, and duration of therapy differ significantly between these two situations. Prophylatic antimicrobials are chosen based on the most common bacteria encountered in the area of the surgical site; treatment regimens should be narrowed based on culture data from the infected site. A regimen for antimicrobial prophylaxis ideally involves one agent and lasts less than 24 hours. Treatment regimens can involve multiple antimicrobials with durations lasting weeks to months depending on desired antimicrobial coverage and the surgical site.

Types of Surgical Operations

KEY CONCEPT Surgical operations are classified at the time of operation as clean, clean-contaminated, contaminated, or dirty. Antimicrobial prophylaxis is appropriate for clean, clean-contaminated, and contaminated operations. Dirty operations take place in situations of existing infection and antimicrobials are used for treatment, not prophylaxis (Table 85–1).

Microbiology

LO 4

KEY CONCEPT Appropriate prophylactic antimicrobial selection relies on anticipating which organisms will be encountered during the operation. SSIs associated with **extraabdominal** operations are the result of skin flora organisms in nearly all cases. These organisms include gram-positive cocci, with *S. aureus* and *Staphylococcus epidermidis* being among the most frequently isolated SSI pathogens[6,7,11] (Table 85–2). *Streptococcus* spp. may also be implicated.

Table 85–2

Major Pathogens in Surgical Wound Infections[11]

Pathogen	Percentage of Infections
Staphylococcus aureus	30.4
Coagulase-negative Staphylococci	11.7
Escherichia coli	9.4
Enterococcus faecalis	5.9
Pseudomonas aeruginosa	5.5
Streptococcus spp.	4.9
Enterobacter spp.	4
Klebsiella (pneumonia/oxytoca)	4
Enterococcus spp.	3.2
Proteus spp.	3.2
Enterococcus faecium	2.5
Serratia spp.	1.8
Candida albicans	1.3
Acinetobacter baumannii	0.6

Intraabdominal operations involve a diverse flora with the potential for polymicrobial SSIs. *Escherichia coli* make up a large portion of bowel flora and are frequently isolated as pathogens.[6,7] Other enteric gram-negative bacteria, as well as anaerobes (especially *Bacteroides* spp.), may be encountered during intra-abdominal operations.

Candida albicans continues to be an increasing cause of SSIs.[7] Increased use of broad-spectrum antimicrobials and rising prevalence of immunocompromised and human immunodeficiency virus-infected individuals are factors in fungal SSIs. Despite this increase, antifungal prophylaxis for surgery is not currently recommended.

Choosing an Antibiotic

LO 5

Ideal criteria for an antimicrobial in surgical prophylaxis include the following:

- Spectrum that covers expected pathogens
- Inexpensive

Table 85–1

National Red Cross Wound Classification, Risk of SSI, and Antimicrobial Indication

Classification	Description	SSI Risk	Antimicrobial Prophylaxis
Clean	No acute inflammation or transection of GI, oropharyngeal, GU, biliary, or respiratory tracts; elective case, no technique break	Low	Indicated
Clean-contaminated	Controlled opening of aforementioned tracts with minimal spillage or minor technique break; clean procedures performed emergently or with major technique breaks	Medium	Indicated
Contaminated	Acute, nonpurulent inflammation present; major spillage or technique break during clean-contaminated procedures	High	Indicated
Dirty	Obvious preexisting infection present (abscess, pus, or necrotic tissue present)	—	Not indicated; antimicrobials used for treatment

GI, gastrointestinal; GU, genitourinary.

Data from Refs. 9 and 13.

- Parenteral
- Easy to use
- Minimal adverse-event potential
- Longer half-life to minimize need for redosing during procedure

Operations can be separated into two basic categories: extraabdominal and intraabdominal. SSIs resulting from extraabdominal operations are frequently caused by gram-positive aerobes. Cefazolin, an antimicrobial with strong gram-positive coverage that fits the above criteria, is a mainstay for surgical prophylaxis of extraabdominal procedures. For patients with a **β-lactam allergy**, clindamycin or vancomycin can be used as an alternative.

Intraabdominal operations necessitate broad-spectrum coverage of gram-negative organisms and anaerobes. Antianaerobic cephalosporins, cefoxitin, and cefotetan are widely used. Fluoroquinolones or aminoglycosides, paired with clindamycin or metronidazole, should provide adequate coverage for intraabdominal operations; these regimens are recommended as appropriate regimens for use in patients with β-lactam allergies.

Guidelines do not recommend routine use of vancomycin for surgical procedures.[12,13] Vancomycin should be considered when a cluster of methicillin-resistant *S. aureus* (MRSA) or coagulase-negative staphylococci have been identified. Additionally, vancomycin is appropriate to use in patients with known MRSA colonization or at high risk for MRSA colonization. Vancomycin use in institutions where MRSA rates are "high" may not translate into a lower incidence of SSI. The incidence of SSI for patients on cefazolin or vancomycin did not differ despite a high MRSA rate at the study institution.[14] However, patients who received cefazolin were more likely to develop an SSI due to MRSA.[13]

Newer antimicrobials may be alternative agents for surgical prophylaxis, especially as drug shortages limit availability of routinely used antimicrobials. Ertapenem was superior to standard cefotetan in the prevention of SSIs after elective colorectal surgery.[15] However, the ertapenem treatment group had a larger proportion of *Clostridium difficile* infections than those in the cefotetan treatment group. Ertapenem has been included as an approved antimicrobial for colon surgery.[12] Routine use of newer antimicrobials for surgical prophylaxis is inappropriate; overuse of these antimicrobials may contribute to **collateral damage** and the development of bacterial resistance.

Guideline recommendations for antimicrobials are based on national trends of antimicrobial susceptibilities available at the time of publication. Local antibiogram data may be helpful in evaluating which agents recommended in the guidelines may not be as effective in a specific institution due to significant resistance. Responsibility for determining appropriate use of antimicrobial prophylaxis falls on each institution and interpretation of institutional resistance data.

β-Lactam Allergy

LO 6

Allergy to β-lactam antimicrobials such as penicillin is one of the most common reported drug allergies. Concerns over cross-reactivity between antimicrobials may limit the use of β-lactams for surgical prophylaxis. KEY CONCEPT A thorough drug allergy history should be taken to discern true allergy (eg, anaphylaxis) from medication intolerance (eg, upset stomach). Allergy testing may be helpful in confirming penicillin allergy and could spare vancomycin. Despite lack of commercial availability of minor determinants of penicillin allergy, skin testing with commercial major determinants provides greater than or equal to 95% accuracy for lack of penicillin allergy; addition of an oral challenge dose improves accuracy to near 100%.[16] Penicillin skin testing may be useful in outpatient and planned surgical procedures but may be difficult to perform in urgent/emergent surgical indications. Multiple studies have demonstrated a low incidence, ie, less than 1%, for cross-reactivity between penicillins and cephalosporins.[17–19] However, in the case of severe penicillin allergy (anaphylaxis), cephalosporins should be avoided.

Alternative Methods to Decrease SSI

LO 7

Several nonantimicrobial methods have been studied for reducing the risk of SSI.[20–34] Perioperative glucose levels of less than 200 mg/dL should be maintained in all patients, regardless of a diabetes comorbidity.[1] More intensive glucose control in the setting of surgical procedures have not been critically evaluated by randomized controlled trials. Current guidelines recommend maintenance of normotheria.[1] Studies have demonstrated a significant difference in SSI in patients who received supplemental oxygenation compared to normal controls.[19] However, despite these findings, there are insufficient data to make definitive recommendations on the use of these approaches.

Alternative topical routes of antimicrobial prophylaxis such as antimicrobial-impregnated bone cement, implantable antimicrobial collage sponges, antimicrobial irrigations, and topical administration of antimicrobial powders have not been well studied. Studies demonstrating an advantage often lack rigorous design and only show superiority when compared to placebo.[12,21,22] Irrigation with detergent solutions, rather than antimicrobials, appears to provide the same results but with less wound-healing problems encountered with antimicrobial irrigation.[25] Confounding this issue is the lack of standards for topical administration routes. An array of drugs, from aminoglycosides to macrolides, is used in these preparations. Some bone cements are produced commercially, whereas others are made in the operating room. The long-term durability of impregnated cements is also unknown, as the addition of antimicrobials may reduce the tensile strength of bone cement. Irrigation solutions may be compounded in the surgical suites and result in variable concentrations. High concentrations can result in local irritation, systemic absorption, and toxicity. Alternatively, low concentrations can contribute to the development of resistant organisms may occur. Further study is required before topical administration is recommended for use in surgical prophylaxis.

Increased importance has been placed on screening for *S. aureus*, especially MRSA and **decolonization**. Surgical patients with nasal colonization of *S. aureus* have a higher risk of an SSI due to *S. aureus*, and decolonization leads to a lower incidence of SSIs.[25–27] Guidelines endorse the use of mupirocin for *S. aureus* decolonization, especially in cardiac and orthopedic surgery. The most studied approach to eradication of methicillin-sensitive *S. aureus* (MSSA) and/or MRSA has been mupirocin applied to the anterior nares for 5 days prior to surgery.[12,30] Additionally, skin decolonization with 4% chlorhexidine for 5 days prior to surgery has also been recommended. Although decolonization of the anterior nares is the most common and most studied, some controversy exists because patients may be colonized elsewhere (rectum, throat, vagina, etc) and often do not receive complete decolonization.[30] Furthermore, decolonization usually does not lead to lifelong eradication. Other drugs, both topical and systemic, have been studied for decolonization/eradication of MRSA, but a review of randomized controlled trials for the eradication of MRSA found insufficient evidence for the use of any

agent for eradication of MRSA.[31] A significantly lower incidence of infections was demonstrated in surgical patients who were nasal colonized with *S. aureus* and completed a 5-day treatment of intranasal mupirocin twice daily and chlorhexidine wash daily. Although no MRSA infections were noted in the patients included in this study, the authors suggest that this treatment strategy would be beneficial in MRSA-colonized patients as long as those strains were susceptible to mupirocin. Although MRSA screening has gained more acceptance, less than 10% of centers screen for mupirocin and/or chlorhexidine resistance.[12,33] Mupirocin resistance rates have varied from 1.9% to 5.6% of *S. aureus* isolates.[34] Further studies are needed to elucidate this area of surgical prophylaxis, including cost-effectiveness.

Principles of Antimicrobial Prophylaxis

▶ Route of Administration

Intravenous (IV) antimicrobial administration is the most common delivery method for surgical prophylaxis. IV administration ensures complete bioavailability while minimizing the impact of patient-specific variables. Oral administration is also used in some bowel operations. Nonabsorbable compounds such as erythromycin base and neomycin are given during the 24 hours prior to surgery to reduce microbial concentrations in the bowel. Note that oral agents are used adjunctively and do not replace IV agents.

▶ Timing of First Dose

KEY CONCEPT For prevention of SSIs, correct timing of antimicrobial administration is imperative so as to allow the persistence of therapeutic concentrations in the blood and wound tissues during the entire course of the operation. The National Surgical Infection Prevention Project recommends infusing antimicrobials for surgical prophylaxis within 60 minutes of the first incision. Exceptions to this rule are fluoroquinolones and vancomycin, which can be infused 120 minutes prior to avoid infusion-related reactions.[2,12] No consensus has been reached on whether the infusion should be complete prior to the first incision.

Administration of the IV antimicrobial should begin as close to the first incision as possible. This is important for antimicrobials with short half-lives so that therapeutic concentrations are maintained during the operation and reduce the need for redosing. Beginning the antimicrobial infusion after the first incision is of little value in preventing SSI. Administration of the antimicrobial after the first incision had SSI rates similar to patients who did not receive prophylaxis.[35]

▶ Dosing and Redosing

LO 8

KEY CONCEPT The goal of antimicrobial dosing for surgical prophylaxis is to optimize the pharmacodynamic parameter of the selected agent against the suspected organism for the duration of the operation. Dosing recommendations can vary between institutions and guidelines. Clinical judgment should be exercised regarding dose modifications for renal function, age, and especially weight. Obese patients often require higher antimicrobial doses than do nonobese patients.[36] The newest guidelines available regarding specific antimicrobial dosing recommended higher doses of cefazolin based on population pharmacokinetic/pharmacodynamics data: 2 g for all patients less than 120 kg; 3 g for patients more than or equal to 120 kg.[12] Clindamycin should be given as a 900-mg preoperative IV dose.[11]

If an operation exceeds two half-lives of the selected antimicrobial, then another dose should be administered.[2,12] Repeat dosing reduces rates of SSI. For example, cefazolin has a half-life of about 2 hours, thus another dose should be given if the operation exceeds 4 hours. The clinician should have extra doses of antimicrobial ready in case an operation lasts longer than planned.

▶ Duration

KEY CONCEPT The duration of antimicrobial prophylaxis should not exceed 24 hours (48 hours for cardiac surgery); additional doses of antimicrobial past this time point do not demonstrate added benefits.[2,12] In clean and clean-contaminated procedures, antimicrobials are not needed after the surgical incision is closed.[1] Antimicrobial prophylaxis does not need to be continued until all drains and catheters have been removed.

PROPHYLAXIS REGIMENS

Antimicrobial Prophylaxis in Specific Surgical Procedures

LO 9

Table 85–3 lists the recommended regimens for antimicrobial prophylaxis of specific surgical procedures.

▶ Gynecologic and Obstetric

- Possible pathogens: enteric gram-negative bacilli, anaerobes, group B streptococci, enterococci
- Prophylaxis for hysterectomy: cefazolin, cefotetan, cefoxitin, ampicillin-sulbactam
  - Alternatives for β-lactam allergy: clindamycin or vancomycin combined with aminoglycoside, aztreonam, or fluoroquinolone; metronidazole combined with aminoglycoside or fluoroquinolone
- Prophylaxis for cesarean section: cefazolin
  - Alternatives for β-lactam allergy: clindamycin and aminoglycoside

Cesarean sections are stratified into low- and high-risk groups. Patients who undergo emergency operations or have cesarean sections after the rupture of membranes and/or onset of labor are considered high risk. Prophylactic antimicrobials are most beneficial for high-risk patients but are used in both groups. Antimicrobials should not be administered until after the first incision and the umbilical cord has been clamped. This practice prevents potentially harmful antimicrobial concentrations from reaching the newborn.

▶ Orthopedic Surgery

- Possible pathogens: gram-positive cocci, mostly staphylococci
- Prophylaxis for total joint arthroplasty (hip or knee): cefazolin
  - Alternatives for β-lactam allergy: clindamycin, vancomycin

Antimicrobial-impregnated bone cement can be useful in lowering infection rates in orthopedic surgery but has not been approved for prophylaxis.

▶ Cardiothoracic and Vascular Surgery

- Possible pathogens: gram-positive cocci, mostly staphylococci
- Prophylaxis for cardiac surgeries: cefazolin, cefuroxime
- Prophylaxis for noncardiac thoracic surgeries: cefazolin, ampicillin-sulbactam
- Prophylaxis for vascular surgeries: cefazolin
- For all cardiothoracic and vascular surgeries alternatives for β-lactam allergy: clindamycin, vancomycin

Table 85–3

Recommended Regimens for Antimicrobial Prophylaxis of Specific Surgical Procedures[a]

Type of Operation	Recommended Prophylaxis Regimen *(Duration is for a total of 24 hours unless specified)*[b]	Alternative Regimen for β-Lactam Allergy *(Duration is for a total of 24 hours unless specified)*
Vascular	Cefazolin 2–3 g[c] IV every 8 hours	Clindamycin 900 mg IV every 6–8 hours *or* vancomycin 15 mg/kg every 8–12 hours
Neurosurgery	Cefazolin 2–3 g[c] IV every 8 hours	Clindamycin 900 mg IV every 6–8 hours *or* vancomycin 15 mg/kg IV every 8–12 hours
Head and neck (clean with prosthesis placement excluding tympanostomy tubes)	Cefazolin 2–3 g[c] IV every 8 hours *or* cefuroxime 1.5 g every 8 hours	Clindamycin 900 mg IV every 6–8 hours
Head and neck (clean-contaminated)	(Cefuroxime 1.5 g every 8 hours AND metronidazole 500 mg every 8 hours) *or* amipicillin-sulbactam 3 g every 6 hours	Clindamycin 900 mg IV every 6–8 hours
Urologic (clean)	Cefazolin 2–3 g[c] IV × 1	Clindamycin 900 mg IV × 1 *or* vancomycin 15 mg/kg × 1
Urologic (lower tract instrumentation with risk factors for infection, transrectal prostate biopsy)	Ciprofloxacin 400 mg IV × 1 *or* levofloxacin 500 mg IV × 1 *or* trimethoprim-sulfamethoxazole *or* cefazolin 2–3 g[c] × 1	Gentamicin 5 mg/kg × 1 with or without clindamycin 900 mg × 1
Cesarean section	Cefazolin 2–3 g[c] IV × 1	See hysterectomy
Hysterectomy	Cefazolin 2–3 g[c] IV × 1 *or* cefotetan 2 g × 1 *or* cefoxitin 2 g × 1 *or* ampicillin-sulbactam 3 g × 1	(Clindamycin 900 mg × 1 or vancomycin 15 mg/kg × 1) AND (gentamicin 5 mg/kg × 1 or aztreonam 2 g *or* ciprofloxacin 400 mg *or* levofloxacin 500 mg)
Gastroduodenal (high-risk only: obstruction, acid suppression, morbid obesity, hemorrhage, malignancy)	Cefazolin 2–3 g[c] IV × 1	(Clindamycin 900 mg × 1 *or* vancomycin 15 mg/kg × 1) AND (gentamicin 5 mg/kg × 1 *or* aztreonam 2 g *or* ciprofloxacin 400 mg *or* levofloxacin 500 mg)
Biliary tract (open procedure or high-risk laparoscopic only: age > 70 years, acute cholecystitis, obstructive jaundice, duct stones, nonfunctioning gallbladder)	Cefazolin 2–3 g[c] IV × 1 *or* cefotetan 2 g × 1 *or* cefoxitin 2 g × 1 *or* ceftriaxone 2 g × 1 *or* ampicillin-sulbactam 3 g × 1	(Clindamycin 900 mg × 1 *or* vancomycin 15 mg/kg × 1) AND (gentamicin 5 mg/kg × 1 *or* aztreonam 2 g *or* ciprofloxacin 400 mg *or* levofloxacin 500 mg) or (metronidazole 500 mg × 1) AND (gentamicin 5 mg/kg × 1 *or* ciprofloxacin 400 mg *or* levofloxacin 500 mg)
Colorectal	[d]Oral: neomycin 1 g plus erythromycin base 1 g (give 19, 18, and 9 hours prior to procedure)	
	IV: (Cefazolin 2–3 g[c] × 1 and metronidazole 500 mg × 1) *or* cefoxitin 2 g × 1 *or* cefotetan 2 g × 1 *or* ampicillin-sulbactam 3 g × 1 *or* (ceftriaxone 2 g × 1 AND metronidazole 500 mg × 1) *or* ertapenem 1 g × 1	See biliary tract
Appendectomy	Cefoxitin 2 g IV × 1; cefotetan 2 g IV × 1; cefazolin 2–3g[c] × 1 AND metronidazole 500 mg × 1	Metronidazole 0.5–1 g IV AND gentamicin 1.5 mg/kg IV × 1
Orthopedic	Cefazolin 2–3 g[c] IV every 8 hours	Vancomycin 15 mg/kg every 8–12 hours *or* clindamycin 900 mg every 6–8 hours
Cardiothoracic	Cefazolin 2–3 g[c] IV every 8 hours for a total of 48 hours *or* cefuroxime 1.5 g IV every 12 hours for a maximum of 48 hours	Vancomycin 15 mg/kg every 8–12 hours for a total of 48 hours *or* clindamycin 900 mg every 6–8 hours for a maximum of 48 hours

[a]Dosing recommendations are based on common clinical doses for adult patients with normal renal function; dosing for individual patients and institutions may vary.

[b]In clean and clean-contaminated procedures, additional antimicrobials after incision is closed are not necessary.

[c]3 g dose for weight ≥ 120 kg.

[d]Oral regimens should be used in conjunction with IV prophylaxis.

Data from Refs. 8, 12, 13, and 17.

Debate exists on the duration of antimicrobial prophylaxis for cardiothoracic operations. SSIs are rare after cardiothoracic operations, but the potentially devastating consequences lead some clinicians to support longer periods of prophylaxis. The National Surgical Infection Prevention Project cites data that extending prophylaxis beyond 24 hours does not decrease SSI rates and may increase bacterial resistance.[2,12] However, the Society of Thoracic Surgeons issued practice guidelines in 2006 which recommended a duration of up to 48 hours following cardiac surgeries.[37] Duration of therapy should be based on patient factors and risk of development of an SSI.

▶ *Colorectal Surgery*

- Possible pathogens: gram-positive, gram-negative, and anaerobic organisms
- Parenteral prophylaxis: cefazolin and metronidazole; cefoxitin; cefotetan; ampicillin-sulbactam; ceftriaxone and metronidazole; ertapenem
  - Alternatives for β-lactam allergy: clindamycin combined with aminoglycoside, aztreonam, or fluoroquinolone; metronidazole combined with aminoglycoside or fluoroquinolone

Oral routes for prophylaxis include the combination of neomycin with either erythromycin or metronidazole and are administered at 19, 18, and 9 hours prior to surgery. These oral routes should be given with mechanical bowel preparation. For most patients, this oral regimen should be combined with a parenteral regimen.

Appendectomy is one of the most common intraabdominal operations. Antimicrobial prophylaxis used for appendectomy is similar to that used for colorectal regimens. In the case of ruptured appendix, antimicrobials are used for treatment, not prophylaxis.

Patient Encounter Part 1

WL is a 55-year-old man with no significant past medical history who presented to the clinic with ongoing right knee pain. His knee pain continued to worsen despite oral analgesics and intraarticular steroid injections. WL chooses to undergo an elective right knee total joint replacement. He states that he was told as a child that he had a "bad reaction" to amoxicillin.

VS: BP 110/65 mm Hg, HR 75 beats/min, RR 20 breaths/min, T 97.9°F (36.6°C), Ht 72 inches (182.88 cm), Wt 272 lbs (123 kg)

Labs: WBC 4.2 × 10^3/mm^3 (4.2 × 10^9/L), serum creatinine 1.2 mg/dL (106.1 mmol/L), glucose 110 mg/dL (6 mmol/L)

What organisms are likely to be encountered for this operation and why?

What agents need to be avoided in this patient?

The patient shares that he has taken cephalexin before for a skin rash and tolerated it well. What drug and dose would you recommend for this patient?

Patient Encounter Part 2

In preparation for his surgery today, WL is given a chlorhexidine bath. His vitals and glucose are taken prior to surgery.

VS: BP 110/65 mm Hg, HR 75 beats/min, RR 20 breaths/min, T 99.0°F (37.2°C), Ht 72 inches (182.88 cm), Wt 267 lbs (121.1 kg)

Labs: glucose 225 mg/dL (12.5mmol/L)

What additional steps should be taken to reduce WL's risk of developing a surgical site infection?

The surgeon is behind schedule and WL's surgery is delayed. The incision on his surgery was initially scheduled to start in 45 minutes but has been delayed for at least 2 hours. When should his prophylactic antimicrobials be administered?

OUTCOME EVALUATION

The clinician should consistently follow up postoperative patients and screen for any sign of SSI. KEY CONCEPT According to CDC criteria, SSIs may appear up to 30 or 90 days after an operation depending on the type and site of operation.[6] This period often extends beyond hospitalization, so educate patients on warning signs of SSI and be encouraged to contact a clinician immediately if necessary. The presence of fever or leukocytosis in the immediate postoperative period does not constitute SSI and should resolve with proper patient care. Distal infections, such as pneumonia, are not considered SSIs even if these infections occur in the 30-day period. Check the appearance of the surgical site regularly and document any changes (eg, erythema, drainage, or pus). The presence of pus or other signs suggestive of SSI must be treated accordingly. Any wound requiring incision and drainage is considered an SSI regardless of appearance. Collect prompt cultures and initiate appropriate antimicrobial therapy to reduce any chance of morbidity and mortality.

Patient Encounter Part 3

WL is seen in the orthopedic office 3 months after his procedure. His chief complaint is increased redness on the right knee, which has been present for the past few days. Further radiologic investigation shows the presence of fluid collection near the prosthetic implant.

VS: BP 99/55 mm Hg, HR 85 beats/min, RR 20 breaths/min, T 99.5°F (37.5°C), Ht 72 inches (182.88 cm), Wt 250 lbs (113.4 kg)

Labs: WBC 12.9 x 10^3/mm^3 (12.9 × 10^9/L)

Based on the available data, does WL have an SSI?

What further steps should be taken in regard to this possible SSI?

Patient Care Process

Collect Information:

- Conduct thorough medication history.
- Obtain serum creatinine and weight.
- Document allergies and the type of reaction.
- Document type of operation that patient is to receive.

Assess the Information:

- Consider penicillin allergy testing in patients with unclear documentation of penicillin allergy.

Develop a Care Plan:

- Determine appropriate antibiotics based on the type of operation and medication allergies.
- Determine appropriate dosing based on weight and renal function.

Implement the Care Plan:

- Start antimicrobials within 1 hour of surgical incision (2 hours for vancomycin, fluoroquinolones).
- Monitor patient for signs of allergic reaction.
- Document any major breaks in surgical technique and adjust length of antimicrobial therapy if surgical classification changes.

Follow-up: Monitor and Evaluate:

- Monitor for signs and symptoms of postoperative infection (30 or 90 days postoperation, based on operation).
- Draw cultures to further guide therapy if SSI is suspected.

Abbreviations Introduced in This Chapter

CDC	Centers for Disease Control
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NHSN	National Healthcare Safety Network
SSI	Surgical site infection

REFERENCES

1. Berrios-Torres SI, Umscheid CA, Bratzler DW et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection. JAMA Surg. 2017; 152: 784–791.
2. Bratzler DW, Houck PM; Surgical Infection Prevention Guideline Writers Workgroup. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Am J Surg. 2005;189:395–404.
3. Barie PS, Eachempati SR. Surgical site infections. Surg Clin North Am. 2005;85:1115–1135.
4. Kirkland KB, Briggs JP, Trivette SL, et al. The impact of surgical site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol. 1999;20:725–730.
5. Hollenbeak CS, Murphy D, Dunagan WC, et al. Nonrandom selection and the attributable cost of surgical-site infections. Infect Control Hosp Epidemiol. 2002;23:174–176.
6. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. Infect Control Hosp Epidemiol. 1999;20:247–266.
7. Department of Health and Human Services: Centers for Medicare & Medicaid Services. Medicare Program; Changes to the Hospital Inpatient Prospective Payment Systems and Fiscal Year 2008; Final Rule. Federal Register. 2007;72: 47200–47206.
8. Surgical Site Infection (SSI) Event. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/9pscssicurrent.pdf. Accessed November 26, 2017.
9. Dionigi R, Rovera F, Dionigi G, et al. Risk factors in surgery. J Chemother. 2001;13:6–11.
10. Pessaux P, Atallah D, Lermite E, et al. Risk factors for prediction of surgical site infections in "clean surgery." Am J Infect Control. 2005;33:292–298.
11. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Preventions. Infect Control Hosp Epidemiol. 2013;34:1–14.
12. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical Practice Guidelines for Antmicrobial Prophylaxis in Surgery. Am J Health System Pharm. 2013;70:195–283.
13. Devlin JW, Kanji S, Janning SW, et al. Antimicrobial prophylaxis in surgery. In: Dippers JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiologic Approach, 5th ed. New York: McGraw-Hill; 2002:2111–2122.
14. Finkelstein R, Rabin G, Mashie T, et al. Vancomycin versus cefazolin prophylaxis for cardiac surgery in the setting of a high prevalence of methicillin-resistant staphylococcal infections. J Thorac Cardiovasc Surg. 2002;123:326–332.
15. Itanu KMF, Wilson SE, Awad SS, et al. Ertapenem versus cefotetan prophylaxis in elective colorectal surgery. N Engl J Med. 2006;355:2640–2651.
16. Sogn DD, Evans R, 3rd, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. Arch Intern Med. 1992;152:1025–1032.
17. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics. 2005;115:1048–1057.
18. Apter AJ, Kinman JL, Bilker WB, et al. Is there cross-reactivity between penicillins and cephalosporins? Am J Med. 2006;119:354. e11–e20.
19. Weed HG. Antimicrobial prophylaxis in the surgical patient. Med Clin North Am. 2003;87:59–75.
20. Anderson DJ, Kaye KS, Classen D, et al. Strategies to prevent surgical site infections in acute care hospitals. Infect Control Hosp Epidemiol. 2014;29:S51–S61.
21. Greif R, Akca O, Horn E, et al; Outcomes Research Group. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med. 2000;342:161–167.
22. Chiu FY, Chen CM, Lin CF, et al. Cefuroxime-impregnated cement in primary total knee arthroplasty. J Bone Joint Surg. 2002;84:759–762.

23. Joseph TN, Chen AL, Di Cesare PE. Use of antibiotic-impregnated cement in total joint arthroplasty. J Am Acad Orthop Surg. 2003;11:38–47.
24. Fletcher N, Sofianos D, Berkes MB, Obremskey WT. Prevention of perioperative infection. J Bone Joint Surg Am. 2007; 89:1605–1618.
25. Wilcox MH, Hall J, Pike H, et al. Use of perioperative mupirocin to prevent methicillin-resistant *Staphylococcus aureus* (MRSA) orthopaedic surgical site infections. J Hosp Infect. 2003;54:196–201.
26. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. N Engl J Med. 2002;346:1871–1877.
27. Munoz P, Hortal J, Giannella M, et al. Nasal carriage of *S. aureus* increases the risk of surgical site infection after major heart surgery. J Hosp Infect. 2008;68:25–31.
28. Coia JE, Duckworth GJ, Edwards DI, et al. Guidelines for the control and prevention of meticillin-resistant *Staphylococcus aureus* (MRSA) in healthcare facilities. J Hosp Infect. 2006; 63:S1–S44.
29. Harbath S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and noscomial infection in surgical patients. JAMA. 2008;299:1149–1157.
30. Loveday HP, Pellowe CM, Jones SRLJ, Pratt RJ. A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant *Staphylococcus aureus* (1996–2004): Report to the Joint MRSA Working Party (Subgroup A). J Hosp Infect. 2006;63:S45–S70.
31. Loeb M, Main C, Walker-Dilks C, Eady A. Antimicrobial drugs for treating methicillin-resistant *Staphylococcus aureus* colonization. Cochrane Database Syst Rev. 2003;CD003340.
32. Bode LGM, Kluytmans JAJW, Wertheim HFL, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. N Engl J Med. 2010;362:9–17.
33. Diekema D, Johannsson B, Herwaldt, et al. Current practice in *Staphylococcus aureus* screening and decolonization. Infect Control Hosp Epidemiol. 2011;32:1042–1044.
34. Deshpande LM, Fix AM, Pfaller MA, et al. Emerging elevated mupirocin resistance rates among staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000): correlations of results from disk diffusion, Etest, and reference dilution methods. Diagn Microbiol Infect Dis. 2002;42:283–290.
35. Stone HH, Hooper CA, Kolb LD, et al. Antibiotic prophylaxis in gastric, biliary and colonic surgery. Ann Surg. 1976;184:443–452.
36. Forse RA, Karam B, MacLean LD, et al. Antibiotic prophylaxis for surgery in morbidly obese patients. Surgery. 1989;106:750–756.
37. Edwards FH, Engelman RM, Houck P, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery, part I: Duration. Ann Thorac Surg. 2006;81:397–404.

86 Vaccines and Toxoids

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LEARNING OBJECTIVES

LO

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

1. Define vaccination and immunization.
2. Discuss the impact individual vaccines have on public health.
3. Recommend an immunization schedule for a child, including immunocompromised children.
4. Recommend an immunization schedule for an adult based on comorbid conditions and lifestyle choices.
5. Evaluate an adverse reaction and its probable association with a vaccine.

INTRODUCTION

The development and widespread use of vaccines is one of the greatest public health achievements of the 20th century. Other than safe drinking water, no other modality has had a greater impact on reducing mortality from infectious diseases.[1] The first accounts of deliberate inoculation to prevent disease date back as far as the 10th century. However, it wasn't until 1798 that Edward Jenner published his work on inoculation of natural cowpox as a means to prevent smallpox infection that documented the first scientific attempt at prevention by inoculation. Since 1900, the widespread use of vaccines has resulted in the eradication of smallpox worldwide and wild-type poliovirus from the Western hemisphere. There have also been dramatic declines in the incidence of diphtheria, pertussis, tetanus, measles, mumps, rubella, and *Haemophilus influenzae* type b infections.[2] In the United States, there are immunization recommendations against 17-vaccine preventable diseases affecting all age groups.

KEY CONCEPT Vaccines have traditionally been preparations of killed or attenuated microorganisms that provide active immunity against a variety of viral and bacterial infections. Most vaccines are designed to prevent acute infections that can be rapidly controlled and cleared by the immune system. Successful immunization involves activation of antigen-presenting cells with processing of the antigen by lysosomal or cytoplasmic pathways. T and B lymphocytes will be activated to replicate and differentiate to form large pools of memory cells for protection against subsequent exposure to the antigen.[2]

Vaccines against viral infections may be **attenuated** live viruses or inactivated viral particles. Attenuation may be accomplished by several methods to decrease the viruses' virulence while retaining their **immunogenicity**. Bacterial vaccines utilize antigenic particles of the outer membrane to elicit an immune response. KEY CONCEPT Outer membrane polysaccharides are poorly immunogenic in children younger than 2 years unless conjugated with a carrier protein. Also, bacterial toxins may undergo chemical treatment to render them nontoxic to form **toxoids** against infectious agents.

LO 1

Often the terms *vaccination* and *immunization* are used interchangeably even though they are distinct concepts. Vaccination refers to the act of administering a vaccine, whereas immunization refers to the development of immunity to a pathogen. The delivery of a vaccine does not imply that the individual mounted an adequate immune response to the vaccine to elicit protection. However, immunization implies that the act of vaccination resulted in the development of protective immunity.

LO 2

Herd immunity refers to high levels of immunization in one population, resulting in protection of another unvaccinated population. For example, concentrated vaccination of children with the pneumococcal conjugate vaccine resulted in decreased invasive *Streptococcus pneumoniae* infection not only in the vaccinated children, but also in elderly persons within the same community.[3]

Cocoon immunization is a strategy used to immunize all persons surrounding another high-risk individual, such as vaccinating parents, siblings, and grandparents of a new infant who is too young to be vaccinated. This strategy is used to protect individuals who are not able to be vaccinated themselves.

VACCINE ADMINISTRATION SCHEDULES

LO 3 LO 4

Most vaccines are administered in two- to four-shot series in order to elicit the best protection. KEY CONCEPT Childhood and adult immunization schedules are revised frequently and published annually by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). Current immunization schedules can be found at www.cdc.gov/vaccines/. Recommendations will be published throughout the year in the *Morbidity and Mortality Weekly Report* (*MMWR*) as new vaccines are licensed or new information necessitates a change in previous recommendations.[4] See **Table 86–1** for vaccine dosing.

The childhood immunization schedule is complex and requires a large number of injections. In small infants, the number of injections can be intolerable to the infant, parent, and health care provider. Limiting the number of injections at each visit can lead

Table 86–1

Vaccine Dosing

Vaccine	Common Abbreviation	Dose	Route	Cautions and Adverse Effects
Diphtheria and tetanus toxoid	DT	0.5 mL	Intramuscular	History of arthus-type hypersensitivity reaction
Diphtheria, tetanus, acellular pertussis	DTaP	0.5 mL	Intramuscular	Systemic neurologic reaction from previous vaccine History of arthus-type hypersensitivity reaction Temperature > 40.6°C (105°F)
Haemophilus influenzae type b	HIB	0.5 mL	Intramuscular	
Hepatitis A	HepA	C: 0.5 mL A: 1 mL	Intramuscular	
Hepatitis B	HepB	C: 0.5 mL A: 1 mL	Intramuscular	
Human papillomavirus	HPV9	0.5 mL	Intramuscular	Pregnant women
Inactivated influenza	IIV3, IIV4	0.5 mL 0.1 mL	Intramuscular Intradermal	Severe egg allergy History of Guillain-Barré syndrome
Inactivated influenza, recombinant	RIV	0.5 mL	Intramuscular	History of Guillain-Barré syndrome
Measles, mumps, rubella	MMR	0.5 mL	Subcutaneous	Pregnant women Immunocompromised host
Meningococcal conjugate	MenACWY	0.5 mL	Intramuscular	
Meningococcal, serogroup B	MenB	0.5 mL	Intramuscular	
Pneumococcal 13-valent conjugate	PCV13	0.5 mL	Intramuscular	
Pneumococcal polysaccharide	PPSV23	0.5 mL	Intramuscular route preferred; subcutaneous	Children < 2 years
Poliovirus, inactivated	IPV	0.5 mL	Intramuscular, subcutaneous	Pregnancy
Rotavirus vaccine	RV (RV1, RV5)	1 or 2 mL	Oral	Immunocompromised host
Tetanus and diphtheria toxoid	Td	0.5 mL	Intramuscular	History of arthus-type hypersensitivity reaction
Tetanus, reduced diphtheria, acellular pertussis	Tdap	0.5 mL	Intramuscular	Systemic neurologic reaction from previous vaccine History of arthus-type hypersensitivity reaction
Varicella	VAR	0.5 mL	Subcutaneous	Pregnant women Immunocompromised host
Zoster, live	ZVL	0.65 mL	Subcutaneous	Immunocompromised host
Zoster, recombinant	RZV	0.5 mL	Intramuscular	

A, adult; C, children.

to missed vaccinations and increased expense for return visits. KEY CONCEPT Use of combination vaccines decreases the number of injections and increases the likelihood that the immunization schedule will be completed. Using combination vaccine does not adversely affect the immunity or increase adverse effects. Vaccine administration should not be delayed for mild to moderate respiratory tract illnesses or fevers.[4]

THE ROUTINE VACCINES

Diphtheria, Tetanus, and Pertussis Vaccines

Diphtheria is a contagious bacterial respiratory infection characterized by membranous pharyngitis. The impact of diphtheria is not from the causative bacteria, *Corynebacterium diphtheriae*, but rather from complications attributed to its exotoxin, such as myocarditis and peripheral neuritis. Diphtheria is rarely reported in the United States since the introduction of vaccination with diphtheria toxoid; however, diphtheria continues to be a major problem in developing countries.

The tetanus vaccine differs from others in that it does not protect against a contagious disease such as diphtheria, but rather against an environmental pathogen. *Clostridium tetani*, the causative pathogen, is widely found in the environment, especially in dirt and soils. Tetanus is rarely seen in developed countries.[5]

Pertussis is a highly contagious respiratory tract infection caused by the bacteria *Bordetella pertussis*. Pertussis is characterized by a protracted severe cough with or without posttussive vomiting, whoop, difficulty breathing, difficulty sleeping, and rib fractures. It is often referred to as "whooping cough" or the 100-day cough.[6]

▶ *Use of Diphtheria, Tetanus, and Acellular Pertussis Vaccine*

Diphtheria and tetanus toxoids and acellular pertussis vaccine should be administered in a five-shot series to all children beginning at 2 months of age. The shots are given at 2, 4, 6, and 15 to 18 months, and 4 to 6 years. Immunity to diphtheria, tetanus, and pertussis is achieved after the third vaccination.

▶ *Use of Tetanus and Diphtheria Toxiod Vaccine*

Immunity to tetanus and diphtheria wanes with increasing age necessitating the need for booster doses every 10 years. The preferred agent to use in adults is tetanus and diphtheria toxoid in order to also give a booster for diphtheria. Tetanus immunization status should be assessed in the management of moderate and severe wounds or contaminated wounds in individuals seeking medical care. A tetanus booster should be administered if necessary.

▶ *Use of Tetanus Toxiod, Reduced Diphtheria, and Acellular Pertussis Vaccine*

Pertussis continues to be reported in adolescents and adults of all ages indicating a waning immunity following primary immunization. Additionally, adults with pertussis may infect young infants who have not received the first three doses of primary vaccination resulting in hospitalizations and death. A tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine is recommended for use in adolescents and adults.

Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine should be administered to adolescents 11 through 18 years as a single booster. Ideally it should be given at 11 to 12 years of age. Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine is also recommended for adults 19 years and older as a single booster dose in individuals who have not already received it. This may be given as a routine vaccination or for wound management.[7]

Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine is also used as part of cocoon immunization strategy to protect young infants. The vaccine should be administered to pregnant women during the third trimester (27–36 weeks preferred) of each pregnancy in order for transfer of maternal antibodies to the newborn infant. Additionally, individuals with close contact to infants less than 12 months of age, such as fathers, grandparents, health care workers, and child care workers, should also be vaccinated. Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine may be given at any interval following a tetanus vaccine.[8]

Haemophilus Influenzae Type b Vaccine

H. influenzae is a bacterial respiratory pathogen that causes a wide spectrum of disease ranging from upper respiratory infections to bacterial meningitis. Approximately two-thirds of the cases of *H. influenzae* type b meningitis resulted in a high degree of hearing loss or neurologic deficits among survivors.[9] Since the introduction of the vaccine, invasive disease due to *H. influenzae* type b has been nearly eliminated.

The *H. influenzae* type b vaccine is a protein conjugate that elicits an enhanced immune response in younger children including infants. *H. influenzae* type b conjugate vaccine is a recommended routine childhood vaccination beginning at 2 months of age. There are currently three licensed monovalent *H. influenzae* type b conjugate vaccines and three combination vaccines containing *H. influenzae* type b conjugate. The vaccines have different dosing schedules and use 2 or 3 doses for the primary series. Vaccine providers need to be aware of the brand being used and related dosing schedule. The immune response to *H. influenzae* type b is similar among the different vaccines. The different brands are interchangeable without affecting the primary immune response or booster response.[9] A booster dose of *H. influenzae* type b vaccine is also recommended in adolescents and adults at high risk for becoming infected with *H. influenzae*.

H. influenzae type b and influenza vaccines have the potential for confusion and medication errors because of the similarity of the names. Care should be taken when ordering, dispensing, and administering these vaccines.

Hepatitis A Vaccine

Hepatitis A virus continues to be a frequent cause of illness despite the availability of a highly effective vaccine. Frequently, children younger than 6 years are asymptomatic with primary infection and play a pivotal role in spreading disease to adults. The economic burden of hepatitis A is greater than $300 million annually in combined direct and indirect costs. Widespread use of the hepatitis A vaccine significantly decreases the disease burden caused by hepatitis A infection.[10]

Hepatitis A vaccine was licensed in the United States in 1995. It is an inactivated whole virus vaccine that is administered in a two-dose series. More than 94% of children, adolescents, and adults will have protective antibodies 1 month after receiving the first dose and 100% following the second dose. The hepatitis A vaccine is recommended for all children following the first birthday, with the second dose administered 6 months later. Adults who are at high risk for hepatitis A should receive two doses at least 6 months apart. High-risk adults include persons with clotting disorders or chronic liver disease, men who have sex with men, illicit drug users, and international travelers going to areas with high to intermediate endemicity of hepatitis A, persons with anticipated close contact with an international adoptee, or any other person who wishes to become immune.[10]

Hepatitis B Vaccine

Hepatitis B virus is transmitted following exposure to infected blood and body fluids. Individuals with chronic hepatitis B infection are at risk for cirrhosis, liver cancer, liver failure, and death. Vaccination with hepatitis B vaccine is the most effective way to prevent hepatitis B infection.[11]

Hepatitis B vaccine is manufactured using recombinant DNA technology to express hepatitis B surface antigen (HBsAg) in yeast. Hepatitis B vaccine is available as a single component or in combination vaccines.

Hepatitis B vaccine is recommended for routine use in infants and children in a three-dose series. The first dose should be given 12 to 24 hours following birth. The remaining two doses should be administered with other routine infant vaccinations during

Patient Encounter 1

A mother brings her infant girl to the pediatrician for her 6th-month check-up and vaccinations. The mother is apprehensive about more vaccines because her baby had a fever and cried uncontrollably following the 4th-month vaccinations. You note that the infant was born at 32 weeks gestation and spent 4 weeks in the neonatal intensive care unit (NICU) prior to discharge from the hospital.

What routine vaccines should this infant receive at this visit?

The infant has already received three hepatitis B vaccinations. Should the infant receive another at this visit?

What advise could be given to the mother to lessen her anxiety regarding her infant receiving vaccines at this visit?

the first 6 months of life. The dosing schedule will depend on the use of single component or combination vaccines. Adolescents should receive the three-dose series if not previously vaccinated.[11]

Hepatitis B vaccine is recommended for adults at high risk for hepatitis B infection, including health care workers, and those requesting protection from hepatitis B. The vaccine is administered in a three-dose series over 4 to 6 months.[11] Frequently, individuals do not follow through with the complete three-dose series and questions arise about restarting the series. Hepatitis B vaccine produces an amnesic response; therefore, the series may be continued at any time in order to complete the three doses.

Following vaccination with hepatitis B vaccine, hepatitis B virus serologic markers will remain negative, with the exception of antibody to hepatitis B surface antigen (anti-HBs), which will be positive indicating immunity. Persons with anti-HBs concentration greater than 10 mIU/mL (10 IU/L) after vaccination will have complete protection against acute and chronic infection.[11] There is no need for booster doses in immunocompetent individuals when anti-HBs concentrations fall below 10 mIU/mL (10 IU/L), since a good memory response will occur following exposure to hepatitis B virus. However, a booster dose may be warranted in immunocompromised individuals.

Human Papillomavirus Vaccine

Human papillomavirus (HPV) is the most common sexually transmitted virus and is associated with a wide range of diseases, including cervical cancer and genital warts. More than 150 HPVs have been identified and classified on their ability to cause malignant disease. HPV 16 and 18 are highly associated with causing cervical cancer, as well as anal, oropharyngeal, penile, vaginal, and vulval cancers. HPV 6 and 11 are associated with 90% of genital warts.[12]

The Food and Drug Administration (FDA) has approved three HPV vaccines, but only the 9-valent (9vHPV) is available in the United States. 9vHPV protects against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. The HPV vaccine is unique in that preventing infection by HPV will translate into prevention of cancer. Areas with high uptake of HPV vaccine have started to see declines in HPV infections and related diseases such as genital warts and high-grade cervical disease.[13]

HPV vaccination is recommended for all adolescents at age 11 or 12 years. It is also recommended for females through 26 years and males through 21 years if not previously vaccinated. HPV vaccine is given in a 2-dose series prior to the 15th birthday or a 3-dose series if started after the 15th birthday.[13]

The overall rate of HPV vaccination continues to increase, but remains below other recommended adolescent vaccines. The main reason cited for not vaccinating teens is related to knowledge gaps among clinicians and parents regarding recommendations for use and safety concerns. The adverse event profile is similar to other vaccines administered to adolescents.[9]

Influenza Vaccine

Influenza is a contagious viral respiratory infection that usually occurs during the winter months in the Northern Hemisphere and Southern Hemisphere, and year round in the tropics. All age groups are affected by influenza; however, children have the highest rate of infection. Serious illness and death due to influenza usually occurs in extremes of age, those older than 65 years or younger than 2 years.

Influenza A and B viruses are responsible for causing human disease. Both influenza A and B undergo frequent antigenic drift, creating new influenza variants. Immunity to the surface antigens decreases the likelihood of infection. Unfortunately, antibody to one influenza subgroup does not give complete protection against other influenza subtypes.

The best way to protect against seasonal influenza is through vaccination. The current trivalent influenza vaccine contains two A strains, 1 A(H1N1), 1 A(H3N2), and one B strain. The quadrivalent influenza vaccine contains the same components of the trivalent and an additional B strain. Inactivated influenza vaccine is available in both trivalent and quadrivalent presentations.[14]

All individuals 6 months of age and older should receive yearly seasonal influenza vaccination. There is no preference for vaccine presentation when multiple types are available within an approved age range. In persons 65 years and older, the high-dose trivalent-inactivated influenza vaccine produced increased immunity and protection against confirmed influenza when compared to regular dose influenza vaccine.[15] The adjuvanted trivalent vaccine also showed improved protection against influenza when compared to unadjuvanted vaccine. These two vaccines should be considered for use in older adults.

Recommendations for influenza vaccination are update yearly, and should be consulted for information on use of specific products.

Measles, Mumps, and Rubella Vaccine

Measles, mumps, and rubella are acute viral infections that can cause serious disease and complications. Aggressive vaccination programs have made these infections uncommon in the United States. Measles and rubella have been eliminated from the United States. Recent outbreaks have been caused from importation of infected persons from other parts of the world where measles are still circulating. Some outbreaks also occur in communities with high levels of unvaccinated individuals.

Measles, mumps, and rubella vaccine is a live attenuated vaccine that causes a mild subclinical infection producing long-term immunity. Measles, mumps, and rubella vaccine is recommended for routine vaccination after the first birthday and a second dose administered at 4 through 6 years of age. Measles, mumps, and rubella vaccine is available in combination with varicella vaccine. This vaccine is not recommended for the first dose due to the increased risk of febrile seizures when compared to giving measles, mumps, and rubella and varicella separately at the same visit.[16] Measles, mumps, and rubella vaccine should also be given to adults older than 18 years who are found to be nonimmune.

Measles, mumps, and rubella vaccine should be avoided in immunocompromised persons because of the risk of acquiring measles from the vaccine. However, HIV-infected persons, who are not severely immunocompromised, including those on antiretroviral therapy, can be vaccinated if not immune.[16]

Measles, mumps, and rubella vaccine is a safe vaccine and rarely associated with severe reactions. The most common reaction is fever which usually occurs more than a week after vaccination. Children with a personal or family history of febrile seizures or epilepsy are at increased risk for measles, mumps, and rubella vaccine–associated febrile seizures.[16]

Meningococcal Vaccines

Neisseria meningitidis is a significant cause of meningitis and bacteremia. Invasive meningococcal disease is associated with a high morbidity and mortality rate. Morbidity in survivors is substantial, with approximately 20% having loss of limb

or neurologic sequelae. The highest rates of meningococcal disease are among young children. Thirteen meningococcal serogroups have been identified; however, five serogroups, A, B, C, Y, and W-135, are responsible for epidemic and endemic disease worldwide. Despite the availability of highly active antibacterial agents against *N. meningitidis*, there has been little impact on decreasing the morbidity and mortality due to invasive meningococcal disease.[17]

The quadrivalent meningococcal vaccine (A,C,Y,W-135) is recommended for routine vaccination of adolescents. The first dose should be administered at 11 to 12 years with a booster dose at age 16 years. Meningococcal vaccine is also recommended for high-risk individuals older than 2 months.[14] Serogroup B meningococcal (MenB) vaccine is recommended for individuals aged 16 to 23 years. There are two serogroup B meningococcal vaccines available, with no preference given between them. However, the vaccines are not interchangeable so the series should be completed with the same vaccine.[18]

Pneumococcal Vaccines

S. pneumoniae causes approximately 3000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and more than 1 million cases of otitis media each year.[19] The increasing prevalence of drug-resistant *S. pneumoniae* has emphasized the need for vaccination. Pneumococcal vaccines are highly effective in preventing disease from the common *S. pneumoniae* serotypes that cause human disease.

The 13-valent pneumococcal conjugate vaccine contains the serotypes that most commonly cause disease in children. The 23-valent pneumococcal polysaccharide vaccine contains 23 serotypes that are responsible for causing more than 80% of invasive *S. pneumoniae* infections in adults. The pneumococcal vaccines have demonstrated good immunogenicity and prevention of invasive pneumococcal disease.

The 13-valent pneumococcal vaccine is part of the routine childhood immunization schedule beginning at 2 months of age. Children older than 6 years who are at high risk of invasive pneumococcal disease should receive a single 23-valent pneumococcal polysaccharide vaccine, with a booster dose given in 5 years.[19]

Both the 13-valent pneumococcal conjugate and 23-valent pneumococcal polysaccharide vaccines are recommended for routine use in all adults 65 years of age or older. The 13-valent vaccine should be administered first followed by the 23-valent vaccine 1-year later. If an individual has already received the 23-valent pneumococcal vaccine, the 13-valent vaccine should be administered at least 12 months after the 23-valent vaccine. Adults 19 through 64 years who are at increased risk for invasive pneumococcal disease are recommended to receive a single vaccination with the 13-valent pneumococcal conjugate vaccine. This is followed in 8 weeks with a 23-valent pneumococcal polysaccharide vaccine, and a booster dose in 5 years.[20]

Revaccination with the 23-valent pneumococcal polysaccharide vaccine is recommended for adults older than 65 years if the first dose was administered when they were younger than 65 years and at least 5 years have passed. A dose of the 13-valent pneumococcal vaccine should be administered prior to receiving the 23-valent vaccine.[20]

Poliovirus Vaccine

Poliomyelitis is a highly contagious disease that is often asymptomatic; however, approximately 1 in every 100 to 1000 cases will develop a rapidly progressive paralytic disease. Since the introduction of the first poliovirus vaccine, there has been a significant reduction in the number of polio cases. Today, polio caused by wild-type poliovirus has been eradicated from the Western hemisphere with the goal of eradicating it from the world.[21]

The last reported case of indigenous wild-type poliovirus in the United States was in 1979; subsequent cases were all vaccine associated attributed to the oral poliovirus vaccine. In 1997, a transition period to the inactivated poliovirus vaccine was begun to reduce the risk of vaccine-associated paralytic poliomyelitis. By January 2000, the oral vaccine was no longer recommended for routine use. Currently, the inactivated poliovirus vaccine is recommended for routine use in the United States. It is available as a single component or in combination vaccines. A booster dose should be given after age 4 years; no matter how many doses were given in the infant vaccination series.[22]

Rotavirus Vaccine

Rotavirus is the most common cause of severe diarrheal disease in children younger than 5 years. It is a major cause of diarrhea hospitalizations for dehydration worldwide. Rotavirus G1 is the most prevalent strain found in the United States. However, in any given year, other strains (G2, G3, G4, and G9) may predominate.

There are two rotavirus vaccines available for use. They are a pentavalent human-bovine reassortant vaccine that contains outer capsid proteins for G1, G2, G3, G4, and P1, and a monovalent, G1 vaccine. The exact mechanism by which these vaccines produce an immune response is unknown; however, these live virus vaccines replicate in the small intestine and induce immunity.

The rotavirus vaccine is administered in either a two-dose or a three-dose series that is orally administered. The first dose is given to infants between 6 and 12 weeks of age. The impact of the rotavirus vaccine has been dramatic with a significant decrease in rotavirus hospitalizations and all-cause diarrhea hospitalizations in children younger than 5 years. The vaccine has also offered protection to children too old to receive the vaccine and young adults.[23] The most severe adverse events associated with rotavirus vaccine is **intussusception**, a telescoping of the intestines on to itself. Postlicensure monitoring has shown a minimal risk of the vaccine with 1 to 5 excess cases of intussusception per 100,000 vaccinated children.

Varicella Vaccine

Varicella zoster virus is a highly contagious herpes virus. Primary infection with varicella zoster causes chickenpox and was one of the most common childhood diseases in the prevaccine era. Following primary infection, varicella becomes latent in cranial nerve, dorsal roots, and autonomic ganglia where it may reactivate to cause shingles (Zoster) in older adults. Since the introduction of the varicella virus vaccine in 1995, there has been a 90% reduction in varicella infections and hospitalization in all age groups.[24]

The varicella vaccine is a live attenuated vaccine. Children younger than 12 years will have a 97% seroconversion rate following a single vaccination. Adolescents and adults older than 13 years will only have 78% seroconversion after a single inoculation, but will have 99% conversion following a second dose. Therefore, varicella vaccine is recommended to be administered in a two-dose series. The first dose should be administered after 12 months of age and a second dose at 4 years of age. Adolescents and adults without evidence of immunity to varicella zoster should receive two doses of varicella vaccine

Patient Encounter 2

A mother brings her son to the family physician for his 1-year-old visit. It is late September and the child has been suffering from poorly controlled asthma and has numerous food allergies. The mother has research childhood vaccines on the Internet and is reluctant to have any vaccines administered because of the risks of seizures and autism. The mother also feels they are unnecessary as these diseases no longer occur.

What routine vaccines should this child receive?

Does the child's asthma and food allergies impact the vaccines that should be administered?

How should the mother's concerns regarding autism be addressed?

How should the mother's concerns regarding the necessity of vaccines be addressed?

given 4 to 8 weeks apart. Antibody titers appear to persist for at least 20 years following immunization.

Varicella vaccine is well tolerated with tenderness at the injection site and mild rash the most common adverse events. Rashes due to the vaccine strain typically occur more than 20 days following vaccination. A few cases of secondary transmission to household contacts have been reported.[21]

Zoster Vaccine

Later in life, approximately 15% of the population will develop herpes zoster (shingles). Zoster is the reactivation of latent varicella zoster virus in the sensory ganglia. Zoster most frequently occurs in the elderly and immunocompromised individuals who have decreased circulating antibodies to varicella zoster virus.

There are two available Zoster vaccines: Zoster vaccine live and Zoster vaccine recombinant. Both vaccines are FDA-approved for use in individuals 50 years and older. However, ACIP recommends use of Zoster vaccine live in individuals 60 years and older.[25]

Zoster vaccine recombinant has been shown to have higher and longer lasting efficacy compared to Zoster vaccine live. Therefore, ACIP recommends the preferred use of Zoster vaccine recombinant over Zoster vaccine live. Zoster vaccine recombinant

Patient Encounter 3

An 18-year-old girl is receiving a physical prior to going to college. It is noted that the patient needs to be caught up on some of the routine adolescent vaccines.

What vaccines should this girl be evaluated for and receive if necessary?

The mother is reluctant to have the HPV series administered because her daughter is not sexually active. How should these concerns be addressed?

What precautions should be taken with this patient when administering vaccines?

Patient Encounter 4

A 65-year-old patient presents to the pharmacy to pick up his prescriptions. While there, he shows you the pictures of his new granddaughter. The pharmacist reviews the patient's vaccine history and offers to vaccinate the gentleman; he accepts all recommended vaccines.

What routine vaccines should this man receive?

What is the rationale for offering Tdap to this man?

What warnings should be given to the patient?

is administered in a two-dose series for immunocompetent individuals 50 years and older. If an individual has previously received Zoster vaccine live, it is recommended they also receive vaccination with Zoster vaccine recombinant.[26] Use of the zoster vaccines has shown a reduction in the incidence of zoster and postherpetic neuralgia.

VACCINE SAFETY

Vaccination is one of the most powerful tools used to prevent disease. As with all drugs, most vaccines have been reported to cause adverse reactions. The reactions are either acute or are related to the risk of developing another disease. Health care professionals should discuss the risks versus benefits of vaccines with individuals or caregivers prior to vaccination. Vaccine information sheets (VIS) provide written information about each vaccine and are required to be given to individuals prior to vaccination.[4]

LOS

Vaccine safety is monitored by the FDA and CDC through a passive reporting system that allows anyone, health professionals or lay public, to report any event through the Vaccine Adverse Event Reporting System (VAERS). KEY CONCEPT Health care professionals are mandated to report certain events through VAERS. Additionally, any serious, life-threatening, or unusual reactions should also be reported.

The VAERS database is continually monitored to determine whether the prevalence of reactions is changing and to identify previously unreported reactions to a particular vaccine. Large epidemiologic safety studies are conducted through the Vaccine Safety Datalink; a partnership between the CDC and nine large health care organizations.

Pain at the injection site is one of the most commonly reported adverse effects of vaccination. The reaction is usually mild, with complaints of pain and tenderness at the injection site that may or may not be accompanied by erythema. Local reactions tend to be more frequent with repeated doses or booster doses of vaccine.[4] Tetanus-containing vaccines are well known for causing localized reactions.

Fever is the most frequently reported adverse effect in children. Elevated temperature is usually self-limiting and resolves in a few days. Rarely febrile seizures may occur following vaccination with measles, mumps, and rubella vaccine.

Reports of syncope following vaccination have been increasing since the approval of HPV and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines. Syncope most commonly occurs in adolescent girls and young adults. Health care professionals should implement measures to mitigate secondary injuries when vaccinating this age group.[4]

Autism

Thimerosal is a preservative used in vaccines that has been purported to cause autism in children. The assumption is that thimerosal, also known as ethyl mercury, causes similar effects as methyl mercury, which has neurotoxic and nephrotoxic effects at high doses. Numerous epidemiologic studies have not shown a higher rate of autism among children receiving thimerosal-containing vaccines when compared with the normal background rate of autism. Despite lack of linkage to autism and other serious adverse effects, the United States created thimerosal-free versions of all childhood vaccines beginning in 2001. Additionally, the mercury exposure with vaccination is much lower than through many other environmental exposures.[27]

Guillain-Barré Syndrome

Guillain-Barré syndrome is a transient neurologic disorder causing flaccid paralysis. It is thought to be caused from the development of autoimmune antibodies that cause damage to the peripheral nerves. Guillain-Barré syndrome has been temporally associated with several bacterial and viral infections as well as vaccinations.

The association with vaccination and Guillain-Barré syndrome was first recognized with the Swine flu vaccine of 1976. Since that time a clear association of influenza vaccination and Guillain-Barré syndrome has not been clearly established. Caution is still recommended with influenza vaccines since the influenza strains contained in the vaccine has the potential to change each year.[28]

Several large epidemiologic studies have sought to establish a temporal association of Guillain-Barré syndrome and other routine vaccines. The evidence is inconclusive in determining a cause-and-effect relationship. Overall the risk of Guillain-Barré syndrome following vaccination is minimal with 1 to 2 cases per 100,000 vaccines administered. The benefits of vaccination far outweigh the risk of Guillain-Barré syndrome.[28]

SPECIAL POPULATIONS

Immunocompromised Host

The number of immunocompromised persons is continually increasing as advances are made in medicine. The life expectancy for persons with cancer, HIV infection, and solid organ or bone marrow transplantation is increasing. Vaccination provides one tool to prevent infection in the immunocompromised host. However, the individual's immunosuppressed state will alter the response to the vaccine. In general, all vaccinations should be updated prior to the person becoming immunosuppressed. KEY CONCEPT Once a person becomes significantly immunosuppressed, live virus vaccines should be avoided.

Infants, children, and adults with HIV should receive all routine vaccinations according to the recommended immunization schedule as long as T-lymphocyte CD4 count is more than 200 cells/mm^3 (200 × 10^6/L). Live vaccines should be used with caution when T-lymphocyte CD4 counts are less than 200 cells/mm^3 (200 × 10^6/L). All HIV-infected persons should receive yearly inactivated influenza vaccination.[29]

Following hematopoietic stem-cell transplantation, the patient will need most routine vaccines to be administered 6 to 12 months following transplantation. Diphtheria, tetanus, acellular pertussis, *H. influenzae* type b, hepatitis B, meningococcal, pneumococcal, and inactivated poliovirus should be given. Inactivated influenza vaccine is given yearly, starting 6 months after transplant. Measles, mumps, and rubella can be given 2 years after transplant and varicella and zoster vaccines are contraindicated.[29]

Solid organ transplant recipients have a blunted immune response to vaccines because the immunosuppressive regimens used to prevent organ rejection inhibit both T- and B-cell proliferation. Prior to transplant, children should complete primary immunization schedules if possible. Otherwise primary immunization schedule with inactivated vaccines may continue 2 months following transplantation. Adults should have all vaccinations updated prior to transplantation. Yearly inactivated influenza vaccination may be given 6 months following transplantation.[29]

Household contacts of immunocompromised persons should have all routine vaccines as scheduled, including yearly influenza vaccination. Children in the household may receive live virus vaccines without special precautions; however, if a rash develops following varicella vaccination, contact should be avoided with the immunocompromised host until the rash resolves.

Pregnancy

Vaccination during pregnancy can protect not only the mother but also the newborn infant. A fully immunized mother is less likely to infect their infant with critical diseases such as influenza, tetanus, and pertussis. Mothers who are vaccinated in the second half of the pregnancy will have maternal transfer of antibodies through the placenta giving protection to the newborn infant. Pregnant women should be vaccinated with inactivated influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines during each pregnancy. Ideally the vaccines should be administered after 20-week gestation, but can be administered at any time during the pregnancy.[30] Household members (eg, fathers, grandparents, siblings) of newborns should also be current in their vaccinations to prevent transmission to the infant.

Live virus vaccines should be avoided during pregnancy due to the theoretical concern of the virus being transported across the placenta and infecting the fetus. Women found to be nonimmune to rubella or varicella may be vaccinated soon after delivery, but not during the pregnancy.[30]

Health Care Professionals

Health care professionals are in a unique position to protect themselves and their patients by receiving immunizations against vaccine preventable diseases. Health care professionals should have documented immunity to measles, mumps, rubella, and varicella. The vaccine series should be administered if found nonimmune. Health care professionals with direct patient contact should also receive the hepatitis B vaccine series and have proven immunity following the series. As concerns regarding the rise of pertussis among adults, it is now recommended that all health care professionals receive at least one dose of tetanus, reduced diphtheria, and acellular pertussis vaccine to protect against pertussis. This dose may be administered at any interval following a tetanus booster.[31]

The CDC recommends all health care professionals receive yearly influenza vaccination. Many health care facilities are now mandating that employees receive yearly influenza vaccination or wear masks during influenza season.[31]

OUTCOME MEASURES

KEY CONCEPT Vaccines are a cost-effective means for disease prevention. From a societal perspective, for every dollar spent on routine childhood vaccines, there will be a $10 savings in direct and indirect costs.[32] The rates of vaccination for young children are 90% or more for most recommended vaccines. This has been

attributed to the requirements for proof of vaccination by States for enrollment into daycare centers and school. For vaccines not required by schools, the rate of vaccination is lower.

Adolescents present a unique challenge for vaccinating because they do not have as many encounters with health care professionals as young children do. However, the constantly changing immunization schedule makes this population vulnerable to missing newly approved vaccines and catch-up doses of vaccines that were not recommended when they were younger. Every encounter with a health care establishment should be viewed as an opportunity to evaluate and vaccinate if necessary. Adolescents may also have incomplete medical records due to changes in health care providers. Therefore, it is important for health professionals to regularly utilize universal State immunization databases that document pediatric and adult vaccinations. This eliminates the problems of lost immunization records if a child changes health care providers.[4]

The vaccination rate in adults is much lower than that in children. Only 50% to 60% of adults who meet criteria have received pneumococcal vaccination, and less than 40% have received seasonal influenza vaccine. Comprehensive initiatives need to be implemented to increase the adult vaccination rate. Some proven concepts are providing reminders to patients that vaccines are due and implementation of standing orders for vaccines. This latter concept allows nurses and pharmacists to screen patients to determine whether pneumococcal, influenza, or other vaccines are needed and to vaccinate without a direct physician's order.

Patient Care Process

Collect information:

- Perform a complete vaccine history. Ask the patient, parent, or caregiver which vaccines the patient has received and when they were administered.
- Review the patient's medical record for vaccinations.
- Review the State immunization database.

Assess the Information:

- Compare the patient's vaccine history to published immunization schedules.

Develop a Care Plan:

- Determine if any immunizations need to be administered at this visit.
- Inform the patient, parent, or caregiver that immunizations are needed.

Implement the Care Plan:

- Provide Vaccine Information Sheets (VIS) to the patient, parent, or caregiver. Answer any questions that they may have.
- Vaccinate the patient with the needed vaccines.

Follow-up: Monitor and Evaluate:

- Observe the patient for 15 minutes for signs of immediate reactions.
- Document administration of vaccines in the patient's medical record and State immunization database.
- Provide the patient with vaccine administration card.

Abbreviations Introduced in This Chapter

ACIP	Advisory Committee on Immunization Practices
anti-HBs	Antibody to hepatitis B surface antigen
CDC	Centers for Disease Control and Prevention
HBsAg	Hepatitis B surface antigen
VAERS	Vaccine Adverse Event Reporting System
VIS	Vaccine information sheets

REFERENCES

1. Centers for Disease Control and Prevention. Achievements in public health 1900–1999. Control of infectious diseases. MMWR. 1999;48:621–629.
2. MacKay IR, Rosen FS. Vaccines and vaccination. N Engl J Med. 2001;345:1042–1053.
3. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003;348:1737–1746.
4. Kroger AT, Duchin J, Vazque M. General best practice guidelines for immunization. Best practice guidance of the Advisory Committee on Immunization Practices (ACIP). Available from: www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf. Accessed August 28, 2017.
5. Rhee P, Nunley MK, Demetriades D, Velmahos G, Doucet JJ. Tetanus and trauma: a review and recommendations. J Trauma. 2005;58:1082–1088.
6. Hewlett EL, Edwards KM. Pertussis—not just for kids. N Engl J Med. 2005;352:1215–1222.
7. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine in adults aged 65 years and older—Advisory Committee on Immunization Practices (ACIP), 2012. MMWR. 2012;61:468–470.
8. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. MMWR. 2013;62:131–135.
9. Briere EC, Rubin L, Moro PL, Cohn A, Clark T, Messonnier N. Prevention and control of Haemophilus influenzae type b disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2014;63(No. RR-1):1–20.
10. Centers for Disease Control and Prevention. Prevention of Hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2006;55(No. RR-7):1–23.
11. Schille S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67(No. RR-1):1–31.
12. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination. Recommendations of Advisory Committee on Immunization Practices (ACIP). MMWR. 2014;63(RR-No. 5):1–29.
13. Meites E, Kempe A, Markowitz Le. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the Advisory Committee on Immunization Practices. MMWR 2016;65:1405–1408.
14. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2017–2018 influenza season. MMWR Recomm Rep. 2017;66:1–20.

15. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza in older adults. N Engl J Med. 2014;371:635–645.
16. Centers for Disease Control and Prevention. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013. Summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2013;62(No. RR-4):1–34.
17. Centers for Disease Control and Prevention. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2013;62(RR-2):1–22.
18. Patton ME, Stephens D, Moore K, MacNeil JR. Updated recommendations for use of MenB-FHbp serogroup B meningococcal vaccine—Advisory Committee on Immunization Practices, 2016. MMWR 2017;66:509–513.
19. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6–18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2013;62:521–524.
20. Kobayashi M, Bennett NM, Gierke R et al. Intervals between PCV13 and PPSV23 vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2015;64:944–947.
21. Centers for Disease Control and Prevention. Poliomyletis prevention in the United States: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2000;49(RR-5):1–22.
22. Centers for Disease Control and Prevention. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding routine poliovirus vaccination. MMWR. 2009;58:829–830.
23. Tate JE, Parashar UD. Rotavirus vaccines in routine use. Clin Infect Dis. 2014:59;1291–1301.
24. Baxter R, Tran TN, Ray P, et al. Impact of vaccination on the epidemiology of varicella: 1995–2009. Pediatrics. 2014; 134:24–30.
25. Hales CM, Harpaz R, Ortega-Sanchez I, Bialek S. Update on recommendations for use of Herpes zoster vaccine. MMWR. 2014;63:729–731.
26. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of Herpes Zoster Vaccine. MMWR. 2018;67:103–108.
27. Maglione MA, Das L, Raaen L, et al. Safety of vaccines used for routine immunization of US children: A systematic review. Pediatrics. 2014;134:325–337.
28. Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. Drug Saf. 2009;32:309–323.
29. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014:58:e44–e100.
30. Rasmussen SA, Watson AK, Kennedy ED, Broder KR, Jamieson DJ. Vaccines and pregnancy: past, present, and future. Semin Fetal Neonatal Med. 2014:19:161–169.
31. Kaltsas A, Sepkowitz K. Vaccinations for healthcare personnel: update on influenza, hepatitis B, and pertussis. Curr Opin Infect Dis. 2013:26;366–377.
32. Zhou F, Shefer A, Wenger J, et al. Economic evaluation of the routine childhood immunization program in the United States, 2009. Pediatrics. 2014;133:577–585.

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87 Human Immunodeficiency Virus Infection

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LEARNING OBJECTIVES

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

1. Explain the routes of transmission for human immunodeficiency virus (HIV) and its natural disease progression.
2. Identify typical and atypical signs and symptoms of acute and chronic HIV infection.
3. Identify the desired therapeutic outcomes for patients living with HIV.
4. Recommend appropriate first-line pharmacotherapy interventions for patients with HIV infection.
5. Recommend appropriate second-line pharmacotherapy interventions for patients with HIV infection.
6. Describe the components of a monitoring plan to assess effectiveness and adverse effects of pharmacotherapy for HIV infection.
7. Educate patients about the disease state, appropriate lifestyle modifications, and drug therapy required for effective treatment.

INTRODUCTION

Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS). HIV primarily targets $CD4^+$ T-lymphocytes, which are critical to proper immune system function. If left untreated, patients experience a prolonged asymptomatic period followed by rapid, progressive immunodeficiency. Therefore, most complications experienced by patients with AIDS involve opportunistic infections and cancers. AIDS occurs when a patient with HIV has a CD4+ cell count below 200 cells/mm^3 (200×10^6/L), a CD4+ cell percentage of total T-lymphocytes less than 14% (0.14), or one of the Centers for Disease Control and Prevention (CDC) AIDS defining conditions.[1]

EPIDEMIOLOGY

Although the global incidence of HIV has fallen 39% since 2000, HIV prevalence has increased, largely due to life-extending antiretroviral therapy. Combination antiretroviral therapy (cART) has increased both the length and quality of life for HIV-infected patients; however, to date, there are no treatments that eradicate HIV from the body.[2]

As of 2016, approximately 36.7 million people are infected with HIV worldwide. Approximately 70% of these cases are in Sub-Saharan Africa, with a prevalence of approximately 4%. In 2016 alone, approximately 1 million people worldwide died from HIV-related illnesses and 1.8 million people were newly infected with HIV. Most of these infections were acquired through heterosexual transmission. As of 2016, women accounted for 48.5% of all people living with HIV worldwide.[2]

In the United States, at the end of 2014, an estimated 1.1 million persons (aged 13 years or older) were living with HIV/AIDS. Approximately 15% of these are undiagnosed and unaware of their HIV infection and could be unknowingly transmitting the virus to others.[3]

In 2015, 45% of HIV diagnoses were in African Americans although this population comprises only 12% of the US population. Although HIV/AIDS rates in African American women dropped by 42% from 2005 to 2014, incidence in this population is three times the rate for Caucasian females and four times the rate for Hispanic females.[3]

PATHOPHYSIOLOGY AND ETIOLOGY

HIV-1 is a retrovirus and member of the genus *Lentivirus*. There are two molecularly and serologically distinct but related types of HIV: HIV-1 and HIV-2. These viruses have a prolonged latency period. HIV-2 is a less common cause of the epidemic and is found primarily in West Africa. HIV-1 is categorized by phylogenetic lineages into three groups (M [main or major], N [new], and O [outlier]). HIV-1 group M can be further categorized into nine subtypes: A through D, F through H, and J and K. HIV-1 subtype B is primarily responsible for the North American and Western European epidemic.

LO 1

HIV is primarily transmitted by sexual contact, by contact with blood or blood products, and from mother to child during gestation, delivery, or breast-feeding. HIV is transmitted through certain body fluids—blood, semen, preseminal fluid, rectal fluids, vaginal fluids, and breast milk—which must come into contact with a mucous membrane, damaged tissue, or be directly injected into the bloodstream. Risk factors for HIV/AIDS infection include men who have sex with men (MSM), history of or current IV drug use (needle or equipment sharing), unprotected sexual intercourse with high-risk individuals, the presence of other sexually transmitted infections (STIs) (eg, *Chlamydia trachomatis* or *Neisseria gonorrhoeae*), persons with coagulation/hemophilia disorders, and previous blood product recipients.

The most common method for transmission for HIV is receptive anal and vaginal intercourse, with the probability of transmission highest with receptive anal intercourse

(138 infections per 10,000 exposures).[4] The probability of transmission increases when the infected partner has a high level of viral replication (which occurs at the beginning of infection or late in disease) and subsequent high viral load or when the uninfected partner has ulcerative disease, compromised mucosal surfaces, or (in the case of men) has not been circumcised.

Parenteral transmission of HIV primarily occurs through injection drug use by sharing contaminated needles or injection-related supplies. Less than 1% of all cases of HIV infection occur as a result of transfusions of contaminated blood, blood products, or infected transplant organs.[3] Health care workers have a 0.23% estimated risk of acquiring HIV infection through percutaneous needlestick injury.[5]

Perinatal infection (also known as vertical transmission or mother-to-child transmission [MTCT]) can occur during gestation, at or near delivery, and during breast-feeding. In the absence of specific intervention including medications, the risk of MTCT up to and including delivery is approximately 25%. The risk of transmission during breast-feeding is approximately 15% to 20% within the first 6 months of life.[6] Because a high rate of HIV replication in the blood is a significant risk factor for transmission of HIV, it is important to treat women living with HIV during pregnancy regardless of the clinical stage of disease or CD4 count. After delivery, mothers are strongly recommended not to breast-feed if safe alternatives are available. Due to widespread availability of formula feeding options in the United States, breastfeeding should be avoided.

Understanding the life cycle of the virus is important to recognize how antiretroviral drugs are combined for optimal therapy (Figure 87–1). Once HIV enters the body, an outer glycoprotein (gp120) binds to CD4 receptors found on the surface of dendritic cells, T-lymphocytes, monocytes, and macrophages. This allows further binding to other chemokine receptors on the cell surface (CCR5 and/or CXCR4). Greater than 95% of newly infected patients have viruses that preferentially use CCR5 to enter the cell, and most patients with advanced disease have viruses that preferentially use CXCR4 to enter the cell.

After the virus has attached to CD4 and chemokine receptors, another viral glycoprotein (gp41) assists with viral fusion to the cell and internalization of the viral contents. The viral contents include single-stranded ribonucleic acid (RNA), an RNA-dependent deoxyribonucleic acid (DNA) polymerase (also known as **reverse transcriptase**), and other enzymes. Using the single-stranded viral RNA as a template, reverse transcriptase synthesizes a complementary strand of DNA. The single-stranded viral RNA is removed from the newly formed DNA strand by ribonuclease H, and reverse transcriptase completes the synthesis of double-stranded DNA. The viral reverse transcriptase enzyme is highly error-prone, and many mutations occur in the conversion of RNA to DNA. This inefficient reverse transcription activity is responsible for the ability of HIV to rapidly mutate and develop drug resistance.

A chronic infection is established when the double-stranded DNA migrates to the host cell nucleus and is integrated into the host cell chromosome by the HIV enzyme integrase. Once the cell becomes activated by antigens or cytokines, HIV replication starts. Host DNA polymerase transcribes viral DNA into messenger RNA, and messenger RNA is translated into viral

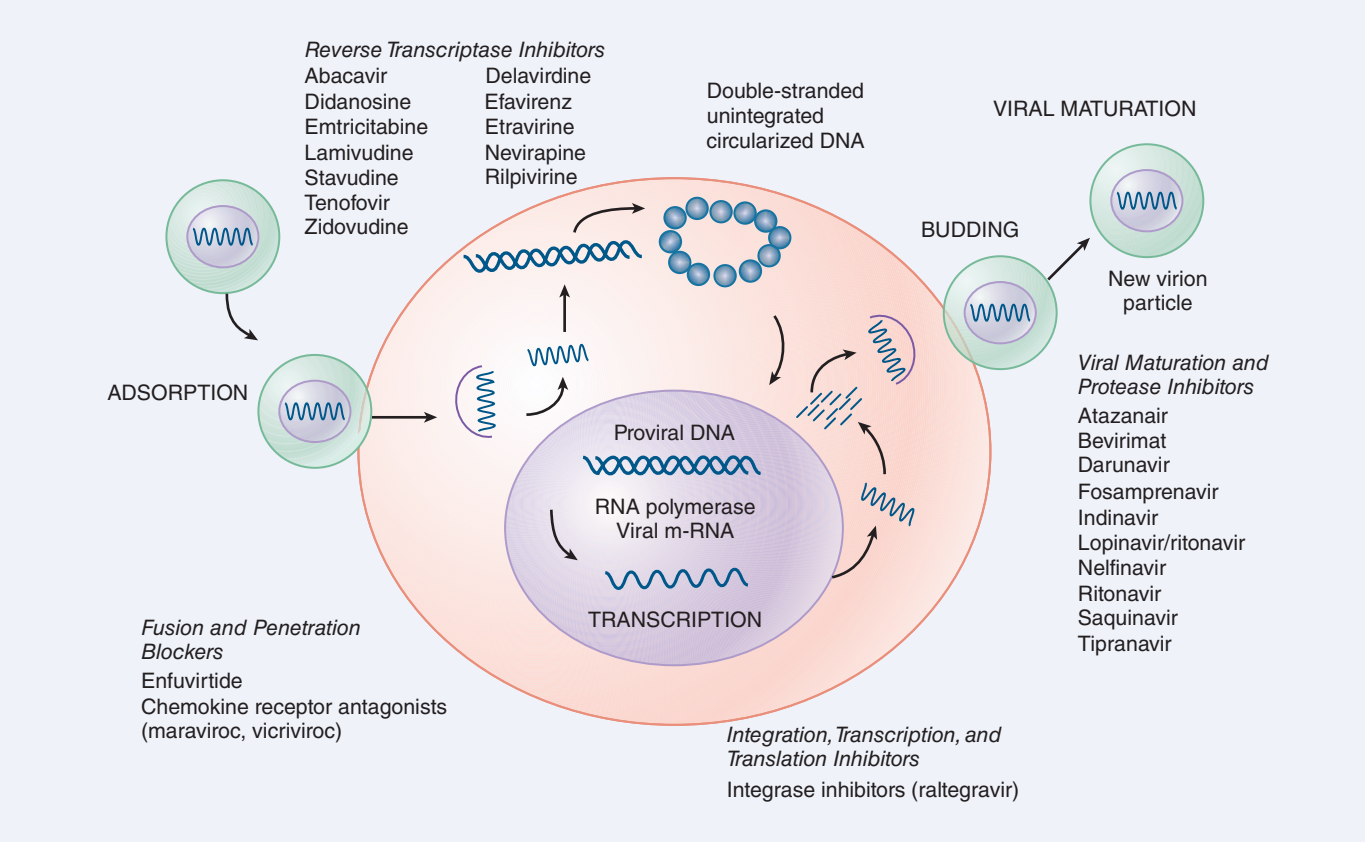

FIGURE 87–1. Life cycle of HIV and targets for antiretroviral drugs. (From Anderson PL, Kakuda TN, Fletcher CV. Human immunodeficiency virus infection. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York: McGraw-Hill; 2014; with permission.)

proteins. These proteins assemble beneath the bilayer of the host cell, a nucleocapsid forms containing these proteins, and the virus buds from the cell. After budding, the virus matures when an HIV **protease** enzyme cleaves large polypeptides into smaller functional proteins. Without this process, the virus is unable to infect other cells.

During the early stages of infection, approximately 10 billion virions can be produced each day. Most of the cells containing these viruses will be lysed as a result of budding virions, cytotoxic T-lymphocytes, or apoptosis. However, HIV will be protected within some cells (macrophages, T cells in lymph nodes), which can stay dormant for years.

The initial immune response against HIV is relatively effective; however, it is unable to completely clear the infection, and the patient enters a latent, asymptomatic, or mildly symptomatic stage lasting 5 to 15 years. During this time, a high rate of viral replication can be seen in the lymph nodes. Eventually immune deficiency occurs when the body is no longer able to replenish helper T cells at a rate equal to that at which HIV is destroying them.

KEY CONCEPT The goal of therapy is to maximally and durably suppress HIV replication to restore and preserve immune system function and minimize morbidity and mortality. Because HIV replication has been found in all areas of the body, it is important to use potent combination drug therapy that can achieve adequate concentrations in all tissues, including protected sites such as the brain and genital tract.

CLINICAL PRESENTATION AND DIAGNOSIS

LO 2

Patients who are acutely infected with HIV may be asymptomatic or present with signs and symptoms associated with any viral infection, such as fever, myalgias, lymphadenopathy, pharyngitis, or rash. Taken together, these are the "acute retroviral syndrome," and 40% to 90% of acutely infected individuals will have symptoms.[8] Providers should consider the possibility of HIV infection in any patient with these findings and inquire about recent high-risk sexual encounters or other modes of high-risk exposures. In the United States, 1 in 6 patients living with HIV are not aware of their status, thus identifying acutely infected patients and providing referral into HIV care is critical for preventing HIV transmission.[3] In acute infection, HIV RNA concentrations in blood and the genital tract are very high, increasing the risk of transmission to others. These patients will generally have plasma HIV RNA concentrations greater than 10^6 copies/mL (10^9 copies/L). Increased infectiousness coupled with undiagnosed HIV infection in these patients may account for a substantial proportion of sexual HIV transmission.

If patients are not identified during acute infection, they may later present with nonspecific symptoms such as myalgias, fatigue, weight loss, thrush, or symptoms associated with opportunistic infections. The US CDC recommends that patients aged 13 to 64 years in all health care settings undergo opt-out HIV testing, meaning that a separate consent form for testing is not needed after the patient has been informed that testing will be completed. For those patients in the high-risk groups mentioned above, HIV testing should be performed on an annual basis, and pregnant women should be tested with each pregnancy.[7]

Diagnosis of HIV begins with a 4th generation combination immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p-24 antigen. No further testing is required for specimens that are nonreactive. Specimens that are reactive on the initial immunoassay should be tested with an antibody immunoassay that differentiates

Clinical Presentation and Diagnosis of HIV

LO 2

Patients with acute HIV infection may display symptoms described as acute retroviral syndrome. Patients with chronic HIV infection may present with these same nonspecific symptoms and/or opportunistic infections.

Acute Retroviral Syndrome

The majority of patients may present with fever, lymphadenopathy, pharyngitis, and/or rash.
Other symptoms include the following:

- Myalgia or arthralgia
- Diarrhea
- Headache
- Nausea and vomiting
- Hepatosplenomegaly
- Weight loss
- Thrush
- Neurologic symptoms (meningoencephalitis, aseptic meningitis, peripheral neuropathy, facial palsy, or cognitive impairment or psychosis)

Opportunistic Infections

Depending on the severity of immunosuppression (the CD4 count), patients may present with the following opportunistic infections (grouped by CD4 count):

- *Any CD4 count*
  - *Mycobacterium tuberculosis* disease
  - Bacterial pneumonia (commonly *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa*, and *Staphylococcus aureus*)
  - Herpes simplex virus disease
  - Varicella zoster virus disease
  - Bacterial enteric disease (most commonly *Salmonella, Campylobacter*, and *Shigella*)
  - Syphilis
  - Bartonellosis
- *Less than 200 cells/mm^3 (200 × 10^6/L)*
  - Coccidioidomycosis
  - *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP or PJP)
  - Oropharyngeal and esophageal candidiasis
  - Kaposi sarcoma or human herpesvirus-8 disease
- *Less than 150 cells/mm^3 (150 × 10^6/L)*
  - Disseminated histoplasmosis
- *Less than 100 cells/mm^3 (100 × 10^6/L)*
  - *Toxoplasma gondii* encephalitis
  - Cryptosporidiosis
  - Microsporidiosis
- *Less than 50 cells/mm^3 (50 × 10^6/L)*
  - Disseminated *Mycobacterium avium* complex disease
  - Cytomegalovirus disease (CMV)
  - Cryptococcosis
  - Aspergillosis

HIV-1 from HIV-2 antibodies. Nonreactive or indeterminate specimens on the HIV-1/HIV-2 antibody differentiation immunoassay should be tested with an HIV-1 nucleic acid test (NAT). Positive results from this test indicate the need for HIV medical care that includes additional testing such as HIV-1 viral load and CD4 count to stage the disease. At-home HIV-1 test kits (eg, Home Access Systems, OraQuick) allow patients to self-collect blood or oral swab samples and obtain confidential results in the privacy of their home. Positive results require confirmation.

KEY CONCEPT HIV treatment response and disease progression is determined by following: (a) the CD4 T-lymphocyte count (CD4 count) and percentage, and (b) plasma HIV RNA (viral load). The CD4 percentage is followed because the absolute count may fluctuate and does not necessarily indicate a change in the patient's condition.

TREATMENT

LO 3

KEY CONCEPT The goals of treatment are to maximally and durably suppress viral replication, avoid the development of drug resistance, restore and preserve immune function, prevent opportunistic infections, minimize drug adverse effects, and prevent disease transmission. Elimination or cure of HIV is not possible with currently available therapies. Instead, maximal suppression of viral replication (defined as plasma HIV RNA concentrations undetectable by the most sensitive assay available) is desired. After the initiation of antiretroviral therapy, a rapid decline to undetectable plasma HIV RNA in 12 to 24 weeks is a predictor of improved clinical outcomes.[8]

KEY CONCEPT Degree of immune function preservation is also correlated with decreased viral replication and is measured by CD4 T-cell counts. CD4 measures are the best predictor of progression to AIDS and help clinicians determine when to initiate opportunistic infection prophylaxis. At CD4 T-cell counts of 200 cells/mm^3 (200 × 10^6/L) and lower, patients require drug prophylaxis for opportunistic infections. Table 87–1 details the monitoring points of HIV treatment for plasma HIV RNA and CD4 T-cell counts. In addition to these parameters, basic blood chemistry tests, liver function tests (LFT), complete blood counts, and lipid profiles should be monitored every 3 to 6 months in patients receiving antiretroviral therapy.[8]

Six classes of drugs are available to treat HIV infection: nucleoside (NRTI)/nucleotide (NtRTI) **reverse transcriptase** inhibitor, protease inhibitor (PI), nonnucleoside reverse transcriptase inhibitor (NNRTI), fusion inhibitors, CCR5 inhibitors, and integrase strand transfer inhibitors (INSTI). KEY CONCEPT Currently, combination antiretroviral drug therapy with three or more active drugs is the standard of care, at any CD4 count, which increases the durability of viral suppression and decreases the potential for the development of resistance. Two nucleoside (nucleotide) reverse transcriptase inhibitors AND an INSTI OR a PI with a pharmacokinetic enhancer OR an NNRTI are the recommended initial regimens of combination therapy. Combination regimens decrease plasma HIV RNA to less than 40 copies/mL (40 × 10^3 copies/L) in 80% to 90% of patients in clinical trials.[8] Therefore, monotherapy with any agent or the use of NRTIs without another drug class are not recommended treatment options. Fusion inhibitors are only Food and Drug Administration (FDA)-approved for use in treatment experienced patients with drug

Table 87–1

Monitoring End Points for CD4 T-Cell Counts and HIV RNA

CD4$^+$ T Cell Counts			HIV RNA Concentration		
When to Monitor?	**Why?**	**Goal**	**When to Monitor?**	**Why?**	**Goal**
Initial diagnosis	Assess immune function		Initial diagnosis/ evaluation	Establish baseline	
	Assess need for OI prophylaxis	Start prophylaxis when counts < 200 cells/ mm^3 (200 × 10^6/L)	2–8 weeks after starting or changing cART[a]	Early assessment of regimen efficacy	Undetectable concentrations
Every 3–6 months	Receiving cART: monitor success of treatment[b]	Average increase of 100–150 cells/mm^3/ year (100 × 10^6–150 × 10^6/L/year)	Every 3–6 months	Receiving cART: assess success and durability of virologic suppression and adherence with current regimen	Steadily decreasing and/ or consistently undetectable concentrations
	Not receiving cART: assess urgency to begin therapy	Start cART in appropriate patients	Every 3–6 months	Not receiving cART: Optional[c]	Start therapy in appropriate patients
	Assess need for OI chemoprophylaxis	Start prophylaxis when counts < 200 cells/ mm^3 (200 × 10^6/L)			

[a]If viral load is detectable, repeat every 4 to 8 weeks until less than 200 copies/mL (200 × 10^3/L), then resume every 3- to 6-month schedule.

[b]In clinically stable patients with viral loads less than 50 copies/mL (50 × 10^3/L) for more than 2 years, monitoring can be extended to every 12 months for CD4 count 300–500 cells/mm^3 or optionally for CD4 count > 500 cells/mm^3.

[c]For patients who choose to delay therapy, repeat viral load testing while not on therapy is optional. HIV RNA concentration should be determined prior to initiating therapy.

cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; OI, opportunistic infection; RNA, ribonucleic acid.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents [online]. Department of Health and Human Services. July 14, 2016. [cited 2017 Aug 16]. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

resistance to NRTIs, NNRTIs, and/or PIs. Figure 87–1 details the mechanisms of action of the drug classes within the life cycle of HIV.

Nonpharmacologic Interventions

LO 7

KEY CONCEPT Patient adherence is a key component in treatment success. Drug therapy is required indefinitely, as the virus begins to replicate at high levels when medications are stopped.

Patient Encounter 1, Part 1: Treatment Initiation

A 42-year-old white man presents to your clinic with complaints of thrush, weight loss, myalgias, and general fatigue. During a detailed social history, you learn that for the past 10 years, he has occasionally had unprotected sexual intercourse with women and also uses IV heroin. His last HIV test was over 12 years ago and was negative. Based on his presentation and risk factors today, you decide to perform general STD as well as HIV testing.

PMH: Type II diabetes, atrial fibrillation, asthma

FH: Mother—breast cancer, osteoporosis; Father—HTN, seizure disorder, type II diabetes

SH: Retail store clerk; sexual history as above with no condom use. He reports moderate (4–5 times weekly) IV heroin use.

Meds: Metformin 1000 mg BID, rivaroxaban 20 mg daily, albuterol 2 inhalations every 4 to 6 hours as needed

All: Latex (rash)

ROS: Positive for weight loss, decreased appetite; Negative for shortness of breath, cough, chest pain, nausea, vomiting, diarrhea

PE:

Within normal limits

VS: BP 110/69 mm Hg, P 85 beats/min, RR 20 breaths/min, T 37.5°C

HEENT: Thrush, lymph nodes (+) lymphadenopathy

CV: RRR, normal S1, S2; no murmurs, rubs, gallops

Abd: Soft, nontender, nondistended; (+) bowel sounds, no hepatosplenomegaly

Rectal: Deferred

Labs: Sodium 142 mEq/L (142 mmol/L), potassium 4.3 mEq/L (4.3 mmol/L), chloride 102 mEq/L (102 mmol/L), bicarbonate 25 mEq/L (25 mmol/L), blood urea nitrogen 10 mg/dL (3.57 mmol/L), creatinine 1.2 mg/dL (106 µmol/L), WBC 4 × 10^3/mm^3 (4 × 10^9/L), hemoglobin 11.4 g/dL (114 g/L or 7.07 mmol/L), hematocrit 32% (0.32), platelets 79 × 10^3/mm^3 (79 × 10^9/L), neutrophils 45% (0.45), bands 9% (0.09), lymphocytes 20% (0.20), monocytes 1% (0.01), eosinophils 1% (0.01), basophils 0% (0.00)

What information is suggestive of HIV?

What are the risk factors present for having HIV?

What is the likely time frame of this patient's HIV infection?

How can the diagnosis of HIV be made in this patient?

What additional laboratory measurements would be useful?

Combination therapy used in the past for HIV was exceedingly complicated for patients, with multiple daily doses, varying food restrictions, and large pill burdens. Advances in delivery and formulations now make possible once- or twice-daily dosing with fewer pills per day. Currently, three combination tablets are available that provide one pill, once daily NNRTI-containing regimens: tenofovir disoproxil fumarate (TDF) + emtricitabine + efavirenz (Atripla); tenofovir disoproxil fumarate + emtricitabine + rilpivirine (Complera); and tenofovir alafenamide + emtricitabine + rilpivirine (Odefsey). Additionally, three one pill, once daily INSTI-containing combination tablets are available: elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine (Stribild); elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine (Genvoya); and dolutegravir + abacavir + lamivudine (Triumeq). The use of low-dose ritonavir or cobicistat to enhance the concentrations of other PIs or elvitegravir, respectively (known as pharmacokinetic enhancement, or "boosting" agents), allows for significantly fewer daily doses and lower pill burdens. Cobicistat, unlike ritonavir, does not exert antiviral activity. Atazanavir or darunavir with ritonavir boosting are potent, once-daily PI options; once-daily lopinavir/ritonavir may be used in selected treatment-naïve patients. These advances, however, do not replace the need for patient counseling by a trained pharmacist and a multidisciplinary approach to promoting adherence.

LO 7

All patients should be counseled initially and repeatedly on ways to prevent viral transmission. Patients receiving antiretroviral therapy can still transmit virus to sexual partners, although the risk is extremely low when the patient is virally suppressed, and to those with whom they share needles or other drug equipment. Where both partners are living with HIV, safe sex and needle practices reduce the risk of superinfection with differing strains of HIV and the transmission of other sexually transmitted diseases. General guidelines for preventing viral transmission include using condoms with a water-based lubricant for vaginal or anal intercourse, using condoms without lubricant or dental dams for oral sex, and not sharing equipment used to prepare, inject, or inhale drugs. Treating other STIs, particularly genital herpes, in patients living with HIV may help to prevent HIV transmission. The presence of STIs increases genital tract HIV viral load and, correspondingly, the risk of HIV transmission to sexual partners.

KEY CONCEPT Nutrition and dietary counseling should also be included in the care of the HIV patient, as poor nutrition leads to poorer outcomes and complicates treatment. Antiretroviral therapy itself introduces a host of nutritional issues, including drug–food interactions, gastrointestinal (GI) adverse effects that may affect appetite and limit dietary intake, lipid abnormalities, and fat redistribution. The American Dietetics Association currently recommends assessing HIV-infected patients for their level of nutritional risk and involving a registered dietician as part of the clinical team for optimal nutrition care.[9]

Pharmacologic Therapy for Antiretroviral-Naïve Patients

Two expert panels publish guidelines for the treatment of HIV-infected individuals. Although the recommendations are quite similar, slight differences do exist between the Department of Health and Human Services (DHHS) Guidelines[8] and the International Antiviral Society–USA (IAS-USA) Panel Recommendations.[10] The DHHS Guidelines are updated frequently, and current and archived versions are available online at www.aidsinfo.nih.gov.

Due to the intense research and constant modifications to therapeutic approaches in the treatment of HIV, the majority of the treatment algorithms and recommendations presented herein follow the most up-to-date information found in the October 2017 DHHS recommendations.

KEY CONCEPT Initiating highly active antiretroviral therapy is recommended in all patients living with HIV willing to adhere to lifelong therapy to prevent HIV transmission and reduce the morbidity and mortality associated with HIV infection. Other factors to consider include the patient's viral load, decline in $CD4^+$ counts over time, hepatitis B and hepatitis C status, risk for cardiovascular disease, risk of transmission to sex partners, and willingness to begin therapy and maintain medication adherence. The DHHS Guidelines recommend initiating antiretroviral therapy in all HIV-infected individuals to reduce the risk of disease progression regardless of CD4 count. Once the decision is made to initiate treatment, the regimen is selected based on patient-specific factors. KEY CONCEPT All recommended regimens for initial treatment contain two NRTIs (tenofovir [disoproxil fumarate or alafenamide] + emtricitabine OR abacavir + lamivudine) with an INSTI, a PI with a pharmacokinetic enhancer, or an NNRTI. The recommended agents are shown in Table 87–2.

LO 4

Drug resistance testing should be performed at diagnosis and again prior to initiating treatment if treatment is deferred (see Pharmacologic Therapy for Antiretroviral-Experienced Patients for further discussion of drug resistance testing). The results of resistance testing may dictate which drug class is preferred; a minimum of 10% to 17% of newly diagnosed patients will have drug-resistant virus.[11] This initial resistance pattern often involves the NNRTIs, but may involve other drug classes. INSTI-based regimens have the advantage of avoiding many complex drug–drug interactions and toxicities seen with NNRTIs and PIs. However, elvitegravir must be coadministered with cobicistat which is associated with many cytochrome (CYP)-450-mediated drug interactions and should not be initiated in patients with a creatinine clearance (CrCl) less than 70 mL/min (1.17 mL/s) when using the co-formulation with TDF. If transmitted INSTI resistance is a concern, integrase resistance testing must be ordered separately from standard HIV genotyping, which only includes the protease and reverse transcriptase genes.

If abacavir is included in a regimen, patients should undergo human leukocyte antigen (HLA)-B*5701 testing prior to initiation to assess the risk of abacavir hypersensitivity. Patients who test positive for the allele are at high risk (approximately 50%–67%) of developing this reaction and should not be given abacavir.[8] An abacavir allergy should also be documented in the patient's medical record to prevent future administration. Those patients with a negative test may receive abacavir, but should still be counseled and monitored for the development of hypersensitivity. Tenofovir alafenamide is a new formulation of tenofovir that is associated with less nephrotoxicity and impact on bone mineral density than its predecessor tenofovir disproxil fumarate, and may be preferable from a toxicity standpoint.

In patients who cannot tolerate the recommended initial regimens for most patients living with HIV, or have a compelling reason to choose a different agent, the following alternative regimens are recommended (Table 87–3).[8]

PI-based regimens may be preferable in patients in whom adherence is a concern or drug resistance results are pending given the high threshold of this class resistance. NNRTI-based regimens have low pill burdens and may have decreased incidence of long-term adverse effects (eg, dyslipidemia) in comparison with some PI-based regimens. However, this class also has a low threshold for drug resistance (the K103N mutation causes high level cross-class resistance), and patient adherence is a critical consideration. Regimens with demonstrated efficacy but limited by other factors such as toxicities or pull burden are also provided in the guidelines. One of these regimens should only be selected if a first-line or alternate regimen is intolerable or the patient has a compelling reason to avoid drugs in a first-line or alternate regimen.

The guidelines include a list of therapies *not recommended* for initial treatment due to poor potency or significant toxicity. Other therapies that should not be used include darunavir without a pharmacokinetic enhancer ("unboosted"), and ritonavir used without another PI. Drugs that should *not be combined* due to overlapping toxicities include atazanavir plus indinavir (due to enhanced hyperbilirubinemia), two NNRTIs, and didanosine plus stavudine. Emtricitabine and lamivudine should not be combined because of their similar chemical structures, and antagonism can result when stavudine is combined with zidovudine.

Table 87–2

Recommended Initial ART Regimen Options for Most Patients Living with HIV, Regardless of Pre-ART Viral Load or CD4 Cell Count[8]

INSTI-Based Regimen:

Dolutegravir/abacavir/lamivudine *(Only for patients who are HLA-B*5701 negative)*

Dolutegravir + tenofovir disoproxil fumarate/emtricitabine OR tenofovir alafenamide/emtricitabine

Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine *(Only for patients with pre-ART CrCL ≥ 30 mL/min [1.17 mL/s])*

Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine *(Only for patients with pre-ART CrCL > 70 mL/min [1.17 mL/s])*

Raltegravir + tenofovir disoproxil fumarate/emtricitabine OR tenofovir alafenamide/emtricitabine

ART, Antiretroviral therapy; HIV, human immunodeficiency virus.

Table 87–3

Recommended Initial cART Regimen Options in Certain Clinical Situations

PI-Based Regimens:

Darunavir/cobicistat OR Darunavir/ritonavir + tenofovir disoproxil fumarate/emtricitabine OR tenofovir alafenamide/emtricitabine

Atazanavir/cobicistat OR atazanavir/ritonavir + tenofovir disoproxil fumarate/emtricitabine OR tenofovir alafenamide/emtricitabine

Darunavir/cobicistat OR Darunavir/ritonavir + abacavir/lamivudine *(Only for patients who are HLA-B*5701 negative)*

Atazanavir/cobicistat OR atazanavir/ritonavir + abacavir/lamivudine *(Only for patients who are HLA-B*5701 negative and HIV RNA < 100,000 copies/mL)*

NRTI-Based Regimens:

Efavirenz + tenofovir disoproxil fumarate/emtricitabine OR tenofovir alafenamide/emtricitabine

Rilpivirine/tenofovir disoproxil fumarate/emtricitabine OR rilpivirine/tenofovir alafenamide/emtricitabine (If HIV RNA < 100,000 copies/mL and CD4 > 200 cells/mm^3)

INSTI-Based Regimen:

Raltegravir + abacavir/lamivudine *(Only for patients who are HLA-B*5701 negative and HIV RNA < 100,000 copies/mL)*

cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

Patient Encounter 1, Part 2

After receiving the diagnosis of HIV and assessing his laboratory values and willingness to initiate therapy, the patient from Part 1 and his medical team decide to start antiretroviral therapy.

What is the guidance for when to start therapy in a treatment-naïve patient?

What are the recommended regimens according to the DHHS Guidelines?

What is the potential for drug interactions with each of the recommended regimens?

Which concomitant medication complicates initiating therapy in this patient and what are possible ways to manage such drug interactions?

What adverse effects does the patient need to be counseled on with each of the recommended regimens?

Pharmacologic Therapy for Antiretroviral-Experienced Patients

KEY CONCEPT Ongoing viral replication, whether at low levels (plasma HIV RNA < 200 copies/mL) in the face of adequate drug concentrations or at higher levels due to inconsistent systemic concentrations (or low concentrations in sanctuary sites, eg, male and female genital fluids, cerebrospinal fluid, or lymph nodes), will eventually lead to resistance to the prescribed medications. To avoid further progression of resistant mutations, drug-resistance testing should be performed and then a failing regimen should be discontinued as soon as possible.[8] The goal of therapy for patients with antiretroviral resistance is to reestablish virologic suppression or plasma HIV RNA lower than the limit of detection of the assay (typically < 40 *copies/mL* [40 × 10^3 copies/L]).

LOS Treatment considerations for antiretroviral-experienced patients are much more complex than for patients who are naïve to therapy. Prior to changing therapy, the reasons for treatment failure should be identified. A comprehensive review should be performed of the patient's severity of disease, antiretroviral treatment history, adherence to therapy, intolerance or toxicity, concomitant drug therapies, comorbidities, and results of current and past HIV resistance testing. If patients fail therapy due to poor adherence, the underlying reasons must be determined and addressed prior to initiation of a new regimen. Reasons for poor adherence may include problems with medication access, active substance abuse, depression and/or denial of the disease, and a lack of education on the importance of 100% adherence to therapy. Medication intolerance or toxicity can be remedied with therapy for the adverse event, exchanging the drug causing the toxicity with another in the same class, or changing the entire regimen. Pharmacokinetics or systemic drug exposure can be optimized by ensuring maximal drug absorption (taking the drug with or without food can alter exposure by up to 30%) and avoiding interactions with concomitant prescription or nonprescription medications and dietary supplements.

Drug interactions between different antiretroviral agents and between antiretrovirals and concomitant medications should be evaluated for each patient to avoid under- and/or overexposure of either therapy. KEY CONCEPT NNRTIs, PIs, certain INSTIs, and maraviroc are metabolized by CYP-450 enzymes. In addition, NNRTIs, PIs, and cobisistat are inhibitors and/or inducers of this enzyme system. Some of the antiretrovirals are substrates, inhibitors, and/or inducers of transporters such as P-glycoprotein (P-gp) and therefore may lead to drug interactions. Information provided in Table 87–4 describes the drug interaction potential of each antiretroviral. Due to ever-changing drug interactions, the regularly updated DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents are a recommended source of specific drug interactions.[8]

The goals of therapy differ for antiretroviral-experienced patients who have limited drug exposure (ie, developing resistance to their first antiretroviral regimen) versus those with extensive exposure (ie, developing resistance to their third or fourth antiretroviral regimen). It is reasonable to expect maximal viral suppression in those with limited drug exposure. However, this may not be feasible for patients with prior exposure to multiple medications. In antiretroviral-experienced patients, a reasonable goal is to preserve immune function and prevent clinical progression.

Several issues need to be considered in choosing a salvage regimen for HIV infection. Knowing prior medication exposure can assist in identifying which drugs to avoid. However, direct HIV resistance testing can better identify the resistance and susceptibility patterns of the major viral strains. Two types of HIV resistance testing are available, an HIV **genotype** and an HIV **phenotype**. Genotyping involves detecting mutations by genetically sequencing the virus, whereas phenotyping determines the ability of the virus to replicate in the presence of varying antiretroviral concentrations. Phenotyping involves exposing a sample of a patient's HIV to antiretroviral drugs and directly measuring the ability of HIV to grow in the presence of these drugs to determine which drugs will have activity. Genotyping is more rapid and less costly than phenotyping, but results in a list of mutations that may be more difficult to interpret than phenotyping. An HIV virtual phenotype report may also be obtained when genotypes are ordered.[8] This compares the patient's viral sequence to a database of matched genotypes and drug susceptibilities to estimate the patient's phenotype (the likely susceptibility of the patient's virus to different antiretrovirals). Web-based tools are available to assist with interpretation of resistance mutations (eg, Stanford University's HIV Drug Resistance Database; http://hivdb.stanford.edu/index.html). However, interpretation of genotype and phenotype reports is recommended in conjunction with practitioners with advanced infectious diseases training.

Because HIV may be susceptible to certain components of the failing antiretroviral regimen, these drugs can be recycled into future regimens. Resistance testing should be obtained when all patients enter into care, in patients with virologic failure on an antiretroviral regimen, or with suboptimal suppression after initiation of antiretroviral therapy. Testing is generally preferred for antiretroviral naïve patients. For resistance testing to be useful, the patient should have a plasma HIV RNA of at least 1000 copies/mL (1 × 10^6 copies/L) and should be currently taking their antiretroviral medications (or be within 4 weeks of discontinuing antiretroviral therapy). Generally, this viral concentration is necessary to yield reliable amplification of the virus, and the antiretroviral medications are needed because the dominant viral species reverts to **wild-type** within 4 to 6 weeks after medications are stopped.

LOS Management of antiretroviral-experienced patients is complex, and expert opinion is advised before selecting therapy. KEY CONCEPT As with antiretrovial-naïve patients, three or more active drugs should be prescribed.[8] Since considerable cross-resistance can occur between medications within an antiretroviral class, using drugs to which the patient has not been exposed may be insufficient. Complete

Table 87–4

Summary of Currently Available, Commonly Used Antiretroviral Agents[a]

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events	Drug Interaction Potential
Nucleoside (Tide) Reverse Transcriptase Inhibitors						
Abacavir (Ziagen)	300 mg tablet; 20 mg/mL oral solution	300 mg twice daily or 600 mg once daily	Child Pugh Class A: 200 mg twice daily Child Pugh Class B or C: contraindicated	None (alcohol increases abacavir conc. by 41%)	Potentially fatal hypersensitivity reaction (rash, fever, malaise, nausea, vomiting, shortness of breath, sore throat, loss of appetite)—HLA B*5701 test before treatment	Alcohol dehydrogenase and glucuronyl transferase, 82% renal excretion of metabolites
Emtricitabine (Emtriva)	200 mg capsule; 10 mg/mL oral solution	200 mg daily; 240 mg oral solution daily	CrCl (mL/min [mL/s]): / Capsule: / Solution: 30–49 [0.50–0.82] / 200 mg every 48 hours / 120 mg every 24 hours 15–29 [0.25–0.49] / 200 mg every 72 hours / 80 mg every 24 hours < 15/HD [0.25/HD] / 200 mg every 96 hours / 60 mg every 24 hours Dose after dialysis on dialysis days	None	Minimal	Renal excretion; minimal drug interaction potential
Lamivudine (Epivir)	150 mg and 300 mg tablets, 10 mg/mL oral solution	150 mg twice daily or 300 mg once daily	CrCl (mL/min [mL/s]): / Dose: 30–49 [0.50–0.82] / 150 mg every day 15–29 [0.25–0.49] / 150 mg, then 100 mg every day 5–14 [0.08–0.24] / 150 mg, then 50 mg every day < 5/HD [0.08/HD] / 50 mg, then 25 mg every day	None	Minimal	Renal excretion
Tenofovir disoproxil fumarate (Viread)	150-, 200-, 250-, 300-mg tablet; 40 mg per 1g powder	300 mg once daily	CrCl (mL/min [mL/s]): / Dose: 30–49 [0.50–0.82] / 300 mg every 48 hours 10–29 [0.17–0.49] / 300 mg twice weekly ESRD/HD / 300 mg every 7 days	Powder taken with food	Asthenia, headache, diarrhea, renal insufficiency, decreased bone mineral density	Renal excretion
Tenofovir alafenamide (Vemlidy) *Of note, only FDA labelled for HBV infection, not HIV*	25 mg tablet	25 mg once daily	Do not use with CrCL < 15 mL/min (0.25 mL/s)	With food	Headache	32% excreted in feces and < 1% in urine

Zidovudine (Retrovir)	100-mg capsule, 300-mg tablet, 10 mg/mL IV solution, 10 mg/mL oral solution	300 mg twice daily	100 mg three times daily or 300 mg once daily in severe renal impairment (CrCl < 15 mL/min [0.25 mL/s]) or HD	None	Bone marrow suppression: macrocytic anemia or neutropenia; GI intolerance, headache, insomnia, asthenia	Glucuonyl transferase and renal
Zidovudine + lamivudine (Combivir)	Zidovudine 300 mg + lamivudine 150 mg tablet	One tablet twice daily	Do not use with CrCl < 50 mL/min (0.83 mL/s)	None	See adverse events for zidovudine and lamivudine	See zidovudine and lamivudine
Abacavir + lamivudine + zidovudine (Trizivir)	Abacavir 300 mg + lamivudine 150 mg + zidovudine 300 mg tablet	One tablet twice daily	Do not use with CrCl < 50 mL/min (0.83 mL/s)	None	See adverse events for zidovudine, lamivudine, and abacavir	See zidovudine, lamivudine, and abacavir
Abacavir + lamivudine (Epzicom)	Abacavir 600 mg + lamivudine 300 mg tablet	One tablet daily	Do not use with CrCl < 50 mL/min (0.83 mL/s)	None	See adverse events for abacavir and lamivudine	See abacavir and lamivudine
Tenofovir disoproxil fumarate + emtricitabine (Truvada)	Tenofovir disoproxil fumarate 300 mg + emtrcitabine 200 mg	One tablet daily	**CrCl (mL/min [mL/s]):** / **Dose:** 30–49 [0.50–0.82] / One tablet every 48 hours 10–29 [0.17–0.49], ESRD/HD / Not recommended	None	See adverse events for tenofovir disoproxil fumarate and emtricitabine	See tenofovir disoproxil fumarate and emtricitabine
Tenofovir alafenamide + emtricitabine (Descovy)	Tenofovir alafenamide 25 mg + emtricitabine 200 mg	One tablet daily	Do not use with CrCl < 30 mL/min (0.5 mL/s)	None	See adverse events for tenofovir alafenamide and emtricitabine	See tenofovir alafenamide and emtricitabine
Nonnucleoside Reverse Transcriptase Inhibitors						
Efavirenz (Sustiva)	50-, 200-mg capsules or 600-mg tablet	600 mg daily at or before bedtime	Use with caution in patients with hepatic impairment	Take on an empty stomach high-fat/calorie meals increases C_{max} of capsule 39% and C_{max} of tablet 79%	Rash; CNS symptoms (insomnia, irritability, lethargy, dizziness, vivid dreams) usually resolve in 2 weeks; increased LFTs; false-positive cannabinoid test; teratogenic in monkeys	Metabolized by CYP2B6 and CYP3A (3A mixed inducer/inhibitor); 14%–34% excreted in urine (glucuronidated metabolites, < 1% unchanged); 16%–61% in feces
Etravirine (Intelence)	25-, 100-, 200-mg tablets	200 mg twice daily following a meal	No dosage adjustment for Child Pugh Class A or B. Has not been evaluated for Class C.	Take following a meal. Fasting decreases systemic exposure by 50%.	Rash, nausea	Metabolized by CYP3A, 2C9, and 2C19; induces 3A4 and inhibits 2C9 and 2C19

(*Continued*)

Table 87–4

Summary of Currently Available, Commonly Used Antiretroviral Agents[a] (*Continued*)

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events	Drug Interaction Potential
Nevirapine (Viramune, Viramune XR)	200-mg tablet, 100 and 400-mg XR tablet or 50 mg/5 mL oral suspension	200 mg once daily for 14 days; then 200 mg twice daily. For XR tablet, lead-in with 200 mg once daily of IR tablet followed by 400 mg daily XR tab not recommended for initiation in the following groups unless benefit outweighs the risk: 1) adult females with CD4 cell counts > 250 cells/mm^3 2) adult males with CD4 cell counts > 400 cells/mm^3	Use with caution in patients with hepatic impairment; avoid use with moderate to severe hepatic impairment	No food restrictions	Rash including Stevens-Johnson syndrome; symptomatic hepatitis, including fatal hepatic necrosis	Metabolized by CYP2B6 and CYP3A (3A inducer); 80% excreted in urine (glucuronidated metabolites; < 5% unchanged); 10% in feces
Rilpivirine (Edurant)	25-mg tablet	25 mg daily	No dosage adjustment for Child Pugh Class A or B. Has not been evaluated for Class C; use with caution in severe or end-stage renal impairment	Take with food (a normal- to high-calorie meal) Absorption dependent on gastric pH-special considerations needed when coadministered with antacids	Rash; depressive disorders	Metabolized by CYP3A4
Tenofovir disoproxil fumarate + emtricitabine + efavirenz (Atripla)	Tenofovir disoproxil fumarate 300 mg Emtricitabine 200 mg Efavirenz 600 mg	One tablet daily	Do not use in patients with CrCl < 50 mL/min (0.83 mL/s)	High-fat/high-caloric meals increase peak plasma concentrations of efavirenz capsules by 39% and efavirenz tablets by 79%; take on empty stomach	See adverse events of tenofovir, emtricitabine, and efavirenz	See tenofovir, emtricitabine, and efavirenz
Tenofovir disoproxil fumarate+ emtricitabine + rilpivirine (Complera)	Tenofovir disoproxil fumarate 300 mg Emtricitabine 200 mg Rilpivirine 25mg	One tablet daily with a meal	Do not use in patients with CrCl < 50 mL/min (0.83 mL/s)	Take with food (preferably high fat meal), avoid acid suppression	See adverse events of tenofovir disoproxil fumarate, emtricitabine, and rilpivirine	See tenofovir disoproxil fumarate, emtricitabine, and rilpivirine

Tenofovir alafenamide+ emtricitabine + rilpivirine (Odefsey)	Tenofovir alafenamide 300 mg Emtricitabine 200 mg Rilpivirine 25mg	One tablet daily with a meal	Do not use in patients with CrCl < 30 mL/min (0.5 mL/s)	Take with food (preferably high fat meal), avoid acid suppression	See adverse events of tenofovir alafenamide, emtricitabine, and rilpivirine	See tenofovir alafenamide, emtricitabine, and rilpivirine
Protease Inhibitors						
Atazanavir (Reyataz) Atazanavir + cobicistat (Evotaz)	150-, 200-, 300-mg capsules, 50 mg oral packet Evotaz: 300 mg atazanavr plus 150 mg cobicistat tablet	Atazanavir 300mg + ritonavir 100 mg or cobicistat 150 mg OR atazanavir 400 mg daily If taken with tenofovir, use the following: atazanavir 300 mg daily + ritonavir 100 mg daily If taken with efavirenz in treatment of naïve patients only: atazanavir 400 mg daily + ritonavir 100 mg daily (do not use with efavirenz in treatment of experienced patients)	Child-Pugh Class C: Not recommended Treatment-naïve patients on hemodialysis: atazanavir 300 mg + ritonavir 100 mg daily; treatment-experienced patients on hemodialysis: Not recommended	Take with food (AUC increases 30%); pH-sensitive dissolution—special considerations needed when coadministered with antacids	Indirect hyperbilirubinemia; prolonged PR interval (asymptomatic first-degree AV block); use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation; hyperglycemia; fat maldistribution; increased bleeding episodes in patients with hemophilia	CYP3A4 inhibitor and substrate; UGT1A1 inhibitor
Darunavir (Prezista) Darunavir + Cobicistat (Prezcobix)	75-g, 150-mg, 600-mg, 800-mg tablets, 100 mg/mL oral suspension Prezcobix: 800 mg darunavir + 150 mg cobicistat tablet	Darunavir 600 mg + ritonavir 100 mg twice daily in treatment experienced patients with at least 1 darunavir resistance-associated subsitution Darunavir 800 mg daily + ritonavir 100 mg or cobicistat 150 mg daily in treatment naïve patients	Use with caution in patients with hepatic impairment	Take with food	Skin rash (has a sulfonamide moiety, Stevens-Johnson and erythema multiforme have been reported); diarrhea, nausea; headache; hyperlipidemia; transaminase elevation; hyperglycemia; fat maldistribution; possible increased bleeding episodes in patients with hemophilia	CYP3A4 inhibitor and substrate

(*Continued*)

Table 87–4

Summary of Currently Available, Commonly Used Antiretroviral Agents[a] (*Continued*)

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments		Food Restrictions	Significant Adverse Events	Drug Interaction Potential
Lopinavir + ritonavir (Kaletra)	Lopinavir 100 mg + ritonavir 25 mg tablet, Lopinavir 200 mg + ritonavir 50-mg tablet, lopinavir 400 mg + ritonavir 100 mg/5 mL oral solution (contains 42% alcohol)	Two 200/50 mg tablets or 5 mL twice daily, four 200/50 mg tablets once daily; with efavirenz or nevirapine: 3 tablets or 6.5 mL twice daily	Use with caution in patients with hepatic impairment	Take with food (AUC increases 48%–80%)	Nausea, vomiting, diarrhea; asthenia; hyperlipidemia; LFT elevation; hyperglycemia; fat maldistribution; increased bleeding episodes in hemophiliacs		CYP3A4 inhibitor and susbstrate CYP2C9, 2C19, 1A2 inducer
Ritonavir (Norvir)	100-mg tablet or capsule, 80 mg/mL solution (contains 43% alcohol)	100–200 mg/dose when used as pharmacokinetic enhancer	No dosage adjustment in mild hepatic impairment No data for moderate to severe impairment; use with caution	Take with food to improve tolerability	GI intolerance, nausea, diarrhea; paresthesias; hyperlipidemia; hepatitis; asthenia; taste perversion; hyperglycemia; fat maldistribution; increased bleeding in hemophiliacs		CYP3A4 inhibitor (potent) and substrate; CYP2D6 substrate; mixed dose-dependent induction and inhibition of other phase I and II enzymes
Fusion Inhibitors							
Enfuvirtide (Fuzeon)	Injectable, in lyophilized powder Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL	90 mg (1 mL) subcutaneously twice daily	No dosage recommendation	N/A	Local injection site reaction (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in most patients; increased rate of bacterial pneumonia; < 1% hypersensitivity reaction (rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases); do not rechallenge		Catabolism to amino acids, with subsequent recycling in the body pool
Chemokine Receptor Antagonists (CCR5 Antagonists)							
Maraviroc (Selzentry)	25-, 75-, 150-, 300-mg tablets; 20 mg/mL oral solution	150 mg twice daily when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir)	Patients with CrCl < 30 mL/min (0.83 mL/s) should receive maraviroc with a CYP3A inhibitor only if benefit outweighs the risk		No food restrictions	Abdominal pain; cough; dizziness; musculoskeletal symptoms; pyrexia; rash; upper RTI; hepatotoxicity; orthostatic hypotension	CYP3A substrate

		300 mg twice daily when given with NRTIs, enfuvirtide, tipranavir/ritonavir, nevirapine and other drugs that are not potent P450 inhibitors 600 mg twice daily when given with CYP3A inducers, including efavirenz, rifampin, etc. (without a CYP3A inhibitor)				
Integrase Inhibitors						
Dolutegravir (Tivicay)	50-mg tablet	50 mg daily if treatment naïve 50 mg twice daily if coadministered with efavirenz, fosamprenavir, tipranavir/ritonavir, rifampin OR if INSTI-experienced with known or suspected INSTI resistance If co-administered with etravirine, must add lopinavir/ritonavir, atazanavir/ritonavir or darunavir/ritonavir	Use with caution if CrCl < 30 mL/min (0.83 mL/s) No dosage adjustment for Child Pugh Class A or B Not recommended in Class C/has not been studied	Separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	Insomnia, headache, increased serum creatinine	UGT1A1/3/9 and CYP3A4 (minor) substrate
Elvitegravir + cobicistat + tenofovir disoproxil fumarate + emtricitabine (Stribild)	Elvitegravir 150 mg + cobicistat 150 mg + tenofovir disoproxil fumarate 300 mg + emtricitabine 200-mg tablet	One tablet daily	CrCl < 70 mL/min (1.17 mL/s) at initiation of therapy: Not recommended CrCl < 50 mL/min (0.83 mL/s) during therapy: Continued use is not recommended	Take with food; separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	Nausea; diarrhea; proteinuria; increased serum creatinine	Elvitegravir: UGT1A1/3 and CYP3A substrate Cobicistat: CYP3A inhibitor See tenofovir and emtricitabine

(*Continued*)

Table 87–4

Summary of Currently Available, Commonly Used Antiretroviral Agents[a] (*Continued*)

Generic Name [Abbreviation] (Trade Name)	Dosage Forms	Commonly Prescribed Doses	Dose Adjustments	Food Restrictions	Significant Adverse Events	Drug Interaction Potential
Elvitegravir + cobicistat + tenofovir alafenamide + emtricitabine (Genvoya)	Elvitegravir 150 mg + cobicistat 150 mg + tenofovir alafenamide 25 mg + emtricitabine 200-mg tablet	One tablet daily	Do not use if CrCL < 30 mL/min (0.5 mL/s)	Take with food	Nausea; diarrhea; proteinuria; increased serum creatinine	Elvitegravir: UGT1A1/3 and CYP3A substrate Cobicistat: CYP3A inhibitor See tenofovir and emtricitabine
Raltegravir (Isentress)	400-mg tablet, 600 mg HD tablet, 25 mg and 100 mg chewable tablets, 100 mg packets for oral suspension. Formulations not interchangeable	400 mg twice daily 800 mg twice daily if coadministered with rifampin 1200 mg once daily (treatment naïve only)	No dosage adjustment	Separate dose from polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	Nausea; headache; diarrhea; pyrexia; CPK elevation	UGT1A1 substrate (glucuronidation)
Abacavir + lamivudine + Dolutegravir (Triumeq)	Abacavir 600 mg Lamivudine 300 mg Dolutegravir 50 mg	One tablet daily	Do not use if CrCl < 50 mL/min (0.83 mL/s) No dosage adjustment for Child Pugh Class A or B Not recommended in Class C/has not been studied		See adverse events of abacavir, lamivudine, and dolutegravir	See abacavir, lamivudine, and dolutegravir

[a]Note, this is not a comprehensive list of all available antiretroviral agents but represents the agents most commonly used based on guideline recommendations.

ARV, antiretroviral; AUC, area under the time-concentration curve; AV, atrioventricular; C_{max}, maximum concentration; CrCl, creatinine clearance; ESRD, end-stage renal disease; HD, hemodialysis; INSTI, integrase strand transfer inhibitor; LFT, liver function test; NRTI, nucleoside reverse transcriptase inhibitor; UGT, uridine diphosphate-glucuronsyltransferase.

Adapted from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents [online]. Department of Health and Human Services. July 14, 2016. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

cross-resistance occurs within the first generation of NNRTIs (nevirapine , delavirdine, and efavirenz), whereas the NRTIs and PIs have variable overlapping resistance patterns. For this reason, HIV resistance assays are important tools for choosing effective therapies. The use of antiretrovirals with unique mechanisms of action such as enfuvirtide (fusion inhibitor) or maraviroc (CCR5 antagonist) may be warranted as salvage therapy. If maraviroc is chosen, a tropism assay is a test that should be performed to determine if the patient's virus utilizes the CCR5 co-receptor to enter host cells (as opposed to CXCR4 co-receptors). If patients fail therapy with resistance to only one or more drugs, expert consultation is needed.

Given the complexity of selecting appropriate cART therapy and the ability of the virus to rapidly develop resistance, the concept of antiretroviral stewardship is important. Antiretroviral Stewardship encompasses practices aimed at improving antiretroviral medication use with the goal of minimizing medication errors related to cART and optimizing HIV treatment outcomes. Such efforts may entail routine review of patients admitted to an institution on antiretrovirals and provider education in order to ensure an appropriate and complete cART regimen is selected (with regards to drug, dose, formulation, administration considerations) and drug–drug interactions are minimized. Antiretroviral Stewardship can have a significant impact on cART medication error prevention, with a medication error rate reduction rate of 12% to 35% demonstrated in studies, depending on the type of intervention implemented.

Treatment Considerations in Special Populations

► *Acute HIV Infection*

Diagnosis of acute HIV infection is difficult, since many patients are asymptomatic or have nonspecific clinical symptoms similar to other common respiratory infections. The 4th generation antigen/antibody test increases the ability to detect acute HIV-1 infection, but no laboratory assay can detect HIV immediately after it is acquired.

There is limited outcome data for treating acutely infected patients. Treatment of acute infection can decrease the severity of acute disease and decrease the viral set point; this may decrease progression rates and reduce the rate of viral transmission.[8] Limitations include an increased risk of chronic drug-induced toxicities and the development of viral resistance. Resistance testing should be performed prior to initiation of therapy due to an increase in transmitted resistance in antiretroviral naïve patients.[8]

► *Adolescent and Young Adult Patients*

Adolescents infected after puberty acquire HIV in similar ways to adults, and are thus treated as adults. In this population, dosing of antiretroviral drugs should not be based on age, but on the Tanner stage (which considers external primary and secondary sexual characteristics).[8] Adolescents in early puberty should be dosed according to pediatric guidelines, whereas those in late puberty should be dosed as adults. During growth spurts, adolescents should be monitored closely for drug efficacy and toxicity, since rapid changes in weight can lead to altered drug concentrations. Adherence is of concern in this population due to denial of the disease, misinformation, distrust of health care professionals, low self-esteem, and lack of family and/or social support. Additionally, asymptomatic patients this age find it more difficult to adhere to therapy while feeling well.

► *Pediatric Patients*

There are unique considerations in the treatment of HIV-infected children. Specific treatment guidelines exist,[12] but a thorough review is outside the scope of this chapter. Most children acquire HIV infection through perinatal transmission either in utero, intrapartum, or postpartum through breast-feeding, although antiretroviral interventions have dramatically reduced transmission rates.[8] Antiretroviral therapy research is limited in pediatric patients, as some drugs have no dosing recommendations for this population or are not available in a formulation that can be easily administered to children. Additionally, drug exposures can change dramatically during early childhood development due to altered drug-metabolizing enzyme and drug transporter activities.

► *Pregnancy and Women of Reproductive Potential*

The goals of antiretroviral therapy for women of reproductive age and pregnant women are the same as for other adult patients. Specific guidelines for pregnant women living with HIV are available.[13] If a woman is already virally suppressed on an antiretroviral regimen at the time she becomes pregnant, it is recommended that she remain on that regimen. Of note, efavirenz has previously been recommended against during pregnancy. However, because the risk of neural tube defects with efavirenz is highest during the first 5 to 6 weeks of pregnancy, and pregnancy is often not detected before 4 to 6 weeks, it is reasonable for women virologically suppressed on an efavirenz-containing regimen to continue that regimen rather than switch regimens and risk viral rebound. If not already on antiretroviral therapy, recommended therapies in pregnancy include atazanavir + ritonavir, darunavir + ritonavir or raltegravir all administered with a two NRTI backbone (abacavir/lamivudine or TDF/emtricitabine). Alternate regimens include lopinavir/ritonavir or efavirenz administered with a two-NRTI backbone or rilpivirine/TDF/emtricitabine. A dual nucleoside reverse transcriptase inhibitor (NRTI) backbone that includes one or more NRTIs with high levels of transplacental passage, if possible, is recommended. The goal of therapy is to reduce plasma HIV RNA below detectable levels and prevent MTCT of HIV. Limited data are available on some antiretroviral pharmacokinetics in pregnancy, with close plasma HIV RNA and CD4 monitoring in the third trimester of pregnancy. Standard doses are currently recommended for most antiretroviral drugs, although higher doses of some PIs may be indicated depending on the trimester of pregnancy.

Efavirenz, nevirapine, ritonavir, atazanavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, and saquinavir/ritonavir decrease the concentrations of different estrogens and/or progestins in oral contraceptives, which could lead to failure.[8] For patients prescribed these drugs, barrier forms of contraception are preferred to prevent pregnancy. Atazanavir may be taken with oral contraceptives with extreme caution, as it can increase or decrease the exposure to estrogen and progesterone, depending on whether it is used in combination with ritonavir. Depo-Provera(medroxyprogesterone) is likely the safest alternative, as studies have shown no significant interactions between depot medroxyprogesterone acetate and antiretrovirals.[14] Maraviroc, raltegravir, elvitegravir/cobicistat, and dolutegravir have not shown clinically significant effects when used with oral contraceptives.

► *Hepatitis B Coinfection*

Patients living with HIV coinfected with the hepatitis B virus (HBV) have higher concentrations of DNA and hepatitis B early antigen (HBeAg) and higher rates of HBV-associated liver disease than in patients with chronic HBV infection without HIV. Indications to initiate therapy for HBV/HIV coinfected patients are the same as in HIV-negative patients and are based on the HBV DNA level, serum alanine aminotransferase

(ALT), and severity of liver disease. One option to treat HBV is nucleoside/tide analogs. Nucleoside/tide analogs that treat HBV but not HIV are adefovir and entecavir. Entecavir, however, exhibits minimal antiviral activity against HIV, and should never be administered to coinfected patients who are not concurrently receiving fully suppressive HIV therapy. If given without suppressive antiretrovirals, entecavir can select for M184 resistance, leading to HIV resistance to emtricitabine and lamivudine. Nucleoside/tide analogs that are used to treat HBV and HIV are lamivudine, emtricitabine, and tenofovir. Combinations of tenofovir disoproxil fumarate + emtricitabine, tenofovir alafenamide + emtricitabine or tenofovir disoproxil fumarate + lamivudine should comprise the NRTI backbone of a fully suppressive regimen.[15] When changing HIV therapy in a patient with HBV viral suppression, the new regimen should also treat HBV; the lamivudine, emtricitabine, or tenofovir formulation should be continued for treatment of HBV in addition to the new HIV regimen.[8] Abrupt discontinuation of these antiretrovirals may result in significant hepatic injury due to the exacerbation of hepatitis B. Of note, HBV infection should not be treated if a patient is not being treated for HIV.

Vaccination against HBV can effectively prevent transmission. If there is no record of vaccination, or immunization history is unknown, patients living with HIV should be vaccinated.

▶ *Hepatitis C Coinfection*

All patients living with HIV should be screened for hepatitis C virus (HCV) infection. Patients coinfected with HCV and HIV have an increased rate of progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma, and death compared with monoinfected HCV alone.[15] All HCV/HIV coinfected patients should be considered for therapy. Comprehensive treatment guidelines for HIV/HCV-coinfected patients are available and have recently been updated to reflect the rapidly evolving treatment options for HCV.[8,16] It is important to consider the potential for clinically significant drug–drug interactions when selecting an HCV regimen for a patient living with HIV on antiretroviral therapy.

Patient Encounter 2

A 23-year-old African American man presents to your clinic requesting medication to prevent the transmission of HIV. He had learned from his partner living with HIV partner that Truvada (emtricitabine + tenofovir disoproxil fumarate) was a drug used for the prevention of HIV. He also read that there was a newer form of Truvada that was safer for his kidneys and bones and he is interested in learning more about whether or not this is an option for him. He reports engaging in sexual activity with a male partner living with HIV and rarely uses condoms since he states his partner's viral load is always undetectable.

What additional information do you need to know before creating a treatment plan for this patient?

What laboratory tests do you recommend?

What pharmacologic and nonpharmacologic options are available for this patient to protect himself from acquiring HIV?

What monitoring assessments and follow-up would you recommend?

Patient Encounter 3

A 20-year-old woman with HIV and Hepatitis B (virologically suppressed) presents to your clinic for follow-up after initiating Odefsey 4 months ago (baseline HIV viral load: 95,000 copies/mL (95×10^6 copies/L), CD4+ T cell count= 370 cells/mm^3 (370×10^6/L). At her last appointment one month ago, her HIV viral load was 10,000 copies/mL (10×10^6 copies/L) and CD4+ T-cell count = 390 cells/mm^3 (390×10^6/L). Today, her HIV viral load is 12,000 copies/mL (12×10^6 copies/L). Today, she complains of depressed mood and reduced appetite. She states she is taking Odefsey daily as prescribed.

Was this patient initiated on a first-line guideline-recommended treatment regimen for HIV?

What component of Odefsey is likely to be causing depressed mood?

What factors should be considered when trying to determine causes of virologic failure?

You decide to switch the patient's regimen due to side effects and her inability to take the medication as prescribed.

What additional laboratory tests should be obtained at this visit?

Given the patient's comorbidity, what agents should you try to include in this new regimen?

What are some important general counseling points for this patient?

What monitoring assessments and follow-up would you recommend?

Preexposure Prophylaxis (PrEP)

Multiple large-scale clinical trials in populations at highest risk for acquiring HIV have demonstrated that antiretrovirals, particularly tenofovir disoproxil fumarate + emtricitabine, in combination with effective risk-reduction services (eg, counseling, access to condoms, treatment of sexually transmitted disease [STD], etc.), reduce the rate of HIV transmission. Data from these trials has led to the FDA approval of Truvada (fixed-dose combination of TDF 300 mg and emtricitabine 200 mg), as PrEP to reduce the risk of acquiring HIV-1 in adult homosexual men who have sex with men, heterosexually active men and women, and injection drug users who are at substantial risk of HIV acquisition.[17] Patients must be tested for HIV at baseline, and minimally every 3 months while taking PrEP. STD testing should occur at least every 6 months for patients taking PrEP. Additionally, due to the potential toxicities associated with TDF, renal function must be assessed at baseline and at 6-month intervals in patients taking Truvada as PrEP. Patient counseling including stressing the importance of medication adherence should be routinely provided as medication adherence has been linked to PrEP efficacy.[17] Note, at this time, tenofovir alafenamide + emtricitabine (Descovy) is not FDA approved for PrEP; however, studies are ongoing.

OUTCOME EVALUATION

LO 6

KEY CONCEPT The success of antiretroviral therapy is measured by the degree to which the therapy (a) restores and preserves immunologic function, (b) maximally and durably suppresses plasma HIV RNA, (c) improves quality of life, (d) reduces HIV-related morbidity and mortality, and (e) prevents opportunistic

Table 87–5

Serious Adverse Effects and Management

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Hepatotoxicity	Other NNRTIs, PIs, most NRTIs, and MVC	**Onset:** NNRTI—60% within first 12 weeks PI—weeks to months NRTI—months to years **Symptoms:** NNRTI—asymptomatic to nonspecific symptoms, such as anorexia, weight loss, or fatigue PI—generally asymptomatic, some with anorexia, weight loss, jaundice Didanosine NRTI—zidovudine, didanosine, stavudine may cause hepatotoxicity associated with lactic acidosis; lamivudine, emtricitabine, or tenofovir may cause HBV flare when these drugs are withdrawn	HBV or HCV coinfection Alcoholism Concomitant hepatotoxic drugs	Monitor LFTs at least every 3–4 months	Rule out other causes. For symptomatic patients: D/C all antiretrovirals and other potential hepatotoxic agents; after symptoms and LFTs normalize, begin new antiretroviral regimen (without the potential offending agents). For asymptomatic patients: If ALT > 5–10 × ULN, may consider D/C antiretrovirals or continue with close monitoring; after symptoms and LFTs normalize, begin new antiretroviral regimen (without the potential offending agents)
Lactic acidosis/ hepatic steatosis ± pancreatitis	NRTIs (esp. stavudine, didanosine, zidovudine)	**Onset:** Months after initiation **Symptoms:** Nonspecific GI (nausea, anorexia, abdominal pain, vomiting, weight loss, fatigue) Laboratory values: ↑ lactate, ↓ arterial pH, ↓ serum bicarbonate, ↑ AST/ALT, ↑ PT, ↑ T.bili, ↓ serum albumin, ↑ amylase/ lipase (with pancreatitis)	Stavudine + didanosine Female sex Obesity Pregnancy Didanosine + hydroxyurea or ribavirin ↑ Duration of NRTI use	None unless symptoms present Consider lactate concentrations in patients with ↓ serum bicarbonate or ↑ anion gap	D/C all antiretrovirals; symptomatic support with fluids; some patients require IV bicarbonate, hemodialysis, parenteral nutrition, or mechanical ventilation; once syndrome resolves, consider using NRTIs with ↓ mitochondrial toxicity (abacavir, tenofovir, lamivudine, or emtricitabine); monitor lactate after restarting NRTIs; some clinicians use NRTI-sparing regimens
Stevens-Johnson syndrome/toxic epidermal necrosis	Nevirapine > efavirenz, delavirdine, etravirine; also, amprenavir, abacavir, zidovudine, didanosine, indinavir lopinavir/r, atazanavir, darunavir, rilpivirine, raltegravir	**Onset:** First day–weeks after therapy start **Symptoms:** Skin eruption with mucosal ulcerations; fever, tachycardia, malaise, myalgia, arthralgia; for nevirapine may also have hepatic toxicity	Nevirapine—female, black, Asian, Hispanic	Nevirapine: use 2-week lead in 200 mg daily, then 200 mg twice a day Avoid corticosteroid use during dose escalation—may increase rash incidence Educate patients to report symptoms as soon as they appear	D/C all antiretrovirals as well as any other possible cause; aggressive symptom support; do not rechallenge patient with offending agent; if caused by nevirapine, avoid NNRTI class, if possible
Hypersensitivity reaction (HSR)	Abacavir	**Onset:** Median = 9 days; 90% within first 6 weeks **Symptoms:** Acute onset of symptoms (most frequent to least): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms	HLA-B*5701, HLA-DR7, HLA-DQ3 Antiretroviral-naïve patients Higher incidence with 600 mg every day compared with twice a day dosing	HLA-B*5701 screening prior to abacavir if (+), label as abacavir allergic in medical chart Educate patients about signs and symptoms of HSR and the need of prompt report	D/C abacavir and other antiretrovirals; rule out other causes of symptoms, most signs and symptoms resolve 48 hours after abacavir/D/C; do not rechallenge with abacavir after suspected HSR

(*Continued*)

Table 87–5

Serious Adverse Effects and Management (*Continued*)

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Bone marrow suppression	Zidovudine	**Onset:** Few weeks–months **Symptoms:** Fatigue, risk of ↑ bacterial infections due to neutropenia; anemia, neutropenia	Advanced HIV High-dose zidovudine Preexisting anemia or neutropenia Concomitant use of bone marrow suppressants	Avoid in patients at high risk for bone marrow suppression; avoid other suppressing agents; monitor CBC with differential at least every 3 months	Switch to another NRTI; D/C concomitant bone marrow suppressant, if possible; for anemia: Identify and treat other causes; consider erythropoietin treatment or blood transfusion, if indicated; for neutropenia: Identify and treat other causes; consider filgrastim treatment, if indicated
Nephrotoxicity	Indinavir, tenofovir disoproxil fumarate	**Onset:** Indinavir—months after therapy Tenofovir—weeks to months after therapy **Symptoms:** Indinavir—asymptomatic; rarely develop end-stage renal disease; ↑ serum creatinine, pyruria; hydronephrosis, renal atrophy Tenofovir—asymptomatic to symptoms of nephrogenic diabetes insipidus, Fanconi syndrome; ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, nonanion gap metabolic acidosis	History of renal disease Concomitant use of nephrotoxic drugs	Avoid use of other nephrotoxic drugs; adequate hydration if on indinavir; monitor creatinine, urinalysis, serum potassium and phosphorus in patients at risk	D/C offending agent, generally reversible; supportive care; electrolyte replacement as indicated

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood cell count; CPK, creatine phosphokinase; D/C, discontinue; HBV, hepatitis B virus; HCV, hepatitis C virus; LFT, liver function tests; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PT, prothrombin time; T.bili, total bilirubin; ULN, upper limit of normal.

Table 87–6

Other Adverse Effects and Management

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Potential Long-Term Complications					
Cardiovascular	Potentially all PIs and other antiretrovirals (efavirenz, stavudine—unfavorable lipid effect; abacavir, didanosine—unknown)	**Onset:** months to years after therapy initiation **Symptoms:** premature CVD	Other risk factors for CVD	Consider non–PI-based regimen; lifestyle modification, counseling	Early diagnosis, prevention, and pharmacologic therapy for hyperlipidemia, HTN, insulin-resistance/diabetes mellitus; assess cardiac risk factors; switch to NNRTI- or atazanavir-based regimen; avoid stavudine
Hyperlipidemia	All PIs (except atazanavir); stavudine; efavirenz (to a lesser extent)	**Onset:** weeks to months after therapy initiation **Symptoms:** all PIs except atazanavir—↑ LDL and total cholesterol (TC), ↑↓ HDL; lopinavir/r and ritonavir—disproportionate ↑ TG; stavudine—↑ TG; may also ↑ LDL and TC; efavirenz or nevirapine—↑ HDL, slight ↑ TG	Underlying hyperlipidemia PI: Tipranavir/r > lopinavir/r and ritonavir > nelfinavir and amprenavir > indinavir and saquinavir > atazanavir NNRTI: < PIs; efavirenz > nevirapine, etravirine, or rilpivirine NRTI: stavudine > zidovudine and tenofovir most common	Use non-PI, nonstavudine-based regimens; use atazanavir-based regimen; monitor fasting lipid profile at baseline, 3–6 months after new regimen, then at least annually	Assess cardiac risk factor; lifestyle modification; switch to antiretrovirals with fewer lipid effects; consider statin therapy
Insulin resistance/ diabetes mellitus	All PIs	**Onset:** weeks to months after therapy initiation **Symptoms:** polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying diabetes	Underlying hyperglycemia, family history of diabetes mellitus	Use PI-sparing regimens; monitor fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months	Diet and exercise; consider switching to an NNRTI-based regimen; if need for pharmacologic therapy, consider metformin, sulfonylurea, "glitazones," or insulin, where indicated
Osteoporosis/ Osteonecrosis	All PIs, Tenofovir disoproxil fumarate	**Onset:** insidious **Symptoms:** mild to moderate periarticular pain; 85% of cases involve one or both femoral heads	Diabetes Prior steroid use Advanced age Alcohol use Hyperlipidemia	Risk reduction (limit steroid and alcohol use): for asymptomatic cases with < 15% bony head involvement, monitor with MRI every 3–6 months × 1 year, then every 6 months × 1 year, then annually	Conservative: reduce weight-bearing activity on affected joint; reduce risk factors; analgesics as needed; surgical: core decompression ± bone grafting (early disease); total joint arthroplasty (severe disease)
Quality-of-Life Complications					
CNS effects	Efavirenz	**Onset:** first few doses **Symptoms:** one or more of the following: drowsiness, insomnia, abnormal dreams, dizziness, impaired concentration, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation	Preexisting or unstable psychiatric illness Use of other drugs with CNS effects May be more common in African Americans due to genetic predisposition of ↓ clearance	Take no earlier than 2–3 hours before bedtime; take on an empty stomach; counsel patients to avoid operating machinery during first 2–4 weeks of therapy	Symptoms usually diminish or resolve after 2–4 weeks; may consider discontinuing therapy if symptoms persist and significantly impair daily function or exacerbate psychiatric illness

(*Continued*)

Table 87–6

Other Adverse Effects and Management (*Continued*)

Adverse Effects	Drug	Signs and Symptoms	Risk Factors	Prevention/Monitoring	Management
Fat maldistribution	PIs, thymidine analogs (stavudine more common than zidovudine)	**Onset:** gradually, months after therapy initiation **Symptoms:** lipoatrophy—peripheral fat loss (facial thinning, thinning of extremities and buttocks); lipohypertrophy—increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	Lipoatrophy—low baseline body mass index	DEXA scan; lipoatrophy: avoid thymidine analogs or switch from zidovudine or stavudine to abacavir or tenofovir	Switching to other agents may slow or stop progression, but may not reverse effects; injectable poly-L-lactic acid for facial lipoatrophy, human growth hormone
GI intolerance	All PIs, zidovudine, didanosine	**Onset:** first few doses **Symptoms:** nausea, vomiting, abdominal pain; diarrhea commonly seen with nelfinavir, lopinavir/ritonavir, and didanosine-buffered formulations	All patients	Taking with food may reduce symptoms (not for didanosine or unboosted indinavir); may preemptively need antiemetics or antidiarrheals	May spontaneously resolve or become tolerable with time; nausea and vomiting: consider antiemetic prior to dosing; switch to less emetogenic agent; diarrhea: consider antimotility agents, calcium tablets, bulk-forming agents, and/or pancreatic enzymes
Injection site reactions	Enfuvirtide	**Onset:** first new doses **Symptoms:** pain, pruritus, erythema, ecchymosis, warmth, nodules, rarely injection site infection	All patients	Educate regarding use of sterile technique, solution at room temperature, rotation of injection sites, avoidance of sites with little subcutaneous fat or existing reactions	Massaging the area vigorously before and after injection may reduce pain; wear loose clothing around injection site areas; take warm shower or bath prior to injection; rarely, warm compact or analgesics may be necessary

CVD, cardiovascular disease; D/C, discontinue; DEXA, dual-energy x-ray absorptiometry; GI, gastrointestinal; HTN, hypertension; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TG, triglyceride.

infections. KEY CONCEPT The major outcome parameters are plasma HIV RNA, CD4 T-lymphocyte absolute count and percentage. Adequate virologic response in antiretroviral naïve patients is a 1-log decrease in plasma HIV RNA by 2 to 8 weeks after starting medications, followed by concentrations less than 50 copies/mL (50×10^3 copies/L) by 12 to 16 weeks based upon the assay available (if plasma HIV RNA < 100,000/mL [100×10^6/L] or by 16 to 24 weeks if plasma HIV RNA > 100,000/mL [100×10^6/L]). An immunologic response in antiretroviral naïve patients consists of an increase in CD4 cell count that averages 50 to 150 cells/mm^3 (50×10^6 to 150×10^6/L) during the first year of cART (with a faster response in the first 3 months). Virologic failure is defined as the inability to obtain or maintain a plasma HIV RNA less than 200 copies/mL (200×103 copies/L), whereas incomplete virologic response is defined as two consecutive plasma HIV RNA greater than 200 copies/mL (200×103 copies/L) after 24 weeks of therapy.

Upon initiating or changing antiretroviral therapy, plasma HIV RNA should be measured after 2 to 8 weeks and every 4 to 8 weeks until undetectable. Once the viral load is stable (eg undetectable), plasma HIV RNA is monitored generally every 3 to 6 months. In highly treatment-experienced patients, adequate immunologic response may be only a stable, or slightly increased, CD4$^+$ count and a stable HIV RNA. This may be enough to prevent clinical progression. However, with new agents available for treatment-experienced patients, the goal of treatment should be to reestablish maximal viral suppression to less than 20 to 75 plasma HIV RNA copies/mL (20 to 75×10^3 copies/L), depending on the assay used.[8]

There should be a plan for each patient to assess the effectiveness of antiretroviral therapy after initiation. Patients should have follow-up within the first week after initiating a new drug regimen. At each clinic visit, patients should be evaluated for the presence of adverse drug reactions, drug allergies, medication adherence, and potential drug interactions. Antiretrovirals have both class-associated and drug-specific adverse effects (see Table 87–4). If the patient experiences any of the serious, life-threatening effects (Table 87–5), the offending agent should be discontinued promptly, and in most cases the patient cannot be rechallenged. Potential long-term complications that may reduce the quality of life are listed in Table 87–6. If the patient does not tolerate a medication despite efforts to minimize or eliminate barriers to adherence, consider changing the drug.[8]

KEY CONCEPT Treatment of HIV is lifelong. Unplanned short-term treatment interruptions may be necessary due to illness that precludes administration of oral therapy. If a patient must interrupt therapy due to illness, all drugs of the regimen should be stopped at the same time, regardless of half-life. The strategy of scheduling elective treatment interruptions (where patients stop and start antiretroviral therapy based on CD4$^+$ T-cell count criteria) has been evaluated in several clinical trials. Viral rebound occurs quickly after stopping therapy and worsens immune function, causes clinical progression, and may even result in death. More information about treatment interruption can be found in the 2017 DHHS Guidelines.[8]

Patient Care Process: Newly Diagnosed

Collect Information:

- Confirm HIV infection, screen for additional sexually transmitted infections, and assess the risk for opportunistic infections and need for prophylaxis.
- Create a safe and comfortable environment to obtain a thorough medical and medication history (prescription, nonprescription, and natural drug product use). Review and update patient allergies.
- Acquire baseline laboratory data (see Table 87–1) to stage HIV disease and to assist in the selection of cART drug regimens (genotypic resistance testing, HLA-B*5701).

Assess the Information:

- Assess patient's readiness for initiating cART.
- Evaluate comorbid conditions (eg, mental illness, substance abuse) and social issues (economic stability, lack of social support, insurance coverage) that may impair medication adherence.
- Assess the potential for clinically significant drug–drug, drug–food, drug–disease interactions.

Develop a Care Plan:

- Utilize results of genotype in conjunction with patient specific factors to construct a recommended cART regimen.

Implement the Care Plan:

- Provide patient with basic information regarding HIV infection, progression of HIV/prognosis, treatment options, and support services available.
- Inform patient of the benefits of initiating cART, stressing the importance of 100% medication adherence.
- Educate patient on regimen-specific administration and common adverse drug effects (see Table 87–4). Warn patient of the key signs and symptoms of severe toxicity (ie, jaundice and abacavir hypersensitivity reaction [HSR]).
- Provide risk reduction counseling on effective strategies to prevent HIV transmission and disclosure to sexual and/or needle-sharing partners.

Follow-up: Monitor and Evaluate:

- Assess response to cART therapy by drawing plasma HIV RNA within 2 to 4 weeks (no later than 8 weeks) after initiation of cART and every 4 to 8 weeks until plasma HIV RNA is suppressed.
- Monitor immune reconstitution by measuring CD4 count 3 months after initiation of cART.
- Evaluate tolerability of regimen by assessing for adverse events and medication adherence.

Abbreviations Introduced in This Chapter

AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
cART	Combination antiretroviral therapy
CPK	Creatine phosphokinase
CVD	Cardiovascular disease
CYP	Cytochrome P-450 isoenzyme
D/C	Discontinue
DEXA	Dual-energy x-ray absorptiometry
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GERD	Gastroesophageal reflux disease
gp	Glycoprotein
HAART	Highly active antiretroviral therapy
HBeAg	Hepatitis B early antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
HTN	Hypertension
IAS-USA	International Antiviral Society–USA
INSTI	Integrase strand transfer inhibitor
LDL	Low-density lipoprotein
LFT	Liver function tests
MSM	Men who have sex with men
MTCT	Mother-to-child transmission
NAT	Nucleic acid test
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NtRTI	Nucleotide reverse transcriptase inhibitor
P-gp	P-glycoprotein
PCP	*Pneumocystis jiroveci* (formerly *carinii*) pneumonia
PI	Protease inhibitor
PrEP	Preexposure prophylaxis
PT	Prothrombin time
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
STD	Sexually transmitted disease
STI	Sexually transmitted infection
T.bili	Total bilirubin
TDF	Tenofovir disoproxil fumarate
TG	Triglyceride
ULN	Upper limit of normal

REFERENCES

1. Centers for Disease Control. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992;41(RR-17):1–19.
2. Global Health Observatory (GHO) data. World Health Organization. Available from: http://www.who.int/gho/hiv/epidemic_status/en/. Accessed August 19, 2017.
3. HIV surveillance report. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/hiv/statistics/overview/index.html. Accessed August 19, 2017.
4. Patel P, Borkowf CB, Brooks JT, et al. Estimating per-act HIV transmission risk: a systematic review. AIDS. 2014;28:1509.
5. Occupational HIV transmission and prevention among health care workers. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/hiv/pdf/workplace/cdc-hiv-healthcareworkers.pdf. Accessed August 19, 2017.
6. 2015 Progress Report on the Global Plan towards the elimination of new HIV infections among children and keeping their mothers alive. UNAIDS. Available from: http://www.unaids.org/sites/default/files/media_asset/JC2774_2015ProgressReport_GlobalPlan_en.pdf. Accessed August 19, 2017.
7. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006;55:1–17.
8. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Panel on Antiretroviral Guidelines for Adults and Adolescents. Department of Health and Human Services. Available from: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed December 17, 2017.
9. Fields-Gardner C, Campa A; America Dietetics Association. Position of the American Dietetic Association: Nutrition Intervention and Human Immunodeficiency Virus Infection. J Am Diet Assoc. 2010; 110(7):1105–1119.
10. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA panel. JAMA. 2016;316(2):191–210.
11. HIV resistance report, 2012. World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/75183/1/9789241503938_eng.pdf. Accessed December 17, 2017.
12. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Panel on Antiretroviral Therapy and Medical Management in HIV-infected Children. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf. Accessed August 16, 2017.
13. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health *and* interventions to reduce perinatal HIV transmission in the United States. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Available at: http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf. Accessed August 16, 2017.
14. Cohn SE, Watts D, Lertora J, Park JG, Yu S. Depo-medroxyprogesterone in women on antiretroviral thearpy: effective contraception and lack of clinically significant interactions. Clin Pharmacol Ther. 2007; 81:222–227.
15. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. N Engl J Med. 2007;356:1445–1454.
16. Recommendations for testing, managing, and treating hepatitis C. American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Available at: www.hcvguidelines.org. Accessed August 16, 2017.
17. Preexposure prophylaxis for the prevention of HIV infection in the United States, 2014 Clinical Practice Guideline. US Public Health Service. Available from: www.cdc.gov/hiv/pdf/prepguidelines2014.pdf. Accessed September 6, 2014.

88 Cancer Chemotherapy and Treatment

Lisa M. Holle

LEARNING OBJECTIVES

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

1. Describe the etiology of cancer.
2. Define the tumor, nodes, metastases (TNM) system of cancer staging.
3. Classify each drug used in the treatment of cancer and compare and contrast the mechanisms of action, uses, and adverse effects.
4. Outline actions for all health professionals to prevent medication errors with cancer treatments.
5. Discuss the impact that increased use of oral chemotherapy agents may have on oncology practice.
6. Describe what cancer survivorship means and how this impacts future health care needs of an individual.
7. Describe the role of health professionals in the care of cancer patients.

INTRODUCTION

KEY CONCEPT The word cancer covers a diverse array of tumor types that affect a significant number of Americans and individuals worldwide and are a major cause of mortality. The term cancer actually refers to more than 100 different diseases. What is common to all cancers is that the cancerous cell is uncontrollably growing and has the potential for invading local tissue and spreading to other parts of the body, a process called **metastases**. Cancer is the second leading cause of death behind heart disease.[1] In 2018, it was projected that nearly 1.8 million Americans will be diagnosed with cancer, and that an estimated 609,640 Americans will die from the cancer.[1] Figure 88–1 describes cancers by gender, new cases, and deaths.

Once diagnosed, a cancer patient may encounter many different health professionals. All health professionals need to collaborate to ensure safe and appropriate prescribing, preparation, administration, and monitoring of anticancer agents; management of toxicities; resolution of reimbursement issues; and participation in clinical trials. The pharmacist is a pivotal member of the care team because of their medication expertise.[2,3]

As a result of advances in research and technology, available cancer treatments have increased dramatically in the last couple of decades. The fields of radiation therapy, surgery, and drug development have made enormous progress over the years; therefore, patients may not only be receiving less toxic treatments but also treatments that have better outcomes than in the past. Supportive care therapies have improved, and patients now may be at less risk for toxicity and have a better **quality of life** than patients in the past. Twenty years ago, most patients received chemotherapy in the hospital because of side effects. Today, most patients are able to receive chemotherapy in the outpatient clinics and/or take oral anticancer agents at home.

Cancer Prevention

Because most cancers are not curable in advanced stages, cancer prevention is an important and active area of research. Both lifestyle modifications and chemoprevention agents may significantly reduce the risk of developing cancer. Although still an active area of investigation, the Food and Drug Administration (FDA) has approved vaccines that can help prevent cancer. Available vaccines include those that prevent infection with human papillomavirus (HPV), responsible for many cancers of the cervix, vulva, vagina, and anus and a vaccine that prevents hepatitis B viral infections, which can cause liver cancer. Additionally, orally administered medications, such as the selective estrogen receptor modulator (SERM) tamoxifen, reduces the risk of breast cancer in premenopausal women. Another SERM, raloxifene and the aromatase inhibitor (AI) exemestane both have shown a reduction in breast cancer in high-risk postmenopausal women. Because these agents will have adverse effects and possible long-term complications (eg, an increased risk of endometrial cancer with the use of tamoxifen), benefits versus risks needs to be weighed when making a recommendation.

Tobacco

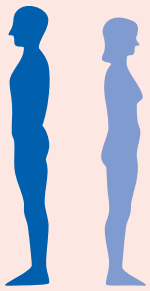
Tobacco smoking increases the risk of developing not only lung cancer but also many other types of cancer, including cancer of the bladder, mouth, pharynx, larynx, and esophagus as well as kidney cancer. Smoking cessation is associated with a gradual decrease in the risk of cancer, but more than 5 years is needed before a major decline in risk is detected. In addition, most studies have found that passive smoking (ie, secondhand smoke) also increases a person's risk of developing lung cancer.[4]

Ultraviolet Radiation

Ultraviolet light (sunlight or tanning booths and lamps) and increased skin exposure may increase the risk of melanoma and

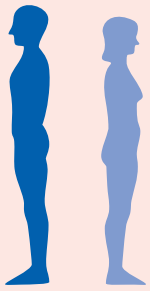
Estimated New Cases

Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All sites	**856,370**	**100%**	**All sites**	**878,980**	**100%**



Estimated Deaths

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	**323,630**	**100%**	**All sites**	**286,010**	**100%**



Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from the most recent observed data.

FIGURE 88–1. Cancer incidences (*top*) and deaths (*bottom*) in the United States for males and females—2018 estimates. (Reproduced, with permission, from American Cancer Society. Cancer Facts and Figures 2018. Atlanta, GA: American Cancer Society, Inc.)

other skin cancers, especially in individuals who have a positive family history, fair skin, light-colored eyes, high degrees of freckling, and a tendency to burn instead of tan. Practitioners can counsel patients on proper sun protection, including minimizing sun exposure, using sunscreens with a sun protection factor (SPF) of 15 or greater on exposed areas, wearing protective clothing and sunglasses, avoiding tanning beds and sun lamps, and the importance of early detection.

CARCINOGENESIS

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The exact cause of cancer remains unknown and is probably very diverse given the vast array of diseases called cancer. It is thought that cancer develops from a single cell in which the normal mechanisms for control of growth and proliferation are altered. Current evidence indicates that there are four stages in the cancer development process. The first step, initiation, occurs when a carcinogenic substance encounters a normal cell to produce genetic damage and results in a mutated cell. The environment is altered by carcinogens or other factors to favor the growth of the mutated cell over the normal cell during promotion, the second step. The main difference between initiation and promotion is that promotion is a reversible process. Third, transformation (or conversion) occurs when the mutated cell becomes malignant. Depending on the type of cancer, up to 20 years may elapse between the carcinogenic phases and the development of a clinically detectable tumor. Finally, progression occurs when cell proliferation takes over and the tumor spreads or develops metastases.

There are substances known to have carcinogenic risks, including chemicals, environmental factors, and viruses. Chemicals in the environment, such as aniline and benzene, are associated with the development of bladder cancer and leukemia, respectively. Environmental factors, such as excessive sun exposure, can result in skin cancer, and smoking is widely known as a cause of lung cancer. Viruses, including HPV, Epstein-Barr virus, and hepatitis B virus, have been linked to cervical cancers, lymphomas, and liver cancers, respectively. Anticancer agents such as the alkylating agents (eg, melphalan), anthracyclines (eg, doxorubicin), and epipodophyllotoxins (eg, etoposide) can cause secondary malignancies (eg, leukemias) years after therapy has been completed. Additionally, factors such as the patient's age, gender, family history, diet, and chronic irritation or inflammation may be considered to be promoters of carcinogenesis.

Cancer Genetics

Because the human genome has been sequenced and with the great improvements in genetic technology, growing knowledge regarding the genetic changes of cancer exist. Two major classes of genes are involved in carcinogenesis: **oncogenes** and **tumor suppressor genes**. **Protooncogenes** are normal genes that, through some genetic alteration caused by carcinogens, change into oncogenes. Protooncogenes are present in all normal cells and regulate cell function and replication. Genetic damage of the protooncogene may occur through point mutation, chromosomal rearrangement, or an increase in gene function, resulting in the oncogene. The genetic damage may either be inherited from an individual's parents (germline mutations) or by way of carcinogenic agents (eg, smoking). The oncogene produces abnormal or excessive gene product that disrupts normal cell growth and proliferation.[5] As a result, this may cause the cell to have a distinct growth advantage, increasing its likelihood of becoming cancerous. Table 88–1 provides examples of oncogenes by their cellular function and associated cancer.[6]

Table 88–1

Examples of Oncogenes and Tumor Suppressor Genes

Gene	Function	Associated Human Cancer
Oncogenes		
Genes for growth factors or their receptors		
EGFR or Erb-B1	Codes for epidermal growth factor (EGFR) receptor	Glioblastoma, breast, head and neck, and colon cancers
HER-2/neu or Erb-B2	Codes for a growth factor receptor	Breast, salivary gland, prostate, bladder, and ovarian cancers
RET	Codes for a growth factor receptor	Thyroid cancer
Genes for cytoplasmic relays in stimulatory signaling pathways		
K-RAS and N-RAS	Code for guanine nucleotide-proteins with GTPase activity	Lung, ovarian, colon, pancreatic cancers Neuroblastoma, acute leukemia
Genes for transcription factors that activate growth-promoting genes		
c-MYC	Codes for transcription factor	Leukemia and breast, colon, gastric, and lung cancers
N-MYC	Codes for transcription factor	Neuroblastoma, small cell lung cancer, and glioblastoma
Genes for cytoplasmic kinases		
BCR-ABL	Codes for a nonreceptor tyrosine kinase	Chronic myelogenous leukemia
ALK	Receptor tyrosine kinase	Lung cancer, lymphomas, neuroblastoma, and ovarian cancer
BRAF	Serine-threonine protein kinase	Colon cancer, lung cancer, melanoma, ovarian, thyroid cancer
KIT (CD117)	Receptor tyrosine kinase	Acute Leukemia, gastrointestinal, stromal tumor, and gastrointestinal stromal tumor
PIK2CA	Lipid kinases	Lung cancer, ovarian cancer
RET	Codes a receptor tyrosine kinase	Lung cancer, thyroid cancer
Genes for other molecules		
BCL-2	Codes for a protein that blocks apoptosis	Indolent B-cell lymphomas
BCL-1 or PRAD1	Codes for cyclin D_1, a cell-cycle clock stimulator	Breast, head, and neck cancers
MDM2	Protein antagonist of p53 tumor suppressor protein	Sarcomas
Tumor-Suppressor Genes		
Genes for proteins in the cytoplasm		
APC	Step in a signaling pathway	Colon and gastric cancer
NF-1	Codes for a protein that inhibits the stimulatory Ras protein	Neurofibroma, leukemia, and pheochromocytoma
NF-2	Codes for a protein that inhibits the stimulatory Ras protein	Meningioma, ependymoma, and schwannoma
Genes for proteins in the nucleus		
MTS1	Codes for p16 protein, a cyclin-dependent kinase inhibitor	Involved in a wide range of cancers
RB1	Codes for the pRB protein, a master brake of the cell cycle	Retinoblastoma, osteosarcoma, and bladder, small cell lung, prostate, and breast cancers
TP53	Codes for the p53 protein, which can halt cell division and induce apoptosis	Involved in a wide range of cancers
PTEN	Phosphatase and tensin homolog deleted on chromosome ten	Lung cancer, ovarian cancer
Genes for protein whose cellular location is unclear		
BRCA1	DNA repair, transcriptional regulation	Breast and ovarian cancers
BRCA2	DNA repair	Breast cancer
VHL	Regulator of protein stability	Kidney cancer
MSH2, MLH1, PMS1, PMS2, MSH6	DNA mismatch repair enzymes	Hereditary nonpolyposis colorectal cancer

From Kiel PJ, Fausel CA. Chronic Leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al. (eds). Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2017: Table 135–2.

Tumor suppressor genes inhibit inappropriate cellular growth and proliferation by gene loss or mutation. This results in loss of control over normal cell growth. The *TP53* gene is one of the most common tumor suppressor genes, and mutations of *TP53* may occur in up to 50% of all malignancies. This gene stops the cell cycle to enable "repairs" of the cell. If *TP53* is inactivated, then the cell allows the mutations to occur. Although mutations of the *TP53* gene are found in many tumors, such as breast, colon, and lung cancer, it is also associated with drug resistance of cancer cells. Deoxyribonucleic acid (DNA) repair genes fix errors in DNA that occur because of environmental factors or errors in replication and can be classified as tumor suppressor genes. Mutations in DNA repair genes have been reported in hereditary nonpolyposis colon cancer and in some breast cancer syndromes.

KEY CONCEPT Numerous cellular changes occur in the genetic material of the cancer cell so that programmed cell death (PD), or apoptosis, does not occur. Proliferation of cancer cells goes unregulated. If mutations persist and cells are not repaired or suppressed, cancer may develop. **Apoptosis**, or PD, may prevent the mutated cell from becoming cancerous. Loss of *TP53* and

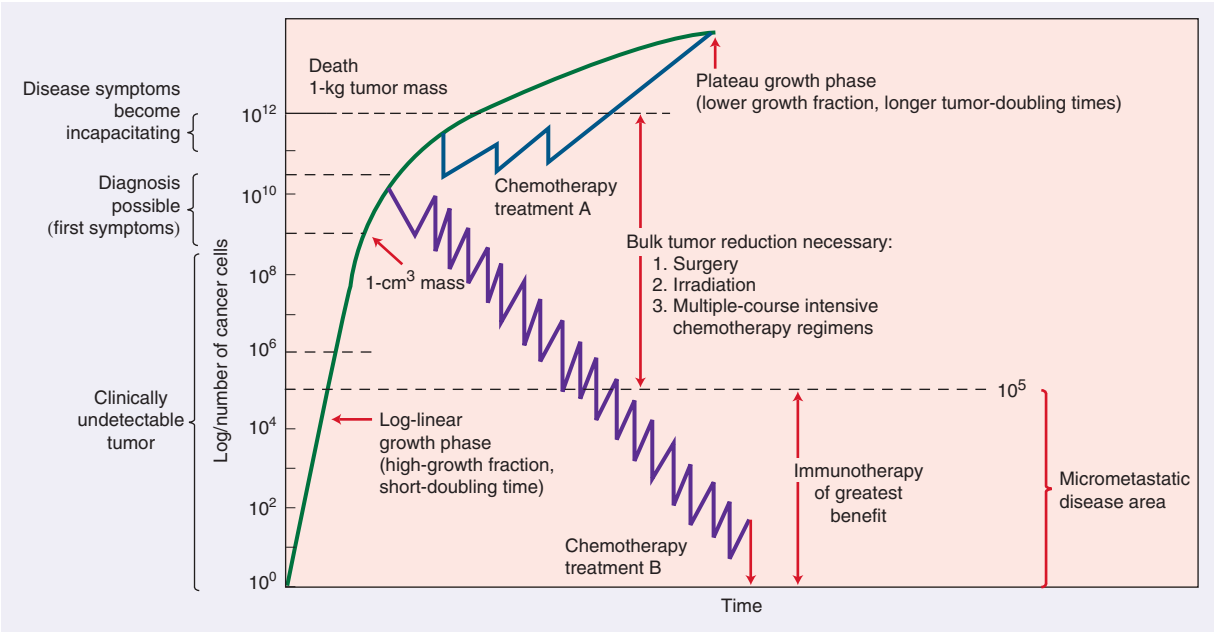

FIGURE 88–2. The Gompertzian growth curve demonstrating symptoms and treatments versus tumor volume.

overexpression of *Bcl-2* are two examples of changes within the cell that occur to result in enhanced cell survival. Cellular senescence refers to cell death that occurs after a preset number of cell doublings. Telomeres are DNA segments at the ends of chromosomes that shorten with each replication to the point where senescence is triggered.

Identification of genes involved in cancer may be conducted for various reasons, including cancer screening to determine if an individual is at an increased risk of cancer, to develop new anticancer agents, to aid in diagnosis, and to predict response and/or the toxicity of the agents used in individual patients.

Principles of Tumor Growth

It takes about 10^9 cancer cells to be clinically detectable by palpation or radiography. Figure 88–2 demonstrates the classic Gompertzian kinetics tumor growth cycle. From the diagram, one can see that malignant cell growth occurs many times before a mass may be detected. The number of malignant cells may decrease drastically because of surgery or in decreasing steps by each administration of chemotherapy. One dosing round, or cycle, of chemotherapy does not eliminate all malignant cells; therefore, repeated cycles of chemotherapy are administered to eliminate tumor cell burden. The cell kill hypothesis states that a fixed percentage of tumor cells will be killed with each cycle of chemotherapy. According to this hypothesis, the number of tumor cells will never reach zero. This theory assumes that all cancers are equally responsive and that anticancer drug resistance and metastases do not occur, which is not the case.[7]

Metastases

A metastasis is a growth of the same cancer cell found at some distance from the primary tumor site.[8] The metastasis may be large, or it may be just a few cells that may be detected through polymerase chain reaction (PCR); however, the presence of metastasis at diagnosis usually is associated with a poorer prognosis than the patient with no known metastatic disease. As the technology to detect malignant cells evolves, the dilemma exists on how to treat patients based on current guidelines that were not based on cellular detection technology.

Cancers spread usually by two pathways: hematogenous (through the bloodstream) or through the lymphatics (drainage through adjacent lymph nodes). The malignant cells that split from the primary tumor find a suitable environment for growth. It is believed that malignant cells secrete mediators that stimulate the formation of blood vessels for growth and oxygen, the process of angiogenesis. The usual metastatic sites for solid tumors are the brain, bone, lung, and liver.

PATHOPHYSIOLOGY

Tumor Origin

Tumors may arise from the four basic tissue types: epithelial, connective (ie, muscle, bone, and cartilage), lymphoid, or nerve tissue. The suffix *-oma* is added to the name of the cell type if the tumor cells are benign. A *lipoma* is a benign growth that resembles fat tissue.

Precancerous cells have cellular changes that are abnormal but not yet malignant and may be described as *hyperplastic* or *dysplastic*. Hyperplasia occurs when a stimulus is introduced and reverses when the stimulus is removed. Dysplasia is an abnormal change in the size, shape, or organization of cells or tissues.

Malignant cells are divided into categories based on the cells of origin. Carcinomas arise from epithelial cells, whereas sarcomas arise from muscle or connective tissue. Adenocarcinomas arise from glandular tissue. *Carcinoma* in situ refers to cells limited to epithelial origin that have not yet invaded the basement membrane. Malignancies of the bone marrow or lymphoid tissue, such as leukemias or lymphomas, are named differently.

Tumor Characteristics

Tumors are either benign or malignant. Benign tumors often are encapsulated, localized, and indolent; they seldom metastasize; and they rarely recur once removed. Histologically, the cells

resemble the cells from which they developed. Malignant tumors are invasive and spread to other locations even if the primary tumor is removed. The cells no longer perform their usual functions, and their cellular architecture changes. This loss of structure and function is called *anaplasia.* Despite improvements in screening procedures, many patients have metastatic disease at the time of diagnosis. Usually, once distant metastases have occurred, the cancer is considered incurable.[9]

DIAGNOSIS OF CANCER

Cancer can present as a number of different signs and symptoms. Unfortunately, many people fear a diagnosis of cancer and may not seek medical attention at the first warning signs when the disease is at its most treatable stage. After the initial visit with the clinician, a variety of tests will be performed, which are somewhat dependent on the initial differential diagnoses. Appropriate laboratory tests, radiologic scans, and tissue samples are necessary. The sample of tissue may be obtained by a biopsy, fine-needle aspiration, or exfoliative cytology. No treatment of cancer should be initiated without a pathologic diagnosis of cancer. During the pathologic workup, genetic analysis may be done. Depending on the type of cancer, the genetic analysis can provide the additional information on prognosis of the malignancy and whether certain therapies may be appropriate.

LO 2

Once the pathology of cancer is established, then staging of the disease is done before treatment is initiated. Cancer staging is usually done according to the primary tumor size, extent of lymph node involvement, and the presence or absence of metastases, also referred to as the tumor, nodes, metastases (TNM) system (Table 88–2).[10] The stage of the disease is a compilation of the primary tumor size, the nodal involvement, and metastases and is usually referred to as stages I, II, III, or IV. Not all cancers can be staged according to this system, but many of the solid tumors are.

Patient Encounter 1, Part 1

The patient is a 67-year-old previously healthy woman who has had symptoms of fatigue, diarrhea and bright red blood with bowel movements for 6 weeks. She has self-treated with dietary changes, occasional use of loperamide, and anti-hemorrhoidal over-the-counter products without relief. Today, she presents to her primary care provider for evaluation. Her complete blood count (CBC) reveals a low hemoglobin level. She is referred to a gastroenterologist for further evaluation.

After a colonoscopy and subsequent CT scans, a diagnosis of metastatic colorectal cancer is made and treatment is planned to start as soon as possible.

What signs and symptoms does this patient have that are consistent with a cancer presentation?

What is your desired outcome when treating this patient?

Staging of the disease is an important part of determining the prognosis of the cancer. Staging also allows comparison of patient groups when examining data from clinical trials; staging reflects the extent of disease. Finally, the clinician uses it as a guide to treatment and may use restaging after treatment to guide further treatment.

Some cancers produce substances (eg, proteins) that are detected by a blood test, that may be useful in following response to therapy or detecting a recurrence; these are referred to as tumor markers. An example of a clinically used tumor marker is the prostate-specific antigen (PSA). The PSA serum level is used to monitor response to treatment. Unfortunately, some tumor markers are nonspecific and may be elevated from nonmalignant causes. In the case of

Clinical Presentation and Diagnosis: Cancer Chemotherapy and Treatment

Signs and Symptoms

The seven warning signs of cancer are:

- Change in bowel or bladder habits
- A sore that does not heal
- Unusual bleeding or discharge
- Thickening or lump in breast or elsewhere
- Indigestion or difficulty in swallowing
- Obvious change in a wart or mole
- Nagging cough or hoarseness

The eight warning signs of cancer in children are:

- Continued, unexplained weight loss
- Headaches with vomiting in the morning
- Increased swelling or persistent pain in bones or joints
- Lump or mass in abdomen, neck, or elsewhere
- Development of a whitish appearance in the pupil of the eye
- Recurrent fevers not caused by infections
- Excessive bruising or bleeding
- Noticeable paleness or prolonged tiredness

Diagnostic Procedures

- Laboratory tests: CBC, lactate dehydrogenase (LDH), renal function, and liver function tests
- Radiologic scans: x-rays, CT scans, MRI, position emission tomography (PET)
- Biopsy of tissue or bone marrow with pathologic evaluation
- Cytogenetics
- Tumor markers

Staging determination of the primary tumor size, extent of lymph node involvement, and the presence or absence of metastases, referred to as the TNM system (see Table 88–2). Most solid tumors are staged according to the TNM classification system. The size of the primary tumor, extent of nodal involvement, and presence of metastases are used to determine the stage. Metastases are cancer cells that have spread to sites distant from the primary tumor site and have started to grow. The most frequently occurring sites of metastases of solid tumors are the brain, bone, liver, and lungs.

Table 88–2

Tumor (T), Node (N), Metastasis (M) Staging for Non–Small Cell Lung Cancer

Primary Tumor	Description
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T_1	Tumor under 3 cm in greatest dimension, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
T_{1a} (mi)	Minimally invasive adenocarcinoma
T_{1a} ss:	Superficial spreading tumor in central airways (spreading tumor of any size but confined to the tracheal or bronchial wall)
T_{1a}	Tumor ≥ 1 cm in greatest dimension
T_{1b}	Tumor > 1 cm but ≤ 2 cm in greatest dimension
T_{1c}	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T_2	Tumor > 3 cm but ≤ 5 cm, or tumor with any of the following features: • Involves main bronchus regardless of distance from the carina but without involvement of the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung • Involving part or all of the lung
T_{2a}	Tumor > 3 cm but ≤ 4 cm in greatest dimension
T_{2b}	Tumor > 4 cm but ≤ 5 cm in greatest dimension
T_3	Tumor > 5 cm but ≤ 7 cm in greatest dimension of associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: • chest wall (including the parietal pleura and superior sulcus) • phrenic nerve • parietal pericardium
T_4	Tumor > 7cm in greatest dimension or associated with separate tumor nodules(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures • diaphragm • mediastinum • heart • great vessels • trachea • recurrent laryngeal nerve • oesophagus • vertebral body • carina
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed.
N_0	No regional lymph node metastases
N_1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N_2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N_3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant metastasis (M)	
M_0	No distant metastasis
M_1	Distant metastasis
M_{1a}	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion
M_{1b}	Single extrathoracic metastasis
M_{1c}	Multiple extrathoracic metastasis in one or more organs

Stage	T	N	M	5-Year Survival
Stage 0	Tis	N_0	M_0	
Stage Ia	T_{1a}	N_0	M_0	92%
Stage Ib	T_{2a}	N_0	M_0	68%
Stage IIa	T_{2b}	N_0	M_0	60%
Stage IIb	T_1, T_2	N_1	M_0	53%
	T_3	N_0	M_0	
Stage IIIa	T_1, T_2	N_2	M_0	36%
	T_3, T_4	N_1	M_0	
	T_4	N_0	M_0	
Stage IIIb	T_1, T_2	N_3	M_0	26%
	T_3, T_4	N_2	M_0	
Stage IIIc	T_3, T_4	N_3	M_0	13%
Stage IVa	Any T	Any N	M_{1a} or M_{1b}	10%
Stage IVb	Any T	Any N	M_{1c}	0%

From Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1):193–203.

PSA, nonmalignant causes such as prostatitis, trauma, surgery, ejaculation, some medications, benign prostatic hypertrophy, or riding on an exercise bicycle can all cause increased PSA levels.[9] Some tumors may express a marker in some patients and not in others. The full role of tumor markers has not been fully elucidated.

TREATMENT

Desired Outcome

Surgery may be able to remove all macroscopic disease; however, microscopic cells may still be present near the surgical site or may have traveled to other parts of the body. When malignant cells have traveled to other parts of the body and become established there and are able to grow in this new environment, they are called metastatic cancer cells. Thus, for chemotherapy-sensitive diseases, systemic therapies may be administered after surgery to destroy these microscopic malignant cells; this is called **adjuvant chemotherapy**. The goals of adjuvant chemotherapy are to decrease the recurrence by eliminating microscopic malignant cells of the cancer and to prolong survival. Chemotherapy may also be given before surgical resection of the tumor; this is referred to as **neoadjuvant chemotherapy**. Chemotherapy given before surgery should decrease the tumor burden to be removed (which may result in a shorter surgical procedure or less physical disfigurement to the patient) and make the surgery easier to perform because the tumor has shrunk away from vital organs or vessels. Neoadjuvant chemotherapy also gives the clinician an idea of the responsiveness of the tumor to that particular chemotherapy.

Chemotherapy may be given to cure cancers, or it may be given to help control the symptoms of an incurable cancer (also known as palliation). **Palliative care**, however, is used throughout therapy to prevent or treat, as early as possible, the symptoms and side effects of the disease and treatment psychological, social, and spiritual problems. It will consist of pharmacologic and nonpharmacologic treatments and is most effective when initiated at the time of other treatments, improving quality of life.[11]

Response

The responses to chemotherapy for solid tumors are described as **complete response (CR)**, **partial response (PR)**, **stable disease (SD)**, or **disease progression**. A cure in oncology implies that the cancer is completely gone, and the patient will have the same life expectancy as a patient without cancer. The Response Evaluation Criteria in Solid Tumors (RECIST) was developed in 2000 and revised in 2009 and is considered to be the standard criteria to evaluate a response to therapy (**Table 88–3**).[12] The term overall objective response rate refers to all patients with a PR or a CR.

Anticancer treatments can be thought of as being analogous to anti-infectives treatments. Cancer cells may be **sensitive** to certain chemotherapy agents, but then with repeated exposure, the cells may become **resistant** to treatment. The resistant cells then may grow and multiply. In some cancers a number of genetic mutations, including epidermal growth factor *(EGFR)*, reticular activating system (*RAS*), and *BRAF* may be used to predict which patients will be sensitive to certain chemotherapy that targets these mutations. These mutations will be discussed in depth in the following cancer-specific chapters.

Nonpharmacologic Therapy

The three primary treatment modalities of cancer are surgery, radiation, and pharmacologic therapy. Surgery is useful to gain tissue for diagnosis of cancer and for treatment, especially those cancers with limited disease. Radiation plays a key role not only in the treatment and possible cure of cancer but also in palliative therapy. Together, surgery and radiation therapy may provide local control of symptoms of the disease. However, when cancer is widespread, surgery may play little or no role, but radiation therapy localized to specific areas may palliate symptoms.

Table 88–3

RECIST 1.1 Criteria: Target Lesion Evalusion

Term	Description
Complete response (CR)	Disappearance of all targeted lesion. All pathological lymph nodes must have decreased to < 10 mm in short axis
Partial response (PR)	At least a 30% decrease in the sum of the longest diameter (SLD) of target lesions from baseline
Progressive disease	SLD increased by at least 20% from the smallest value on study (including baseline, if that is the smallest) The SLD must also demonstrate an absolute increase of at least 5 mm. (Two lesions increasing from 2 mm to 3 mm, for example, do not qualify)
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease

Adapted from Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–247.

Pharmacologic Therapy

Chemotherapy of cancer started in the early 1940s when nitrogen mustard was first administered to patients with lymphoma. Since then, numerous agents have been developed for the treatment of different cancers.

Dosing of Chemotherapy

Chemotherapeutic agents typically have a very narrow therapeutic index. If too much is administered, the patient may suffer from fatal toxicities. If too little is given, the desired effect on cancer cells may not be achieved. Many chemotherapy agents have significant organ toxicities that preclude using steadily increasing doses to treat the cancer. The doses of chemotherapy must be given at a frequency that allows the patient to recover from the toxicity of the chemotherapy; each period of chemotherapy dosing is referred to as a cycle. Each cycle of chemotherapy may have the same dosages; the dosages may be modified based on toxicity; or a chemotherapy regimen may alternate from one set of drugs given during the first, third, and fifth cycles to another set of different drugs given during the second, fourth, and sixth cycles. The **dose density** of chemotherapy refers to shortening of the period between cycles of chemotherapy. This can accomplish two things: First, the tumor has less time between cycles of chemotherapy to grow, and second, patients receive the total number of required cycles in a shorter time period. Administration of dose-dense chemotherapy regimens often requires the use of colony-stimulating factors (eg, filgrastim or granulocyte–colony stimulating factor [G-CSF]) to be administered. These agents shorten the duration and severity

of neutropenia. The chemotherapy regimens that are dose dense tend to be adjuvant regimens, and the goal of therapy is cure.

When a chemotherapy regimen is used as *palliation* (to control symptoms), the dosages of chemotherapy may be decreased based on toxicity or the interval between cycles may be lengthened to maintain quality of life.

Patient and tumor biology also affect how cancer therapy is dosed. Patients with a uridine diphosphate–glucuronosyltransferease 1A1 enzyme (UGT1A1* 28) deficiency can have life-threatening diarrhea and complications from irinotecan related to a decreased ability to metabolize the parent drug. The patient may have a blood test before irinotecan therapy to determine if this genetic mutation is present. In the case of some monoclonal antibodies and targeted agents, flow cytometry results reveal whether the tumor has the receptor where the drug will bind and exert the pharmacologic effect.[13] The therapeutic uses of oncology drugs with valid genomic biomarkers, called targeted therapies, will be discussed briefly in this chapter and in more detail in the following chapters.

Another consideration of chemotherapy administration is the patient. Factors that affect chemotherapy selection and dosing are age, concurrent disease states, and performance status. Performance status can be assessed through either the Eastern Cooperative Oncology Group (ECOG) Scale or the Karnofsky Scale (Table 88–4). Performance status is a very important prognostic factor for many types of cancer. If a patient has renal dysfunction and the chemotherapy is eliminated primarily by the kidney, dosing adjustments will need to be made. If a patient has had a myocardial infarction recently or preexisting heart disease, the clinician will weigh the risks of anthracycline therapy against the benefit of the treatment of the cancer.

Another important consideration for treatment of cancers is insurance coverage for off-label use. Off-label use is when a medication is used to treat a cancer that is not an FDA-approved indication. Because of rapid advancements in oncology, it is estimated that up to 75% of chemotherapy agents are prescribed "off-label." Drugs used according to FDA-approved indications are usually paid for by insurance. If sufficient supportive literature exists and the use is supported by one of the Medicare-approved compendia (eg, AHFS-DI, Clinical Pharmacology, Micromdex DrugDex, NCCN Compendium, others), an insurer should cover the cost of the anticancer treatment that does not have an FDA indication.

During the time of chemotherapy administration, patients will likely experience various toxicities. The National Cancer Institute (NCI) has provided a standardized system for evaluating and grading the toxicity from chemotherapy to provide uniform grading of toxicity and evaluation of new agents and new regimens (Table 88–5).[14]

Combination Chemotherapy

The underlying principles of using combination therapy are to use (1) agents with different pharmacologic actions, (2) agents with different organ toxicities, (3) agents that are active against the tumor and ideally synergistic when used together, and (4) agents that do not result in significant drug interactions (although these can be studied carefully and the interactions addressed). When two or more agents are used together, the risk of development of resistance may be lessened, but toxicity may be increased.

KEY CONCEPT Traditional chemotherapy agents have some similar side effects, usually manifested on the most rapidly proliferating cells of the body. However, there are unique toxicities of various pharmacologic categories of antineoplastic agents. Anthracyclines (eg, doxorubicin) have the potential to cause cardiac toxicity, which is related to the cumulative dose. Microtubule-targeting

Table 88–4

Performance Status Scales

Description: Karnofsky Scale	Karnofsky Scale (%)	Zubrod Scale (ECOG)	Description: ECOG Scale
No complaints; no evidence of disease	100	0	Fully active, able to carry on all predisease activity
Able to carry on normal activity; minor signs or symptoms of disease	90		
Normal activity with effort; some signs or symptoms of disease	80	1	Restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
Cares for self; unable to carry on normal activity or to do active work	70		
Requires occasional assistance but is able to care for most personal needs	60	2	Out of bed > 50% of time; ambulatory and capable of self-care but unable to carry out any work activities
Requires considerable assistance and frequent medical care	50		
Disabled; requires special care and assistance	40	3	In bed > 50% of time; capable of only limited self-care
Severely disabled; hospitalization indicated, although death not imminent	30		
Very sick; hospitalization necessary; requires active supportive treatment	20	4	Bedridden; cannot carry out any self-care; completely disabled
Moribund; fatal processes progressing rapidly	10		
Dead	0	5	Dead

ECOG, Eastern Cooperative Oncology Group.

Table 88–5

Selected National Cancer Institute Common Toxicity Criteria

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General	Mild	Moderate	Severe	Life-threatening	Death
Neutropenia	Lowest baseline: 1500/mm^3 (1.5 × 10^9/L)	< 1500–1000/mm^3 (1.5–1 × 10^9/L)	< 1000–500/mm^3 (1–0.5 × 10^9/L)	< 500/mm^3 (0.5 × 10^9/L)	
Thrombocytopenia	Lowest baseline: 75,000/mm^3 (75 × 10^9/L)	< 75,000–50,000/mm^3 (75–50 × 10^9/L)	< 50,000–25,000/mm^3 (50–25 × 10^9/L)	< 25,000 mm^3 (25 × 10^9/L)	Death
Diarrhea	Increase of < four stools per day over baseline or mild increase in ostomy output compared to baseline	Increase of four to six stools per day over baseline; moderate increase in ostomy output compared with baseline; limiting ADLs	Increase of greater than or equal to seven stools per day over baseline; hospitalization; severe increase in ostomy output compared with baseline; limiting self care ADL	Life-threatening consequences (eg, hemodynamic collapse); urgent intervention indicated	Death
Esophagitis	Asymptomatic clinical or diagnostic only. Intervention not indicated	Symptomatic altered eating or swallowing. Oral supplements indicated	Severely altered eating or swallowing; tube feedings, or TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feedings, TPN or hospitalization indicated > 24 hours	Life-threatening consequences	Death
Vomiting	One to two episodes (separated by 5 minutes) in 24 hours	Three to five episodes in 24 hours; IV fluids indicated < 24 hours	Six episodes or more in 24 hours; IV fluids, tube feeding or TPN indicated ≥ 24 hours	Life-threatening consequences; urgent intervention indicated	Death

ADL, activity of daily living; IV, intravenous; TPN, total parenteral nutrition.

Protocol Development | CTEP. Cancer Therapy Evaluation Program (CTEP). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Accessed July 20, 2018.

agents (eg, vincristine) are associated with various forms of neurotoxicity. Alkylating agents (eg, melphalan) are associated with secondary malignancies.

Currently, anticancer agents are categorized by the mechanism of action. As depicted in Figure 88–3, different agents work in different parts of the cell.[15]

Table 88–6 lists the currently FDA-approved anticancer drugs by drug class and name. The next section will describe the most commonly used anticancer agents or those with unique mechanisms of action.

LO 3

Antimetabolites: Pyrimidine Analogues

► *Fluorouracil and Capecitabine*

5-Fluorouracil (5-FU) is a fluorinated analogue of the pyrimidine uracil. Once administered, this prodrug is metabolized by dihydropyrimidine dehydrogenase (DPD). 5-FU ultimately is metabolized to fluorodeoxyuridine monophosphate (FdUMP), which interferes with the function of thymidylate synthase (TS), a requirement of thymidine synthesis. The triphosphate metabolite of 5-FU is incorporated into ribonucleic acid (RNA) to produce the second cytotoxic effect. Inhibition of TS occurs with the continuous infusion regimens, whereas the triphosphate form is associated with bolus administration. Capecitabine is an orally active prodrug of 5-FU and is enzymatically converted to 5-FU, sharing the same mechanism of action. Patients with a low activity of DPD appear to be at risk for life-threatening toxicities. Folates, such as leucovorin, increase the stability of FdUMP–TS

Patient Encounter 1, Part 2

The decision to treat the patient with a systemic chemotherapy regimen is made. She will be receiving the standard mFOLFOX6 regimen of fluorouracil 400 mg/m^2/day IV bolus followed by 1200 mg/m^2/day continuous IV infusion over 46 hours + leucovorin 400 mg/m^2/day IV + oxaliplatin 85 mg/m^2/day IV every day every 2 weeks.

Before initiating this chemotherapy regimen in the patient, what patient-specific issues need to be addressed?

What adverse effects will the patient likely experience with these two chemotherapy drugs?

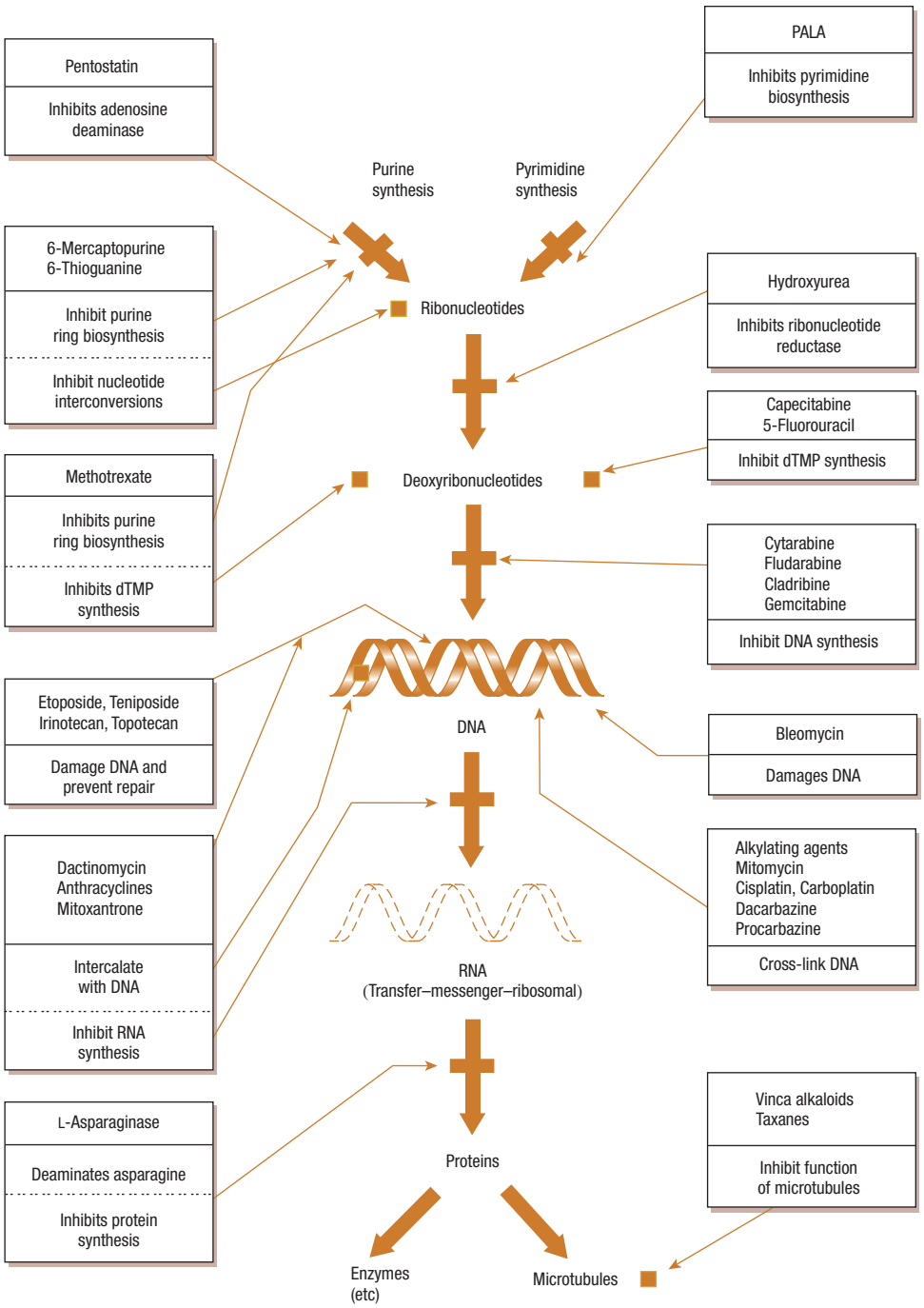

FIGURE 88–3. The mechanisms of action of commonly used antineoplastic agents. (Reproduced with permission from Chabner BA. General Principles of Chemotherapy. In: Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 12th ed. New York, NY: McGraw-Hill, 2010.)

inhibition and enhance the drug activity in certain cancers. These agents have clinical activity in several solid tumors, and are frequently used to treat both breast and colon cancer. The most common toxicities include myelosuppression when administered by intravenous (IV) bolus and palmar-plantar erythrodysesthesia, and diarrhea, when administered as continuous IV infusion or orally. Palmar-plantar erythrodysesthesia, also called hand–foot syndrome (HFS), refers to redness, itching, and blistering of the palms of the hands and soles of the feet. Patients should be counseled to notify the prescriber when this adverse effect occurs. Significant increases in international normalization ratio (INR) and prothrombin time may occur within several days when capecitabine is initiated in patients concomitantly receiving warfarin. The INR should be monitored closely or the patient may be switched to a low-molecular-weight heparin. Other drug interactions can also occur. Patients should be instructed to take capecitabine within 30 minutes after a meal to increase absorption of the drug.

► *Cytarabine*

Cytarabine is a structural analogue of cytosine and is phosphorylated intracellularly to the active triphosphate form,

Table 88–6

Anticancer Drugs

Drug Class	Drug Name
Alkylating agents	
Alkyl sulfonate	Busulfan
Nitrogen mustards	Bendamustine
	Chlorambucil
	Cyclophosphamide
	Ifosfamide
	Melphalan
	Methchlorethamine
Nitrosureas	Carmustine
	Lomustine
Nonclassical	Mitomycin C
	Thiotepa
	Trabectedin
Platinum complexes	Carboplatin
	Cisplatin
	Oxaliplatin
Triazenes and hydrazine	Dacarbazine
	Procarbazine
	Temozolomide
Anthracene derivatives	Daunorubicin
	Doxorubicin
	Epirubicin
	Idarubicin
	Mitoxantrone
Antitumor antibiotics	Bleomycin
Antimetabolites	
Folate Antagonists	Methotrextae
	Pemetrexed
	Pralatrexate
Purine analogs	Cladribine
	Clofarabine
	Fludarabine
	6-Mercaptopurine
	Pentostatin
	Thioguanine
Pyrimidine analogs	Acazacitidine
	Capecitabine
	Cytarabine
	Decetabine
	5-Fluorouracil
	Gemcitabine
	Nelarabine
	Trifluridine/(tipiracil)[a]
Hedgehog inhibitor	Sonidegib
	Vismodegib
Histone deacetylase (HDAC) inhibitors	Belinostat
	Panobinostat
	Romidepsin
	Vorinostat
Hormonal therapies	Bicalutamide
Antiandrogens	Flutamide
	Nilutamide
Androgen receptor antagonist	Apalutamide
	Enzalutamide
Antiestrogens	Raloxifene
	Tamoxifen
Aromatase inhibitors	Anastrazole
	Exemestane
	Letrozole
CYP17 inhibitor	Abiraterone acetate
Luteinizing hormone–releasing hormone agonist	Goserlin
	Leuprolide
Luteinizing hormone–releasing hormone antagonist	Degarelix
Selective estrogen receptor degrader	Degarelix
Isocitrate dehydrogenase 2 (IDH2) inhibitor	Enasidenib
Immunomodulatory agents	Lenalidomide
	Pomalidomide
	Thalidomide
Immunotherapy	
Cell-based immunotherapy	Sipuleucel-T
CAR T-cell	Tisagenlecleucel
	Axicabtagene ciloleucel
Checkpoint inhibitors	Atezolizumab
	Avelumab
	Durvalumab
	Ipilimumab
	Nivolumab
	Pembrolizumab
Miscellaneous immune therapies	Interferons
	Aldesleukin
JAK inhibitor	Ruxolitnib
Microtubule-targeting agents	
Taxanes	Cabazitaxel
	Docetaxel
	Paclitaxel
Vinca alkaloids	Vinblastine
	Vincristine
	Vinorelbine
Other	Eribulin
	Estramustine
	Ixabepilone
Miscellaneous agents	Altretamine
	Arsenic trioxide
	Bexaroxtene
	Hydroxyurea
	Liposome encapsulated doxorubicin-cytarabine
	Omacetaxine mepesuccinate
	Tretinoin
	Ziv-alfibercept
Monoclonal antibodies	Alemtuzumab
	Bevacizumab
	Bevacizumab-awwb
	Blinatumomab
	Cetuximab
	Daratumumab
	Dinutuximab
	Elotuzumab
	Obinutuzumab
	Ofatumumab
	Olaratumab
	Necitumumab
	Panitumumab
	Pertuzumab
	Ramucirumab
	Rituximab
	Trastuzumab
	Trastuzumab-dkst
Antibody-drug conjugate	Berntuximab vedotin
	Inotuzumab ozogamicin
	Gemtuzumab ozogamicin
	Trastuzumab-emtansine
Antibody-radioimmunotherapy conjugate	Ibritumomab tiuxetan

(*Continued*)

Table 88–6

Anticancer Drugs (*Continued*)

Drug Class	Drug Name	Drug Class	Drug Name
mTOR inhibitors	Everolimus Temsirolimus	Bruton's tyrosine kinase (BTK)	Ibrutinib Acalabrutinib
Poly ADP ribose polymerase (PARP) inhibitors	Niraparib Olaparib Rucaparib	Cyclin-dependent kinase (CDK)	Abemaciclib Palbociclib Ribociclib
Proteosome inhibitors	Bortezomib Carflizomib Ixazomib	Epidermal growth factor receptor (EGFR)	Afatanib Erlotinib Osimertinib Vandetanib
Topoisomerase inhibitors			
Camptothecin derivatives	Irinotecan Topotecan	EGFR/HER2	Lapatinib Neratinib
Epidophyllotoxins	Etoposide Teniposide	Mitogen-activated extracellular kinase (MEK)	Trametinib
Tyrosine kinase inhibitors		Multikinase	Axitinib Brigatinib Cabozantinib Lenvatinib Midostaurin Pazopanib Regorafenib Sorafenib Sunitinib Vandetanib
Anaplastic lymphoma kinase (ALK)/tyrosine kinase met (c-met)	Alecitinib Ceritinib Crizotinib		
BCL-2	Venetoclax		
BCR-ABL	Bosutinib Dasatinib Imatinib Nilotinib Ponatinib		
BRAF	Cobimetinib Dabrafenib Vemurafenib	Phosphoinositide 3-kinase (PI3K)	Copanlisib Idelalisib

[a]Tipiracil is a thymidine phosphorylase inhibitor used to increase bioavailability of trifluridine.

which inhibits DNA polymerase. The triphosphate form also may be incorporated into DNA to result in chain termination to prevent DNA elongation. The drug may be administered as a low-dose continuous infusion, high-dose intermittent infusion, and into the subdural space via intrathecal or intraventricular administration. A liposomal formulation is also available for less frequent administration into the central nervous system (CNS). Cytarabine is eliminated by the kidneys with a renal clearance of 90 mL/min (1.5 mL/s). Cytarabine has shown efficacy in the treatment of acute leukemias and some lymphomas. The toxicities of cytarabine in high doses include myelosuppression; cerebellar syndrome (ie, nystagmus, dysarthria, and ataxia); and chemical conjunctivitis, an eye irritation that requires prophylaxis with steroid eye drops. The risk of neurotoxicity is increased with high doses (> 1 g/m^2), advanced age, and renal dysfunction. If cerebellar toxicity does occur, the drug needs to be discontinued immediately, and decisions regarding further therapy need to be carefully considered.[16]

► *Gemcitabine*

Gemcitabine is a deoxycytidine analogue that is structurally related to cytarabine. Gemcitabine inhibits DNA polymerase activity and ribonucleotide reductase to result in DNA chain elongation. Gemcitabine has shown activity in several solid tumors and some lymphomas. The toxicities include myelosuppression; flu-like syndrome with fevers during the first 24 hours after administration; rash that appears 48 to 72 hours after administration; and hemolytic uremic syndrome, a rare but life-threatening adverse effect. Patients should be counseled to use acetaminophen to treat the fevers during the first 24 hours; however, fevers occurring 7 to 10 days after gemcitabine are likely to be febrile neutropenia and need prompt treatment with broad-spectrum antibiotics.

► *Azacitidine and Decitabine*

Azacitidine and decitabine are nucleoside analogues approved for the treatment of patients with myelodysplastic syndrome, a hematopoietic disorder that can transform into acute myeloid leukemia (AML). Both of these agents cause cytotoxicity by directly incorporating in the DNA and inhibiting DNA methyltransferase, which causes hypomethylation of DNA. Hypomethylation of DNA appears to normalize the function of the genes that control cell differentiation and proliferation to promote normal cell maturation. The major side effects reported are myelosuppression and infections.

Antimetabolites: Purine Analogues

► *Mercaptopurine*

6-Mercaptopurine (6-MP) is an oral purine analogue that is converted to ribonucleotides that inhibit purine synthesis. Mercaptopurine is converted into thiopurine nucleotides, which are catabolized by thiopurine *S*-methyltransferase (TPMT). TPMT is subject to genetic polymorphisms and may cause severe myelosuppression; therefore, TPMT status may be assessed before therapy to reduce drug-induced morbidity and the costs of hospitalizations for neutropenic events. 6-MP is used in the treatment of acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML). Significant side effects include myelosuppression, mild nausea, skin rash, cholestasis, and rarely, venoocclusive disease. Mercaptopurine is metabolized

by xanthine oxidase, an enzyme that is inhibited by allopurinol. This represents a major drug–drug interaction. To avoid toxicities of mercaptopurine when these drugs are used concomitantly, the dose of mercaptopurine must be reduced by 66% to 75%.

▶ *Fludarabine*

Fludarabine is an analogue of the purine adenine. It interferes with DNA polymerase to cause chain termination and inhibits transcription by its incorporation into RNA. Fludarabine is dephosphorylated rapidly and converted to 2-fluoro-Ara-AMP (2-FLAA), which enters the cells and is phosphorylated to 2-fluoro-Ara-ATP, which is cytotoxic. Fludarabine is used in the treatment of chronic lymphocytic leukemia (CLL), some lymphomas, and refractory AML. Significant and prolonged myelosuppression may occur, along with immunosuppression, so patients are susceptible to opportunistic infections. Prophylactic antibiotics and antivirals are recommended until CD4 counts return to normal. Mild nausea and vomiting and diarrhea have been observed. Rarely, interstitial pneumonitis has occurred.

Antimetabolites: Folate Antagonists

Folates carry one-carbon groups in transfer reactions required for purine and thymidylic acid synthesis. Dihydrofolate reductase is the enzyme responsible for supplying reduced folates intracellularly for thymidylate and purine synthesis.

▶ *Methotrexate*

Methotrexate inhibits dihydrofolate reductase of both malignant and nonmalignant cells. When high doses of methotrexate are given, the "rescue drug" leucovorin, a reduced folate, is administered to bypass the methotrexate inhibition of dihydrofolate reductase of normal cells and is usually initiated 24 hours after methotrexate administration. This is done to prevent potentially fatal myelosuppression and mucositis. For safety purposes, the term folinic acid, another term used for leucovorin, should not be used because of the potential for a medication error in which folic acid might be given instead. Methotrexate concentrations should be monitored to determine when to stop leucovorin administration. Generally, leucovorin administration may be stopped when methotrexate concentrations decrease to 5×10^{-8} M, although this may vary by the chemotherapy regimen. High dosages of methotrexate may place an individual at risk for methotrexate to crystallize in the acidic environment of the urine, often resulting in acute renal failure and decreased methotrexate clearance. Administration of IV hydration with sodium bicarbonate to maintain urinary pH greater than or equal to 7 is necessary to prevent methotrexate-induced renal dysfunction. Methotrexate is eliminated by tubular secretion; therefore, concomitant drugs (eg, probenecid, salicylates, penicillin G, and ketoprofen) that may inhibit or compete for tubular secretion should be avoided. Methotrexate doses must be adjusted for renal dysfunction and close monitoring of methotrexate concentrations is advised. In patients with toxic levels of methotrexate (> 1 μmol/L) because of impaired renal function, the antidote glucarpidase can be administered. However, efficacy can be compromised so it is not used in patients with normal or slightly elevated levels. Side effects of methotrexate include myelosuppression, nausea and vomiting, and mucositis. Methotrexate also may be administered via the intrathecal route or via an Ommaya reservoir in very low doses as small as 12 mg, so it is crucial for the clinician to know the correct dose by the correct route in order to avoid substantial toxicity. The methotrexate used for intrathecal and intraventricular injection must be preservative-free to prevent CNS toxicity.

▶ *Pemetrexed*

Pemetrexed inhibits four pathways in thymidine and purine synthesis. Pemetrexed has shown activity in the treatment of mesothelioma and non–small cell lung cancer (NSCLC). Side effects include myelosuppression, rash, diarrhea, and nausea and vomiting. Patients should receive folic acid and cyanocobalamin to reduce bone marrow toxicity and diarrhea. Doses of folic acid of at least 400 mcg/day starting 5 days before treatment and continuing throughout therapy, as well as for 21 days after the last pemetrexed dose, have been used. Cyanocobalamin 1000 mcg is given intramuscularly the week before pemetrexed and then every three cycles thereafter. Dexamethasone 4 mg twice daily the day before, the day of, and the day after pemetrexed administration helps to decrease the incidence and severity of rash.[17]

Microtubule-Targeting Agents

▶ *Vinca Alkaloids (Vincristine, Vinblastine, and Vinorelbine)*

The vinca alkaloids (vincristine, vinblastine, and vinorelbine) are derived from the periwinkle (vinca) plant and cause cytotoxicity by binding to tubulin, disrupting the normal balance between polymerization and depolymerization of microtubules, and inhibiting the assembly of microtubules, which interferes with the formation of the mitotic spindle. As a result, cells are arrested during the metaphase of mitosis. The vinca alkaloids are used in several malignancies, primarily hematologic. Even though these agents have similar structures, the incidence and severity of toxicities vary among the agents. The dose-limiting toxicity of vincristine is neurotoxicity, which can consist of depressed tendon reflexes, paresthesias of the fingers and toes, toxicity to the cranial nerves, or autonomic neuropathy (constipation or ileus, abdominal pain, and/or orthostatic hypotension). In contrast, the dose-limiting toxicity associated with vinorelbine and vinblastine is myelosuppression. All of the vinca alkaloids are vesicants and can cause tissue damage; therefore, the clinician must take precautions to avoid extravasation injury. Biliary excretion accounts for a significant portion of elimination of vincristine and its metabolites, so doses need to be adjusted for obstructive liver disease.

Vincristine, vinblastine, and vinorelbine have similar sounding names, which is a potential cause of medication errors. As with all chemotherapy prescribing, dispensing, and administration, the clinician must be very careful with sound-alike, look-alike medications. Unfortunately, vincristine has been involved in numerous cases of fatal chemotherapy errors, including inadvertent intrathecal administration. Because the drug is a vesicant, intrathecal administration of the drug can cause widespread tissue damage in the brain and death. An example of a strategy that health systems can use to decrease the likelihood of an error such as this is for the pharmacy to only dispense vincristine in a mini-bag for IV administration. Many clinicians cap IV vincristine doses at 2 mg to prevent severe neuropathic side effects; however, if the intent of chemotherapy is curative, the vincristine dose may be dosed above the 2-mg cap.[18]

▶ *Taxanes (Paclitaxel, Nanoparticle Albumin-Bound Paclitaxel, Docetaxel, and Cabazitaxel)*

Taxane plant alkaloids are similar to the vinca alkaloids, exhibiting cytotoxicity during the M phase of the cell cycle by binding to tubulin. Unlike the vinca alkaloids, however, the taxanes do not interfere with tubulin assembly. Rather, the taxanes promote microtubule assembly and inhibit microtubule disassembly. Once

the microtubules are polymerized, the taxanes stabilize against depolymerization.

Hepatic metabolism and biliary excretion account for the majority of paclitaxel's elimination. Paclitaxel has demonstrated activity in several solid tumors. The diluent for paclitaxel, Cremophor EL, is composed of ethanol and castor oil. Infusions must be prepared and administered in non–polyvinyl chloride–containing bags and tubings, and solutions must be filtered. Patients receive dexamethasone, diphenhydramine, and an H_2 blocker to prevent hypersensitivity reactions caused by Cremophor EL. Patients also may have asymptomatic bradycardia during the infusion. Approximately 3 to 5 days after administration, patients may complain of myalgias and arthralgias that may last several days. Myelosuppression, flushing, neuropathy, ileus, and total-body alopecia are other common side effects. Because paclitaxel is a substrate for CYP3A4, steady-state concentrations of paclitaxel were 30% lower in patients receiving phenytoin than in patients not receiving phenytoin. Paclitaxel clearance was decreased by 33% when it was administered after cisplatin, so paclitaxel is administered before cisplatin.

A nanoparticle albumin-bound nab-paclitaxel product is also available for the treatment of metastatic breast cancer resistant to conventional chemotherapy. The nab-paclitaxel formulation uses nanotechnology to combine human albumin with paclitaxel allowing for the delivery of an insoluble drug in the form of nanoparticles. This unique formulation allows for an increased bioavailability and higher intracellular concentrations of the drug. It does not have the serious hypersensitivity reactions encountered with paclitaxel solubilized in Cremophor EL, so premedication with H_1 and H_2 blockers and steroids is not necessary. Also, a significantly lower incidence of severe neutropenia occurs. The dose is infused over 30 minutes and does not require a special IV bag, tubing, or filter. The dosing of this product is different from that of the original paclitaxel, so practitioners need to be aware of which product is being prescribed. The pharmacokinetics of the albumin-bound paclitaxel displays a higher clearance and larger volume of distribution than paclitaxel. The drug is eliminated primarily via fecal excretion.[19] Bone marrow suppression, neuropathy, ileus, arthralgias, and myalgias still occur.

Docetaxel has activity in the treatment of several solid tumors also. Dexamethasone, 8 mg twice daily for 3 days starting the day before treatment, is used to prevent the fluid-retention syndrome associated with docetaxel and possible hypersensitivity reactions. The fluid-retention syndrome is characterized by edema and weight gain that is unresponsive to diuretic therapy and is associated with cumulative doses greater than 800 mg/m^2. Myelosuppression, alopecia, and neuropathy are other side effects associated with docetaxel treatment.

Cabazitaxel is a newer taxane used in combination with prednisone for the treatment of metastatic hormone-refractory prostate cancer. Cabazitaxel has shown to have similar adverse effects as paclitaxel and docetaxel. Premedication with an antihistamine, corticosteroid, and H_2 antagonist to prevent hypersensitivity reactions is required.

► *Halichondrins*

Eribulin mesylate is a nontaxane microtubule dynamics inhibitor. It is a synthetic analogue of halichondrin B, which is a product isolated from the sea sponge *Halichondria okadai*. While taxanes inhibit cell division by stabilizing microtubules, eribulin arrests the cell cycle through inhibition of the growth phase of microtubules without interfering with microtubule shortening. The cytotoxicity results from its effects via a tubulin-based antimitotic mechanism, resulting in G_2/M cell-cycle arrest and mitotic blockage. Apoptotic cell death results from prolonged mitotic blockage. Eribulin mesylate is an IV medication that is specifically indicated for the treatment of patients with metastatic breast cancer. The most common adverse effects reported are neutropenic fever, anemia, asthenia or fatigue, alopecia, peripheral neuropathy, nausea, and constipation. Eribulin has been reported to cause significant neutropenia and QT interval prolongation. It has vesicant properties. Dosages should be adjusted in renal and hepatic impairment.[20]

► *Ixabepilone*

Ixabepilone, an epothilone analogue, binds to β-tubulin subunits on microtubules, which results in suppression of microtubule dynamics. Ixabepilone is primarily eliminated by the liver by oxidation through the CYP3A4 system. Ixabepilone, in combination with capecitabine or alone if resistant to capecitabine, is indicated for the treatment of metastatic or locally advanced breast cancer. Studies have shown a possible synergy when used in combination with capecitabine. Side effects include hypersensitivity reactions, myelosuppression, and peripheral neuropathy. To minimize the occurrence of hypersensitivity reactions, patients must receive both H_1 and H_2 antagonists before therapy. If a reaction still occurs, corticosteroids should be added to the premedications.

Topoisomerase Inhibitors

Topoisomerase is responsible for relieving the pressure on the DNA structure during unwinding by producing strand breaks. Topoisomerase I produces single-strand breaks, whereas topoisomerase II produces double-strand breaks.

► *Epipodophyllotoxins (Etoposide and Teniposide)*

Etoposide and teniposide are semisynthetic podophyllotoxin derivatives that inhibit topoisomerase II, causing multiple DNA double-strand breaks. Etoposide has shown activity in the treatment of several types of lymphoma, testicular and lung cancer, retinoblastoma, and carcinoma of unknown primary. Oral bioavailability is approximately 50%, so oral dosages are approximate two times those of IV doses. Teniposide has shown activity in the treatment of ALL, neuroblastoma, and non-Hodgkin lymphoma. Both of these agents should be slowly administered to prevent hypotension. Side effects of these agents include mucositis, myelosuppression, alopecia, phlebitis, hypersensitivity reactions, and secondary leukemias. Hypersensitivity reactions are caused by the solubilizing agents, polysorbate 80 and may be life-threatening.

► *Camptothecin Derivatives (Irinotecan and Topotecan)*

Irinotecan and topotecan, both camptothecins, inhibit the topoisomerase I enzyme to interfere with DNA synthesis through the active metabolite SN38. Topoisomerase I enzymes stabilize DNA single-strand breaks and inhibit strand resealing. Irinotecan has shown activity in the treatment of cancers of the colon, rectum, cervix, and lung. Irinotecan-induced diarrhea is a serious complication and may be life-threatening. One form of diarrhea (early) can occur during or immediately after the infusion. This is a result of a cholinergic process in which the patient may experience facial flushing, diaphoresis, and abdominal cramping. IV atropine should be administered to treat diarrhea that occurs any time during the first 24 hours of administration. Another form of diarrhea (late) can occur several days after administration and can result in severe dehydration. This

adverse effect should be treated immediately with loperamide at a dosage of 2 mg every 2 hours or 4 mg every 4 hours until diarrhea has stopped for 12 hours. Other side effects include myelosuppression, fatigue, and alopecia. Individuals homozygous for *UGT1A1* 28* have an increased risk of febrile neutropenia and diarrhea and should be considered for an empiric dose reduction of one level; heterozygotes should receive closer monitoring, including more frequent complete blood counts (CBCs) to detect myelosuppression.

Topotecan has shown clinical activity in the treatment of ovarian and lung cancer, myelodysplastic syndromes, and AML. The IV infusion may be scheduled daily for 5 days or once weekly. Side effects include myelosuppression, mucositis, and diarrhea. Diarrhea is less common than with irinotecan.

Anthracene Derivatives

▶ *Daunorubicin, Doxorubicin, Idarubicin, and Epirubicin*

Anthracyclines (daunorubicin, doxorubicin, idarubicin, and epirubicin) are also referred to as antitumor antibiotics or topoisomerase inhibitors when considering their mechanism of action. All of the anthracyclines contain a four-membered anthracene ring, a chromophore, with an attached sugar portion. This chromophore results in red-orange urine after administration, which is an important counseling point for patients. Free radicals formed from the anthracyclines combine with oxygen to form superoxide, which can make hydrogen peroxide. These agents are able to insert between base pairs of DNA to cause structural changes in DNA. However, the primary mechanism of cytotoxicity appears to be the inhibition of topoisomerase II. These drugs are widely used in a variety of cancers.

Oxygen-free-radical formation is a cause of cardiac damage and extravasation injury, which is common with these drugs. The anthracyclines can cause cardiac toxicity as manifested by a congestive heart failure or cardiomyopathy symptomatology, alopecia, nausea or vomiting, mucositis, myelosuppression, and urinary discoloration. These drugs are vesicants.

To reduce the risk of cardiotoxicity associated with doxorubicin, the maximum lifetime cumulative dose is 550 mg/m^2; similarly, the other anthracyclines have maximum lifetime cumulative doses. Ventricular ejection fractions should be measured before therapy and periodically if therapy is continued. Therapy should be halted if there is a 10% to 20% decrease from baseline in ejection fraction. Patients at increased risk of cardiotoxicity include patients reaching the upper limit of cumulative lifetime dose; those taking concomitant or previous cardiotoxic drugs, concurrent paclitaxel, or bolus administration; patients with preexisting cardiac disease or mediastinal radiation; and the very young and elderly. Cardioprotectants (eg, dexrazoxane) have been used to decrease risk in some cases. Clinical guidelines exist recommending when cardioprotective agents are warranted.[21]

Liposomal doxorubicin is an **irritant**, not a vesicant, and is dosed differently from doxorubicin, so clinicians need to be very careful when prescribing these two drugs. Liposomal doxorubicin has shown significant activity in the treatment of breast and ovarian cancer along with multiple myeloma (MM) and Kaposi sarcoma. Side effects include mucositis, myelosuppression, alopecia, and palmar-plantar erythrodysesthesia. The liposomal doxorubicin may be less cardiotoxic than doxorubicin.

▶ *Mitoxantrone*

This royal blue–colored drug is an anthracenedione that inhibits DNA topoisomerase II. Mitoxantrone has shown clinical activity in the treatment of acute leukemias, breast and prostate cancer, and non-Hodgkin lymphomas. Myelosuppression, mucositis, nausea and vomiting, and cardiac toxicity are side effects of this drug. The total cumulative dose limit is 160 mg/m^2 for patients who have not received prior anthracycline or mediastinal radiation. Patients who have received prior doxorubicin or daunorubicin therapy should not receive a cumulative dose greater than 120 mg/m^2 of mitoxantrone. Patients should be counseled that their urine will turn a blue–green color.[22]

Alkylating Agents

Although still widely used for many malignancies, the alkylating agents are the oldest class of anticancer drugs. The agents cause cytotoxicity via transfer of their alkyl groups to nucleophilic groups of proteins and nucleic acids. The major site of alkylation within DNA is the N7 position of guanine, although alkylation does occur to a lesser degree at other bases. These interactions can either occur on a single strand of DNA (monofunctional agents) or on both strands of DNA through a cross-link (bifunctional agents), which leads to strand breaks. The major toxicities of the alkylating agents are myelosuppression, alopecia, nausea or vomiting, sterility or infertility, and secondary malignancies.

▶ *Nitrogen Mustards (Cyclophosphamide and Ifosfamide)*

Cyclophosphamide and ifosfamide are commonly used bifunctional alkylating agents, therefore, causing cross-linking of DNA. They each share similar adverse effects and spectrum of activity, being used in a variety of solid and hematologic cancers. Cyclophosphamide and ifosfamide are both prodrugs, requiring activation by mixed hepatic oxidase enzymes to get to their active forms, phosphoramide and ifosfamide mustard, respectively. During the activation process, additional byproducts (acrolein and chloroacetaldehyde) are formed. Acrolein has no cytotoxic activity but is responsible for the hemorrhagic cystitis associated with ifosfamide and high-dose cyclophosphamide. Acrolein produces cystitis by directly binding to the bladder wall. Prophylaxis is necessary with aggressive hydration, administration of 2-mercaptoethane sulfonate sodium (mesna, which binds to and inactivates acrolein in the bladder), frequent voiding, and monitoring in patients receiving ifosfamide and high-dose cyclophosphamide. Patients should be counseled to drink plenty of fluids; void frequently; and report any hematuria, irritation, or flank pain. Dosing regimens of mesna range from an equal milligram dose to the ifosfamide mixed in the same IV bag to 20% of the dose before ifosfamide and 20% of the dose repeated at 4 and 8 hours after the dose.

Chloroacetaldehyde, a metabolite of ifosfamide, can result in encephalopathy, especially in patients receiving ifosfamide that exhibit risk factors such as renal dysfunction or advanced age. This adverse effect can occur within 48 to 72 hours of administration and is usually reversible.

▶ *Busulfan*

Busulfan is an alkylating agent that forms DNA–DNA and DNA–protein cross-links to inhibit DNA replication. Oral busulfan is well absorbed, has a terminal half-life of 2 to 2.5 hours, and is eliminated primarily by metabolism. It is also available in an IV formulation, which is useful when using the high doses required in hematopoietic stem cell transplantation (HSCT). Busulfan has shown significant clinical activity in the treatment of AML and CML and has been used as a conditioning regimen before HSCT. Side effects include bone marrow suppression; hyperpigmentation of skin creases; and rarely, pulmonary fibrosis. High doses

used for HSCT preparatory regimens result in severe nausea and vomiting, tonic–clonic seizures, and sinusoidal obstruction syndrome. Patients receiving high-dose busulfan should receive anticonvulsant prophylaxis. Toxicities associated with busulfan dosing along with a discussion on adaptive dosing of busulfan can be found in Chapter 98.

▶ *Nitrosoureas (Carmustine and Lomustine)*

Carmustine (BCNU) and lomustine (CCNU) are nitrosoureas that are lipophilic in nature and therefore able to cross the blood–brain barrier. Carmustine, which is reconstituted with ethanol, crosses the blood–brain barrier when given IV. It also comes as a biodegradable wafer formulation that may be implanted to treat residual tumor tissue after surgical resection of brain tumors. Lomustine is available in an oral formulation. Carmustine has shown clinical activity in the treatment of lymphoma, MM, and brain tumors. Lomustine has shown clinical activity in the treatment of non-Hodgkin lymphoma and brain tumors. Patients should receive only enough lomustine for one cycle at a time to prevent confusion with their drug regimens and the prolonged neutropenia that can occur. Side effects include myelosuppression, severe nausea and vomiting, and pulmonary fibrosis with long-term therapy.

▶ *Nonclassic Alkylating Agents (Dacarbazine and Temozolomide)*

Although the exact mechanism of action remains unclear, dacarbazine and temozolomide appear to inhibit DNA, RNA, and protein synthesis. Dacarbazine has shown clinical benefit in the treatment of patients with melanoma, Hodgkin lymphoma, and soft tissue sarcomas. Side effects include myelosuppression, severe nausea and vomiting, and a flu-like syndrome that starts about 7 days after treatment and lasts 1 to 3 weeks.

Temozolomide is an orally active agent that is well absorbed and crosses the blood–brain barrier. Temozolomide is converted via pH-dependent hydrolysis to the active metabolite 5-(3-methyltriazeno)-imidazole-4-carboxamide. Temozolomide may be used in the treatment of melanoma, refractory anaplastic astrocytoma, and glioblastoma multiforme. Nausea may be minimized by administering the drug at bedtime. Because patients receiving temozolomide may have confusion secondary to their brain tumors and because dosing can consist of multiple capsule sizes, care must be taken by all providers to simplify regimens to prevent chemotherapy overdose.[23]

▶ *Procarbazine*

Although the exact mechanism of action of procarbazine is unknown, it does inhibit DNA, RNA, and protein synthesis. Procarbazine is used most often in the treatment of lymphoma. Myelosuppression is the major side effect. Nausea, vomiting, and a flu-like syndrome occur initially with therapy. Patients must be counseled to avoid tyramine-rich foods because procarbazine is a monoamine oxidase inhibitor. Patients should be provided a list of foods and beverages to avoid a hypertensive crisis. A disulfiram-like reaction can occur with the ingestion of alcohol.

Heavy Metal Compounds

Platinum drugs form reactive platinum complexes that bind to cells, so the pharmacokinetics of the individual drug may be of the platinum, both free and bound, rather than of the parent drug.

▶ *Cisplatin*

Cisplatin forms inter- and intrastrand DNA cross-links to inhibit DNA synthesis. Cisplatin has shown clinical activity in the treatment of numerous tumor types, from head and neck cancers to anal cancer, including many types of lymphoma and carcinoma of unknown primary. Cisplatin is highly emetogenic, even when low doses are given daily for 5 days, and causes delayed nausea and vomiting as well; patients require aggressive antiemetic regimens for both delayed and acute emesis. Significant nephrotoxicity and electrolyte abnormalities can occur if inadequate hydration occurs. Ototoxicity, which manifests as a high-frequency hearing loss, and a glove-and-stocking neuropathy may limit therapy.

▶ *Carboplatin*

Carboplatin has the same mechanism of action as cisplatin; however, its side effects are similar but less intense than those of cisplatin. Many chemotherapy regimens dose carboplatin based on an area under the curve (AUC), which is also called the Calvert equation. According to the Calvert equation for adults, the dose in milligrams of carboplatin = (CrCl + 25) × AUC desired, where CrCl is expressed in mL/min.[24] Carboplatin has shown clinical activity in the treatment of several solid tumors and lymphoma. Thrombocytopenia, nausea and vomiting, and hypersensitivity reactions are adverse effects.

▶ *Oxaliplatin*

Oxaliplatin has shown clinical activity in the treatment of colorectal cancer. Oxaliplatin, although similar in action to cisplatin and carboplatin in terms of adverse effects, also, causes a cold-induced neuropathy. Patients should be counseled to avoid cold beverages, to use gloves to remove items from the freezer, and to wear protective clothing in cold climates for the first week after treatment. A glove-and-stocking neuropathy also occurs with long-term dosing. Hypersensitivity reactions and moderate nausea and vomiting are also adverse effects.[25]

mTOR Inhibitors

▶ *Temsirolimus and Everolimus*

The mammalian target of rapamycin (mTOR) is a downstream mediator in the phosphatidylinositol 3-kinase/Akt signaling pathway that controls translation of proteins that regulate cell growth and proliferation but also angiogenesis and cell survival. The mTOR is an intracellular component that stimulates protein synthesis by phosphorylating translation regulators, and contributes to protein degradation and angiogenesis.

Temsirolimus is approved for the treatment of advanced kidney cancer. Temsirolimus and its metabolite sirolimus are substrates of the cytochrome CYP3A4/5 isoenzyme system. The primary side effects of temsirolimus include mucositis, diarrhea, maculopapular rash, nausea, leucopenia, thrombocytopenia, and hyperglycemia. Noninfectious pneumonitis can occur and must be identified immediately for best outcomes.

Everolimus is an oral inhibitor of mTOR that is approved for the treatment of patients with advanced kidney cancer, breast cancer, and neuroendocrine tumors. Drug interactions and adverse reactions are similar to those of temsirolimus.

Miscellaneous Agents

▶ *Bleomycin*

Bleomycin is a mixture of peptides with drug activity expressed in units, where 1 unit equals to 1 mg. Bleomycin causes DNA strand breakage. Bleomycin has shown clinical activity in the

treatment of patients with testicular cancer and malignant effusions, squamous cell carcinomas of the skin, and Kaposi sarcoma. Hypersensitivity reactions and fever may occur, so premedication with acetaminophen may be required. The most serious side effect is the pulmonary toxicity that presents as a pneumonitis with a dry cough, dyspnea, rales, and infiltrates. Pulmonary function studies show decreased carbon monoxide diffusing capacity and restrictive ventilatory changes. "Bleomycin lung" is associated with cumulative dosing greater than 400 units and occurs rarely with a total dose of 150 units. The pulmonary toxicity is potentiated by thoracic radiation and by hyperoxia. Additional side effects include fever with or without chills, mild to moderate alopecia, and nausea and vomiting. Bleomycin has been used to manage malignant plural effusions at doses of 15 to 60 units through installation into the affected area. The drainage tube of the effusion is clamped off for some period of time after administration of bleomycin and then the amount of drainage is monitored to determine efficacy of the treatment.[25]

▶ Hydroxyurea

Hydroxyurea is an oral drug that inhibits ribonucleotide reductase, which converts ribonucleotides into the deoxyribonucleotides used in DNA synthesis and repair. Hydroxyurea has shown clinical activity in the treatment of CML, polycythemia vera, sickle cell disease, and thrombocytosis. The major side effects are myelosuppression, nausea and vomiting, diarrhea, and constipation. Rash, mucositis, and renal tubular dysfunction occur rarely.

▶ L-Asparaginase

L-Asparaginase is an enzyme that may be produced by *Escherichia coli*. Asparaginase hydrolyzes the reaction of asparagine to aspartic acid and ammonia to deplete lymphoid cells of asparagine, which inhibits protein synthesis. L-Asparaginase has shown clinical activity in the treatment of ALL and childhood AML. Severe allergic reactions may occur when the interval between doses is 7 days or greater, so while a skin test result may be negative, patients should be observed closely after asparaginase administration. Pancreatitis and fibrinogen depletion may also occur during therapy. Repletion of fibrinogen should be done to prevent disseminated intravascular coagulation and fatal bleeding. If the patient suffers an allergic reaction to L-asparaginase, pegaspargase, which is L-asparaginase modified through a linkage with polyethylene glycol, which extends the half-life and allows for lower doses and less frequent administration, may be given. Cost and limited availability are some reasons pegaspargase may not be used first.

▶ Tretinoin

Tretinoin, also referred to as *ATRA*, which stands for all-trans-retinoic acid, is a retinoic acid that is not cytotoxic but promotes the maturation of early promyelocytic cells and is specific to the t(15;17) cytogenetic marker. The most significant side effect is the acute promyelocytic leukemia (APL) differentiation syndrome, which may occur anywhere from the first couple of days of therapy until the end of therapy and consists of symptoms of fever, respiratory distress, and hypotension. Chest radiographs are consistent with a pneumonia-like process. The syndrome can be confused easily with pneumonia in a patient with possible neutropenia. The treatment for retinoic acid syndrome is dexamethasone 10 mg IV every 12 hours; the syndrome may resolve within 24 hours of the start of dexamethasone therapy. However, the use of steroids in a febrile neutropenic patient may further compromise the treatment of infection.[26]

▶ Immunomodulatory Agents (Thalidomide, Lenalidomide, and Pomalidomide)

Thalidomide was introduced into the market in Europe on October 1, 1957, as a sedative–hypnotic, and when it was taken by pregnant women, it resulted in severe limb deformities (phocomelia) and subsequently was removed from the market. Thalidomide is an angiogenesis inhibitor, but the full mechanism of action is still unknown. Possible mechanisms of action include free radical oxidative damage to DNA, inhibiting tumor necrosis factor α production, altering the adhesion of cancer cells, and altering cytokines that affect the growth of cancer cells. Thalidomide has shown clinical activity in the treatment of MM. Because of thalidomide's potential to cause phocomelia, each patient must be enrolled in the STEPS program and counseled on the risks of thalidomide not only for the patient but also the patient's reproductive partner. Clinicians must be registered to prescribe thalidomide. Common adverse effects include somnolence, constipation, peripheral neuropathy, and deep vein thrombosis (DVT). Recommendations for DVT prophylaxis for all thalidomides include low-molecular-weight heparin or standard-dose warfarin for high-risk patients and aspirin for low-risk patients.[27]

Lenalidomide is approved for the treatment of myelodysplastic syndrome when the 5q deletion is present and MM. Because lenalidomide is an analogue of thalidomide, all of the same precautions must be taken to prevent phocomelia. However, lenalidomide has fewer adverse effects than thalidomide. Dosing adjustments are necessary for renal dysfunction. Lenalidomide is used in the treatment of myelodysplastic syndrome and MM. Other side effects are neutropenia, thrombocytopenia, DVT, and pulmonary embolus.

Pomalidomide is also used in treatment of refractory or progressive MM. Similar precautions to prevent phocomelia should also occur with this drug. Adverse effects include myelosuppression and infections. The use of the immunomudulatory agents in the treatment of MM is discussed thoroughly in Chapter 96.

▶ Proteasome Inhibitors (Bortezomib, Carfilzomib, and Ixazomib)

The proteasome is an enzyme complex that exists in all cells and plays an important role in degrading proteins that control the cell cycle. When the proteasome is inhibited, the numerous pathways that are necessary for the growth and survival of cancer cells are disrupted. Bortezomib specifically inhibits the 26S proteasome, which is a large protein complex that degrades ubiquitinated proteins. This pathway plays an essential role in regulating the intracellular concentration of specific proteins, causing the cells to maintain homeostasis. Inhibition of the 26S proteasome prevents this to occur, ultimately causing a disruption in the homeostasis and cell death. Both carfilzomib and ixazomib inhibit 20S proteasome, which is the proteolytic core with the 26S proteasome.

Bortezomib is approved for the treatment of MM, mantle cell lymphoma, and in some cases of relapsed/refractory AML. It is administered as an IV injection. The most commonly reported adverse effects are asthenia, gastrointestinal (GI) disturbances (nausea, diarrhea, decreased appetite, constipation, vomiting), thrombocytopenia, peripheral neuropathy, anemia, headache, insomnia, and edema. Prophylactic anticoagulation is not routinely required. Reactivation of varicella zoster infection is also common with bortezomib, and antiviral prophylaxis with acyclovir should be considered.

Carfilzomib and ixazomib are second-generation proteasome inhibitors. Carflizomib is administered by IV, whereas ixazomib

is a capsule that should be taken on an empty stomach. Both of these drugs used in the treatment of refractory cases of MM and have similar but fewer side effects compared with bortezomib.

▶ *Omacetaxine Mepesuccinate*

Omacetaxine mepesuccinate is an alkaloid from *Cephalotaxus harringtonia*. The agent reversibly inhibits protein synthesis, causing cell death. It affects both malignant and nonmalignant cells. It is a subcutaneous injection and is indicated for the treatment of CML patients (including those patients with the T315I mutation) showing resistance and/or intolerance to two or more tyrosine kinase inhibitors (TKIs). The most common nonhematological adverse effects are GI disruption, fatigue, and hyperglycemia. Rare but serious adverse reactions include febrile neutropenia, infections, and cerebral hemorrhage.

▶ *Histone Deacetylase (HDAC) Inhibitors (Vorinostat and Romidepsin)*

Vorinostat is indicated for the treatment of cutaneous T-cell lymphoma in patients with progressive, persistent, or recurrent disease after treatment with two systemic therapies. Romidepsin is approved for the treatment of cutaneous or peripheral T-cell lymphoma in patients who have received at least one systemic therapy. These agents catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. Vorinostat is an orally available agent, and romidepsin is only available in an IV formulation. These drugs are metabolized by CYP3A4, so caution should be exercised with monitoring for drug–drug interactions. Side effects include diarrhea, fatigue, nausea and anorexia, hypercholesterolemia, hypertriglyceridemia, and hyperglycemia. Despite anemia, thrombocytopenia, and neutropenia, patients have developed pulmonary embolism and DVT while on therapy.[28]

▶ *Poly ADP Ribose Polymerase (PARP) Inhibitors: Niraparib, Olaparib, and Rucaparib*

PARP enzymes are involved in normal cellular function, including DNA transcription and repair. Thus, PARP inhibitors inhibitor tumor growth. Niraparib, olaparib, and rucaparib are all used to treat ovarian, fallopian tube, or peritoneal cancer. Olaparib is available as both tablets and capsules, but they should not be substituted on a milligram-per-milligram basis due to differences in dosing and bioavailabilty of each formulation. Common side effects include myelosuppessive side effects, GI toxicities, fatigue, upper respiratory tract infections, and arthralgias and myalgias. Rarely, patients can develop myelodysplastic syndrome or AML and pneumonitis. Niraparib also causes hypertension and patients must undergo heart rate (HR) and blood pressure monitoring monthly for the first year.

Immunotherapy

▶ *Tisagenlecleucel*

Tisagenlecleucel is the first gene therapy approved in cancer. It is an autologous T cell immunotherapy comprised of T cells that are genetically modified using a vector to encode an anti-CD19 chimeric antigen receptor (CAR). Tisagenlecleucel is prepared from the patient's own peripheral mononculelar cells, which are obtained through a leukapheresis procedure.[29] The cells are sent to a laboratory whereby they are enriched with the lentiviral vector containing anti-CD19 CAR transgene. The transduced T cells are then expanded and formulated into a suspension that is cryopreserved. Once passing a sterility test, it is shipped back in a patient-specific infusion bag to the institution for administration. Tisagenlecleucel is approved for us in ALL. The most common side effect is a cytokine-release syndrome (CRS), which can be fatal. Immediate identification and treatment is necessary to prevent death. Other side effects include decreased appetite, headache, nausea/vomiting, infections, and diarrhea.

▶ *Aldesleukin*

Aldesleukin, which is a human recombinant *interleukin-2 (IL-2)*, is a lymphokine that promotes B- and T-cell proliferation and triggers a cytokine cascade to attack the tumor. Aldesleukin has shown clinical activity in the treatment of kidney cancer and melanoma. Side effects of IL-2 vary by dose and route. IV high-dose IL-2 causes a drug-induced shock-like picture. Patients may develop hypotension despite aggressive IV hydration. Patients develop a red, itchy skin; liver and kidney function tests change; via immune complex formation in the kidneys, fluid, and electrolyte imbalances occur; and high fevers occur while receiving scheduled acetaminophen and nonsteroidal anti-inflammatory agents. Severe rigors and chills may require symptom control. All the side effects reverse within 24 hours of stopping the drug. The toxicity profile is much less with subcutaneous administration. However, with subcutaneous administration, nodules form at the injection site and may take months to resolve. Corticosteroids should not be administered to patients while they are receiving aldesleukin unless a life-threatening emergency occurs. Steroids reverse all the symptoms and the antitumor effect even with topical administration. The itching, red skin may be treated with topical creams and antihistamines.

Monoclonal Antibodies

The cell surface contains molecules, which are referred to as *CD*, which stands for "cluster of differentiation." The antibodies are produced against a specific antigen. When administered, usually by an IV injection, the antibody binds to the antigen, which may trigger the immune system to result in cell death through complement-mediated cellular toxicity, or the antigen–antibody cell complex may be internalized to the cancer cell, which results in cell death. Monoclonal antibodies also may carry radioactivity, sometimes referred to as *hot antibodies*, and are referred to as *radioimmunotherapy*, so the radioactivity is delivered to the cancer cell. Antibodies that contain no radioactivity are referred to as *cold antibodies*.

All monoclonal antibodies end in the suffix *-mab*. The syllable before *-mab* indicates the source of the monoclonal antibody (Table 88–7).[30] When administering an antibody for the first time,

Table 88–7

Syllable Source Indicators for Monoclonal Antibodies[a]

U	Human
O	Mouse
A	Rat
E	Hamster
I	Primate
Xi	Chimeric: A cross between humanized and animal source
Axo	Rat/mouse hybrid
Xizu	Combination of humanized and chimeric chains

[a]These letters appear before mab, which stands for monoclonal antibody.

Data from Programme on International Nonproprietary Names (INN) Division of Drug Management and Policies, World Health Organization, Geneva. 1997.

one should consider the source. The less humanized an antibody, the greater the chance for the patient to have an allergic-type reaction to the antibody. The more humanized the antibody, the lower the risk of a reaction. The severity of the reactions may range from fever and chills to life-threatening allergic reactions. Premedication with acetaminophen and diphenhydramine is common before the first dose of any antibody. If a severe reaction occurs, the infusion should be stopped and the patient treated with antihistamines, corticosteroids, or other supportive measures.

▶ *Alemtuzumab*

Alemtuzumab is an antibody to the CD52 receptor present on B and T lymphocytes. Alemtuzumab has shown clinical activity in the treatment of CLL. Severe and prolonged (6 months) immunosuppression may result, which necessitates pneumocystis jirovecii pneumonia (PJP) prophylaxis and antifungal and antiviral prophylaxis to prevent opportunistic infections. Infusion-related reactions typically occur with the first dose and can be severe. Premedication with antihistamines and acetaminophen is recommended. Subcutaneous administration will also alleviate the severity of infusion reactions.

▶ *Bevacizumab and Bevacizumab-awwb*

Bevacizumab is a humanized monoclonal antibody that binds to vascular endothelial growth factor (VEGF), which prevents it from binding to its receptors, ultimately resulting in inhibition of angiogenesis. Bevacizumab has shown clinical activity in the treatment of colorectal, kidney, lung, breast, and head and neck cancer. The biosimilar bevacizumab-awwb is the first biosimilar approved in the United States for cancer treatment. A biosimilar is a type of biological product that is highly similar to the originator product and is expected to have no meaningful clinical difference. Patients treated with bevacizumab products may develop hypertension requiring chronic medication during therapy. Impaired wound healing, thromboembolic events, proteinuria, bleeding, and bowel perforation are serious side effects that occur with this drug.

▶ *Blinatumomab*

Blinatumomab is a bispecific CD19-directed CD3 T cell therapy. It activates T cells by connecting the CD3 antigen in the receptor complex with the CD19 surface antigen on both benign and malignant B cells, activating inflammatory cytokine release and T-cell proliferation resulting in apoptosis of CD19+ cells. It is effective in patients with Philadelphia negative B-cell precursor ALL. Common side effects include pyrexia, neutropenia, infections, and infusion-related reactions. Patients should receive dexamethasone before infusion and when restarting an infusion if interrupted for more than 4 hours. Rare but serious side effects include CRS and neurologic toxicity, such as paresthesia, confusion, dizziness, and tremor. CRS occurs when the cytokines are released by activated T cells, producing a systemic inflammatory response. Patients may initially present with a low-grade fever, fatigue, and anorexia which can quickly progress to high fever, hypoxia, and organ failure. Thus, patients are typically hospitalized for the first cycle and first two days of the second cycle. Medication errors can occur when preparing and administering blinatumomab because preparation instructions are more complicated than most other IV drugs. Doses are based on weight, dose, and duration of infusion. Additionally, specific instructions for use of an IV solution stabilizer are provided rather than mixing with the drug for reconstitution and the volume for infusion.

▶ *Brentuximab Vedotin*

Brentuximab vedotin is a CD30-directed antibody–drug conjugate (ADC) that consists of the antibody specific for CD30, a microtubule disrupting agent called monomethyl auristatin E (MMAE), and a protease-cleavable linker that covalently attaches MMAE to the antibody. It is reported that the cytotoxic activity is a result of the binding of the ADC to CD30-expressing cells followed by internalization of the ADC–CD30 complex, and then proteolytic cleavage and release of MMAE into the cell. Binding of MMAE to tubulin disrupts the microtubule network, resulting in cell cycle arrest and apoptosis. This IV agent is indicated for Hodgkin lymphoma patients after failure or ineligibility of autologous HSCT and for patients with systemic anaplastic large cell lymphoma who have failed at least one systemic chemotherapy regimen. In vitro data suggests that MMAE is a substrate and an inhibitor of CYP3A4/5; therefore, patients need to be monitored for drug–drug interactions. The most common adverse effects are neutropenia, peripheral neuropathy, fatigue, nausea and vomiting, diarrhea, anemia, thrombocytopenia, and upper respiratory infection. Dosing modification guidelines for peripheral neuropathy can be found in the prescribing information.[31]

▶ *Cetuximab, Necitumumab, and Panitumumab*

Cetuximab is a chimeric antibody that binds to the EGFR to block its stimulation. Panitumumab binds to the EGFR to prevent receptor autophosphorylation and activation of receptor-associated kinases, which results in inhibition of cell growth and induction of apoptosis. Necitumumab is an anti-EGFR recombinant human monoclonal antibody. Cetuximab has shown clinical activity in the treatment of colorectal and head and neck cancers, necitumumab in non–small cell lung cancer, and pantiumumab in colorectal cancers. Tumors that have *RAS* mutations do not respond to treatment with cetuximab or panitumumab; therefore, tumors should be tested for *RAS* mutations before initiating therapy. An acne-like rash may appear on the face and upper torso 1 to 3 weeks after the start of therapy. Preventive therapies with topical corticosteroids with moisturizer, sunscreen, and oral doxycycline are recommended. Other side effects include hypersensitivity reactions, fever, nausea and vomiting, and interstitial lung disease. Electrolyte disturbances, such as hypomagnesemia and hypocalcemia, can occur; these are more common with necitumumab and panitumumab.

▶ *Daratumumab*

Daratumumab is a monoclonal antibody to the CD38 receptor, highly expressed on myeloma cells and weakly on other hematopoietic stem cells. It is used in patients with MM. Infusion-related reactions are common so patients must be pretreated with acetaminophen, an antihistamine, and IV methylprednisolone and receive an oral corticosteroid for each of the 2 days following infusion to prevent delayed reactions. Also, this drug causes a positive interference with cross matching and red blood cell antibody screening, by causing a positive indirect Coombs test that can persist for 6 months after discontinuation of therapy. Thus, patients should be typed and screened before therapy, and blood banks should be informed when a patient has received daratumumab.

▶ *Elotuzumab*

Elotuzumab is a humanized recombinant monoclonal antibody that specifically targets signaling lymphocytic activation molecule family member 7 protein. It works by directly activating natural killer cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC). Premedications to

prevent infusion-related reactions should include dexamethasone, H_1 blocker, H_2 blocker, and acetaminophen. The most common side effects are fatigue, diarrhea, pyrexia, constipation, and cough.

▶ *Ibritumomab Tiuxetan*

Ibritumomab tiuxetan, a "*hot antibody*," is linked to yttrium and binds to the CD20 receptor of B lymphocytes. Similarly, hematologic toxicity may occur several weeks after administration and may take weeks to resolve.

▶ *Obinutuzumab, Ofatumumab, and Rituximab*

Obinutuzumab, ofatumumab, and rituximab are monoclonal antibodies to the CD20 receptor expressed on the surface of B lymphocytes; the presence of the antibody is determined during flow cytometry of the tumor cells. Cell death results from ADCC. All of these drugs have shown clinical activity in the treatment of B-cell lymphomas that are CD20 positive. Side effects include infusion-related reactions, hypotension, fevers, chills, rash, headache, and mild nausea and vomiting. Premedication with acetaminophen and an antihistamine is recommended for rituximab to minimize the first-dose infusion reaction; acetaminophen, antihistamine, and a glucocorticoid prior to obinutuzumab and ofatumumab. In patients with extensive disease, prevention of tumor lysis syndrome is also recommended. Serious adverse events, including fatal infections, progressive multifocal leukoencephalopathy, and reactivation of hepatitis B, have been reported. Thus, all patients should be tested for hepatitis B and treated before therapy commences.

▶ *Pertuzumab, Trastuzumab, and Trastuzumab-DM1 (T-DM1, Trastuzumab Emtansine)*

Pertuzumab and trastuzumab are humanized monoclonal antibody directed against human epidermal receptor 2 (HER-2). When compared to trastuzumab, pertuzumab recognizes different extracellular epitopes, binds uniquely which causes structural changes and therefore interrupts receptor dimerization. These differences were thought to be able to provide greater inhibition of HER-2 when compared to trastuzumab, but this has not been proven to be the case. Cancer tissue must be tested for the presence of HER-2 because patients who do not express HER-2 do not respond to trastuzumab. Trastuzumab-DM1 or ado-trastuzumab emtansine is a compound in which trastuzumab is used as a drug vehicle to deliver an anticancer agent known as emtansine (a maytansine derivative). Trastuzumab is used for the treatment of breast and gastric cancer. Severe congestive heart failure may occur with concurrent anthracycline administration. Cardiac toxicity may be seen when the drug is administered months after anthracycline administration, so patients must be counseled on the signs and symptoms of heart failure. A common side effect associated with trastuzumab is a first-dose infusion-related reaction which includes chills. The patient may be given acetaminophen and diphenhydramine and/or the infusion may be slowed. Other side effects which are rare include hypersensitivity reactions and pulmonary reactions.[32] Pertuzumab has similar adverse effects as trastuzumab. When used in combination with trastuzumab, it does not appear to increase the incidence of cardiac toxicity. A more detailed discussion of the use of trastuzumab and pertuzumab in breast cancer can be found in Chapter 89.

The most common serious adverse effect with ado-trastuzumab emtansine was thrombocytopenia. The platelet nadir usually occurs about 7 days after treatment and recovers within a week. Other adverse effects included abnormal liver function tests, fatigue, nausea, headache, and hypokalemia. Dosing adjustments for cardiac toxicity differ from trastuzumab.

Checkpoint Inhibitors

The immune system is in a continual state of balance between tolerating "normal" tissue and attacking foreign substances. Immunological tolerance is regulated by immune cells, suppressive cytokines, and immune checkpoint pathways.[33] Immune checkpoints become involved following immune activation, creating an inhibitory feedback loop to reduce involvement of normal tissues. Inhibitors of the immune checkpoints act by inhibiting key regulatory steps, promoting activation and proliferation of T cells to induce tumor infiltration and regression. Tumor responses to checkpoint inhibitors differ from those observed with other anticancer therapies. Responses can be seen long after the start of treatment, and pseudoprogression can be seen immediately after starting therapy which instead of representing a tumor progression can represent inflammation only within the tumor area. Adverse effects of checkpoint inhibitors are related to their effect on the immune system, whereby they attack normal cells as well. This can result in severe and fatal immune-mediated adverse reactions, including enterocolitis, hepatitis, toxic epidermal necrolysis, neuropathy, pneumonitis, and endocrine abnormalities. These symptoms can occur during treatment or weeks to months after discontinuation of the drug. Liver and thyroid function tests should be performed at baseline and before each dose and periodically, respectively. Patients should be monitored for symptoms of inflammatory responses (eg, diarrhea as early sign of colitis, shortness of breath as early sign of pneumonitis). If any of these reactions occur, treatment should be initiated with systemic corticosteroids and the drug should be discontinued permanently. Progressive multifocal leukoencephalopathy has been reported. Typically, these side effects can be more severe with the cytotoxic T lymphocytic–associated antigen 4 (CTLA-4) inhibitor than PD or PD-ligand (PD-L) inhibitors.

▶ *Ipilimumab*

Ipilimumab is a recombinant, human monoclonal antibody that binds to the CTLA-4, which is a molecule on T cells that causes a suppression of the immune response. CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands. This blockage has been reported to enhance T-cell activation and proliferation. Ipilimumab is approved for patients with unresectable or metastatic melanoma and kidney cancer. The antitumor effects appear to be T-cell–mediated immune responses and are the highest with this drug of all the available checkpoint inhibitors.

▶ *Nivolumab and Pembrolizumab*

Nivolumab and pembrolizumab are human monoclonal antibodies that block the interaction of the binding to PD-1 and its ligands PD-L1 and PD-L2. These drugs are active in bladder, cervical (pembrolizumab), gastric, head and neck, kidney, liver, and non–small cell lung cancers; some lymphomas, melanoma, and some types of cancers that have high microsatellite instability. Side effects are much less common with PD-1 inhibitors compared with the CTLA-4 inhibitor ipilimumab.

▶ *Atezolizumab, Avelumab, and Durvalumab*

Atezolizumab, avelumab, and durvalumab are recombinant, human monoclonal antibodies that bind PD-L1 and block interaction with the PD-1 receptors. These drugs are active in

bladder (all) and non–small cell lung cancers (atezolizumab, durvalumab); and Merkel cell (avelumab). Side effects are much less common with PD-L1 inhibitors compared with the CTLA-4 inhibitor ipilimumab.

Tyrosine Kinase Inhibitors

More than 100 different types of tyrosine kinases are present in the body. TKIs have been developed to block either several or a specific tyrosine kinase (see Table 88–6). They are used to treat solid tumors, leukemias, and lymphomas and can be used as alone or in combination with IV chemotherapy, surgery, and/or radiation. Some are continuously administered until disease progression occurs or intolerance develops whereas others are given cyclically (eg, 2 weeks on, 1 week off; then repeat). Side effects often limit use if uncontrolled, and typically are different than those observed traditional chemotherapy or immunotherapy. Drug interactions are common as many of these drugs are metabolized through the CYP450 and p-glycoprotein systems and can have decreased concentrations in the presence of antacids, H_2 blockers and/or proton pump inhibitors.

▶ *Anaplastic Lymphoma Kinase (ALK) Inhibitors: Alecitinib, Crizotinib, and Ceritinib*

Crizotinib is a small-molecule inhibitor of the anaplastic lymphoma kinase gene (ALK) and mesenchymal epithelial transition growth factor (*c-MET*). This orally available agent is approved for the treatment of locally advanced or metastatic NSCLC that is ALK positive (about 2%–7% of NSCLC patients) as detected by an FDA-approved test. Adverse effects reported include mild GI symptoms, edema, and visual disturbances, which have been described as trails of light following objects as they move. Alecitinib and ceritinib are also used in ALK-positive NSCLC patients who have progressed on or are intolerant to crizotinib. Ceritinib, which has shown to be 20 times more potent than crizotinib in enzymatic assays, primarily targets ALK along with additional targets, including insulin-like growth factor 1 receptor, insulin receptor, and ROS1. Alecitinib also inhibits RET; neither inhibit *c-MET*. GI toxicities and elevated liver function tests are most common adverse reactions with these agents. Visual changes, pulmonary disease, and QT prolongation are also observed with both and CK elevations with alecitinib.

▶ *BCR-ABL TKIs: Bosutinib, Dasatinib, Imatinib, Nilotinib, and Ponatinib*

Imatinib was the first FDA-approved TKI. Imatinib inhibits phosphorylation during cell proliferation. The drug was designed to block the breakpoint cluster region tyrosine kinase (BCR-ABL) produced by the Philadelphia chromosome associated with CML and ALL. Imatinib also has shown activity against gastrointestinal stromal tumors (GIST) that are positive for c-kit (CD117). Imatinib is usually well tolerated, but common adverse effects include myelosuppression, rash, GI upset, edema, fatigue, arthalgias, myalgias, and headaches. A cumulative cardiotoxicity is a serious but rare adverse effect; therefore it is recommended to closely monitor patients with preexisting cardiac conditions.

Advanced generation BCR-ABL TKIs are more potent than imatinib and can overcome most BCR-ABL mutations that lead to imatinib resistance. Bosutinib, dasatinib, and nilotinib are second-generation BCR-ABL TKIs and are used frontline in the treatment of CML and in CML with resistance or intolerance to imatinib. Side effects of dasatinib and nilotinib are similar to imatinib and include myelosuppression, nausea and vomiting, headache, fluid retention, and hypocalcemia. Pleural effusions have been reported with dasatinib and imatinib but not with nilotinib. QT prolongation can occur with dasatinib and nilotinib. Abnormalities in indirect bilirubin have been reported with nilotinib.

Nilotinib is a competitive inhibitor of UGT1A1 in vitro, which could increase the concentrations of nilotinib. In a pharmacogenetic analysis, patients with (TA)7/(TA)7 genotype (*UGT1A1∗ 28*) had a statistically significant increase in bilirubin over other genotypes.[39]

Bosutinib is indicated for the first- and second-line treatment of CML in cases of resistance or intolerance to prior TKI therapy. With the exception of *T315I*, bosutinib overcomes most BCR-ABL domain mutations. GI disturbances and rash are common. Bosutinib appears to have a milder side effect profile than other TKIs.

Ponatinib is a third-generation multikinase inhibitor and the only advanced generation TKI that overcomes the *T315I* mutation. Serious adverse effects reported included thrombosis, hepatotoxicity (rare), and death (rare). These are included as black-box warnings. Less serious adverse effects include abdominal pain, dry skin, and rash.

▶ *BRAF Inhibitors: Dabrafenib, Trametinib, and Vemurafenib*

Vemurafenib is a potent inhibitor of mutated *BRAF* and is indicated for the treatment of unresectable or metastatic melanoma in patients with documented *BRAFV600E* mutation as determined by an FDA-approved test. Common adverse effects include arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous cell cancer, photosensitivity, nausea, and diarrhea. Approximately 40% of patients require dosage modifications because of adverse effects.[41]

Trametinib is a reversible inhibitor of mitogen-activated extracellular kinases (MEK)-1 and MEK-2 that is also active against *BRAF V600*-mutated forms of BRAF kinases in melanoma cells. It is indicated as monotherapy and in combination with dabrafenib for unresectable or metastatic malignant melanoma. It is not indicated in patients previously treated with a BRAF inhibitor. Rash, diarrhea, and lymphedema were commonly reported. Cardiomyopathy (defined as heart failure) and bleeding have also been reported.

Dabrafenib is a kinase inhibitor that has activity against BRAF kinases. It is indicated for the treatment of unresectable or metastatic malignant melanoma as monotherapy in patients with *BRAF V600E* mutation or in combination with trametinib in patients with *BRAF V600E* or V600K mutations. Adverse effects associated with this agent include arthralgias, alopecia, headache, palmar-plantar erythrodysesthesia syndrome, elevated liver enzymes, pyrexia, and papilloma.

▶ *Cyclin-Dependent Kinase (CDK) Inhibitors: Abemaciclib, Palbociclib, and Ribociclib*

Abemacicilib, palbociclib, and ribociclib all inhibit CDKs 4 and 6, which prevent phosphorylation and subsequent inactivation of the retinoblastoma tumor suppressor protein, ultimately causing cell cycle arrest and inhibiting cancer cell proliferation. Each of the available CDK4/6 inhibitors is used in the treatment of postmenopausal women with hormone receptor positive but HER2 negative breast cancer. Palbociclib and ribociclib are administered daily for 21 days, followed by 7 days off, whereas abemaciclib is administered daily. Common side effects include neutropenia, GI toxicities, and hair loss. Rarely, abemacicilib is associated with venous thromboembolism, ribociclib with QT prolongation, and both with hepatotoxicity.

▶ *EGFR Pathway Inhibitors: Afatinib, Erlotinib, Lapatinib, Neratinib, and Osimertinib*

Patients with NSCLC in which the tumors have mutations in exon 19 and/or 21 in the EGFR pathway will likely respond to EGFR TKIs such as afatinib and erlotinib. Those with EGFR *T790M* mutations will likely respond to osimertinib. These agents are believed to inhibit the intracellular phosphorylation of the EGFR. Food increases bioavailability to almost 100%, but is variable; experts recommend administering erlotinib on an empty stomach. Smoking increases the clearance of erlotinib by 24%, which may result in treatment failure and different doses are used for smokers versus nonsmokers.[34] Side effects of afatinib and erlotinib include interstitial lung disease, acneiform rash, diarrhea, anorexia, pruritus, conjunctivitis, and dry skin.

Lapatinib and neratinib inhibit the intracellular kinase domains of both EGFR and HER-2 and have been shown to retain activity against breast cancer cells that have become resistant to trastuzumab. Both are indicated for the treatment of patients with breast cancer whose tumors overexpress HER-2. Common side effects include diarrhea, nausea/vomiting, and fatigue; lapatinib is also associated with hand–foot skin reaction (HFSR). HFSR differs than HFS in that it initially develops as erythema and soreness, progressing to blisters and eventually hyperkeratosis.

▶ *Multikinase Inhibitors (Axitinib, Sorafenib, Sunitinib, and Pazopanib)*

Multikinase inhibitors inhibit multiple tyrosine kinases and are used for many different solid tumors. A full list of available multikinase inhibitors is found in Table 88–6. Some of the more common ones are described here. Sorafenib is a multikinase inhibitor that inhibits both intracellular and extracellular kinases and is used in treatment of hepatic, kidney, and thyroid cancers. The primary side effects of sorafenib include rash, HFSR, diarrhea, pruritus, and elevations in serum lipase.

Cabozantinib and pazopanib both primarily inhibit VEGF receptor–1 (VEGFR)-1, VEGFR-2, VEGFR-3, and several other tyrosine kinases. Cabozantinib is available in two dosage forms: tablets and capsules. The tablet formulation and lower dose is to be used for patients with advanced kidney cancer, whereas the capsules are larger dose for patients with medullary thyroid cancer. Pazopanib is used to treat advanced kidney cancer and sarcomas. Common side effects of these drugs are diarrhea, nausea, anorexia, HFSR syndrome, hypertension, and fatigue. Pazopanib also is associated with hair color changes. Serious toxicities that have been observed are fatal hepatotoxicity, prolonged QT intervals and torsades de pointes, hemorrhagic events, arterial thrombotic events, GI perforation, and proteinuria.

Regorafenib is another small molecule inhibitor of multiple membrane-bound and intracellular kinases used in treatment of metastatic colorectal cancer and GI stromal tumor. The proposed mechanism of action is through inhibition of vascular endothelial receptors involved in angiogenesis. GI effects, hypertension, mucositis, infection, rash, and fever are commonly occurring adverse effects. Hepatotoxicity is listed as a black-box warning; therefore, hepatic function should be monitored closely. It is an orally administered agent given for the first 21 days per 28-day cycle and should be taken with a low-fat breakfast (30 grams or less).

▶ *Phosphoinositide 3-Kinase (PI3-K) Inhibitors: Copanlisib and Idelalisib*

Copanlisib and idelalisib are approved for follicular lymphoma and CLL, respectively, and target PI3-K, an essential lipid kinase. Adverse effects associated with copanlisib are associated with hyperglycemia, hematologic abnormalities, fatigue, diarrhea, and hypertension. Idealisib causes GI disturbances, rash, hematological side effects, fatigue, and musculoskeletal pain. Idelalisib has hepatotoxicity, colitis, pneumonitis, infections, and intestinal perforation as black-box warnings.

Hormonal Therapies

Hormonal or endocrine therapies have shown activity in the treatment of cancers whose growth is affected by gonadal hormonal control. Hormonal treatments either block or decrease the production of endogenous hormones. You will learn more about these treatments and outcomes in Chapters 89 and 91, including the breast and prostate cancer chapters.

▶ *Antiandrogens: Bicalutamide, Flutamide, and Nilutamide*

The antiandrogens block androgen receptors (ARs) to inhibit the action of testosterone and dihydrotestosterone in prostate cancer cells. Unfortunately, prostate cancer cells may become hormone refractory. Side effects common to these agents are hot flashes, gynecomastia, and decreased libido. Flutamide tends to be associated with more diarrhea and requires three times daily administration, whereas bicalutamide is dosed once daily. Nilutamide may cause interstitial pneumonia and is associated with the visual disturbance of delayed adaptation to darkness.

▶ *Pure Androgen Receptor Antagonist: Apalutamide, Enzalutamide*

These are antagonists that work by competitively inhibiting androgen binding to ARs and by inhibiting AR nuclear translocation and coactivator recruitment of the ligand-receptor complex. These agents have shown to competitively inhibit androgen binding to ARs and inhibit AR nuclear translocation and interaction with DNA. Both are indicated for nonmetastatic castrate-resistant prostate cancer and enzalutamide is indicated for the treatment of metastatic castration-resistant prostate cancer. The most common side effect of this therapy is fatigue; otherwise it is well tolerated.

▶ *Luteinizing Hormone–Releasing Hormone Agonists: Goserelin and Leuprolide*

Initially, luteinizing hormone–releasing hormone (LHRH) agonists increase levels of luteinizing hormone and follicle-stimulating hormone, but testosterone and estrogen levels are decreased because of continuous negative-feedback inhibition. Major side effects are testicular atrophy, decreased libido, gynecomastia, and hot flashes. Goserelin is injected as a pellet under the skin; therefore, subcutaneous injection of lidocaine around the injection site before administration helps to decrease the pain associated with goserelin administration. Numerous dosage forms are available for leuprolide with varying strengths and dosing intervals. Antiandrogens may be administered during initial therapy to decrease symptoms of tumor flare (eg, bone pain and urinary tract obstruction).

▶ *Gonadotropin-Releasing Hormone Antagonist: Degarelix*

Degarelix is a gonadotropin-releasing hormone (GnRH) receptor antagonist that works by binding reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone. Degarelix is indicated for the treatment of advanced prostate cancer. Adverse events include hot

flashes, injection site reactions, and an increase in liver enzymes. An advantage of degarelix over LHRH agonists is the lack of the tumor flare.[35]

▶ *Abiraterone*

Abiraterone is an orally available androgen biosynthesis inhibitor that inhibits 17α-hydroxylase/C17,20-lyase (CYP17), which is expressed in testicular, adrenal, and prostatic tumor tissues. Abiraterone is indicated in combination with prednisone for the treatment of metastatic prostate cancer. Adverse effects include hypokalemia, edema, muscle discomfort, fatigue, hot flashes, nocturia, urinary frequency, and hypertension. The patient must be counseled to take the oral medication on an empty stomach because food increases absorption and results in adverse reactions.[36]

▶ *Aromatase Inhibitors*

Three AIs are currently available: anastrozole, letrozole, and exemestane. Anastrozole and letrozole are selective nonsteroidal AIs that lower estrogen levels. Anastrozole is a standard adjuvant treatment of postmenopausal women with hormone-positive breast cancer. The length of therapy is usually 5 years; however, evidence exists that suggests a benefit of prolonged treatment in certain situations. Exemestane, a steroidal compound, is an irreversible aromatase inactivator that binds to the aromatase enzyme to block the production of estrogen from androgens. This difference in activity does not appear to translate into improved clinical outcomes when compared to other AI therapies. When compared to tamoxifen, there are less endometrial and uterine cancers, vaginal bleeding, and thrombosis with AI therapy. Common adverse effects associated with the AI therapy include hot flashes and arthralgias. Serious adverse effects include osteoporosis, skeletal-related events, and atherosclerotic cardiovascular disease. The AIs are used exclusively for postmenopausal women. More information on the pharmacology and clinical use of AI therapy can be found in Chapter 89.

▶ *Antiestrogens*

Antiestrogens bind to estrogen receptors (ERs) and block the effect of estrogen on tissue. Two classes of antiestrogens exist: SERMs (tamoxifen, raloxifene) and selective estrogen-receptor downregulators (SERDs, fulvestrant). SERDs were developed in an effort to eliminate the unwanted estrogenic side effects from the SERMs. Tamoxifen is used for the treatment of ER positive premenopausal or postmenopausal metastatic hormone receptor–positive breast cancer, as adjuvant and primary treatment of breast cancer, and in the prevention of breast cancer in high-risk women. The agent has a beneficial effect on bone density and the lipid profile. Unwanted side effects include hot flashes, fluid retention, and mood swings. Thrombosis, endometrial and uterine cancer, corneal changes, and cataracts are harmful adverse effects that occur more frequently with this agent. Although uncommon, there is a disease/tumor flare which can occur during the initiation of therapy in metastatic breast cancer patients with bone metastases. Because tamoxifen is a substrate of CYP3A4, decreased tamoxifen levels have occurred with use of St. John's wort and rifampin. Tamoxifen is also a substrate for CYP450 2D6, and evidence suggests that those who are *CYP2D6*4/*4* may have a poorer response and more toxicity with tamoxifen.[37] Routine pharmacogenomics screening of these patients is not currently recommended. Significant drug interactions exist and drug–drug interactions affecting this enzyme should be avoided if possible.

Raloxifene is another SERM and is used for the treatment of osteoporosis in postmenopausal women and is the chemopreventative agent of choice for the prevention of breast cancer in high-risk women. When compared head to head with tamoxifen for breast cancer prevention, it was demonstrated to have equal efficacy with less toxicity. Raloxifene was not studied in premenopausal women; therefore, tamoxifen is still the preventative agent of choice in these women. Hot flashes, arthralgias, and peripheral edema occur frequently with raloxifene, but thrombosis and endometrial cancer is less common than with tamoxifen.

Fulvestrant is used as second-line treatment in hormone receptor–positive metastatic breast cancer, postmenopausal women with disease progression following antiestrogen therapy. Fulvestrant is given as a monthly intramuscular injection, which might be a deterrent to some patients.

ADMINISTRATION ISSUES

Extravasation

One issue of chemotherapy safety is extravasation. Antineoplastic agents that cause severe tissue damage when they escape from the vasculature are called vesicants. The tissue damage may be severe, with tissue sloughing and loss of mobility, depending on the area of extravasation. Patients need to be educated to notify the nurse immediately if there is any pain on administration. If extravasation of a vesicant occurs, the injection should be stopped and any fluid aspirated out of the injection site. The prevention, risk factors, signs and symptoms, causative agents, and treatment will be discussed thoroughly in Chapter 99.

Hypersensitivity Reactions

Hypersensitivity reactions of cancer treatments are problematic because of cross-reactivity between agents and the desire to continue active therapies against the cancer.[38] For documented immediate hypersensitivity reactions to a particular agent, further administration of the agent may be achieved through extensive premedication with H_1 and H_2 antihistamines and corticosteroids and through use of desensitization protocols which include escalating doses of the offending agent given at doses of one-hundredth, one-tenth, and the balance of the dose (so the total dose administered is equivalent to the normally prescribed dose) administered over a much longer period of time. These treatments must be given in an environment where resuscitation is readily available in case of medical emergency.

Patient Encounter 1, Part 3

The patient has progressed following therapy with mFOLFOX6 and subsequently received 6 cycles of FOLFIRI before progressing a second time. She now will be receiving a new prescription for regorafenib 160 mg orally, once daily.

What education and training should be provided to the patient to ensure their understanding of safe handling procedures as well as thorough knowledge of proper administration?

How should the patient be instructed to take this medication, in regards to meals or the time of day?

Secondary Malignancies

Chemotherapy and radiation therapy treatments may cause cancers later in life; these are referred to as secondary cancers. The most common type of secondary cancer is myelodysplastic syndrome, or AML. The antineoplastic agents most commonly associated with secondary malignancies are alkylating agents, etoposide, teniposide, topoisomerase inhibitors, and anthracyclines. Although the risk for secondary cancers is extremely low, it must outweigh the risk of survival produced by treatment of the primary malignancy. Because secondary malignancies may not occur for several years after treatment, patients with relatively short-term survival owing to the primary malignancy should consider the more immediate benefits of chemotherapy. Radiation therapy rarely may cause solid tumors as secondary cancers decades after treatment. The most common example of radiation therapy–induced secondary malignancy is breast cancer, which rarely occurs after mantle field radiation therapy for Hodgkin disease.

CHEMOTHERAPY SAFETY

One of the first Institute of Medicine (IOM) reports, the health arm of the National Academy of Sciences, starts out with a patient who died from an overdose of chemotherapy; the patient did not have an immediately life-threatening cancer, so her death was hastened by a medication error. Chemotherapy agents may cause harm to patients, health professionals, and the environment if not handled correctly.

KEY CONCEPT Because of the risk of severe toxicities associated with many of the chemotherapy agents, safety precautions must be in place to prevent chemotherapy errors or accidental chemotherapy exposures of health professionals or patients. The American Society of Clinical Oncology, Hematology/Oncology Pharmacy Association, Oncology Nursing Society, and the American Society of Health-System Pharmacists have information to assist in the safe handling of chemotherapy agents.[18,39-41] National, state, and local regulations regarding the safe disposal of chemotherapy agents and the equipment used to administer them need to be followed to protect the environment.

LO 4

KEY CONCEPT Each organization should have chemotherapy safety checks built into the prescribing, preparation, and administration of chemotherapy.[16,39] Dosing based on patient-specific information should be included on every order for chemotherapy, whether it is oral or parenteral. Many chemotherapy regimens are referred to by acronyms (eg, AC, which is doxorubicin cyclophosphamide); these should not be allowed as the only reference to drugs in the prescribing of chemotherapy. Also, abbreviations for the names of chemotherapy agents should be avoided because one abbreviation may stand for two different drug entities. For drugs such as doxorubicin and liposomal doxorubicin, the names should be written out fully, and in this case, the addition of the brand name may help to prevent a mistake.

The measured height and weight, along with the body surface area (BSA), if applicable, should be readily available, along with the dosage in milligrams per meter squared or kilogram, so that the dosage may be checked. If a chemotherapy regimen is a continuous infusion of 800 mg/m^2/day for 4 days, an added safety feature would be to include the total dosage of 3200 mg in order to prevent any ambiguity. In cases where the clinician wants to decrease the dosage based on a laboratory value or side effect, it is recommended that the clinician include that information with the order so that everyone understands what the correct dosage is for that patient. Chemotherapy dosages should be checked for route and dose to determine that the dosages prescribed are correct according to the regimen and do not exceed dosing guidelines. Appropriate laboratory values should be checked to verify that dosages are correct for any organ dysfunction present, drug interactions should be scrutinized closely (Tables 88–8 and 88–9), and if applicable the patient has the appropriate indication (eg, presence of EGFR mutation for use of erlotinib).[42] Health professionals administering chemotherapy should check the dosage calculation for the patient's weight or BSA along with the five Rs of administering medication (ie, right patient, right medication, right dose, and right route, at the right time). If there is any question about the safe dosage or safe administration of a chemotherapy agent, the chemotherapy should not be administered until the question is resolved.

An area of controversy with chemotherapy dosing: What weight should be used for patients who are morbidly obese currently? Based on clinical practice guidelines published by the American Society of Clinical Oncology, it is recommended that clinicians routinely use an obese patient's actual body weight, instead of an ideal body weight or other measurement.[43]

Patient Encounter 2

A 28-year-old man is receiving high-dose methotrexate 12 grams/m^2/day as part of a multi-drug regimen for a newly diagnosed osteosarcoma. While receiving chemotherapy, his serum creatinine has risen from 0.8 mg/dL to 2.1 mg/dL (71–186 µmol/L) in the last 3 days.

What is the likely diagnosis?

What medication should always be included as part of this regimen?

What measures should be taken by patients while receiving high-dose methotrexate therapy?

ORAL CHEMOTHERAPY

KEY CONCEPT Over the past decade, self-administration of oral chemotherapy has increased because of the availability of oral, novel anticancer agents. Although oral chemotherapy has many advantages, such as convenience for the patient, potential increase in quality of life, and decreased treatment-associated costs, it also comes with an increased risk of medication errors, less monitoring of adverse effects and drug, dietary supplements, over-the-counter (OTC) medication, and/or food interactions and accidental exposure to other individuals. Health professionals have an important role in ensuring safe handling of oral anticancer agents, and should be properly trained and perform competently within guidelines for the storage, handling, and disposal of oral agents. The health professionals are also expected to provide proper training and education on safe handling and proper administration (see Table 88–10) for the patient and caregivers.[39,40,44]

LO 5

CANCER SURVIVORSHIP

KEY CONCEPT As early detection of cancers and effective therapies have improved over the last several years, the number of cancer survivors has increased. A cancer survivor by definition, according to the National Coalition for Cancer Survivorship, starts at the point of diagnosis. It is estimated that two out of every three people with cancer live at least 5 years after diagnosis. In 2005, the IOM released a report, "From Cancer Patient to Cancer Survivor: Lost in Transition," which emphasized that a lack of definitive guidance in

LO 6

Table 88–8

Empiric Dose Modifications in Patients with Renal Dysfunction

Agent	Organ Dysfunction	Dose Modification
Aldesleukin	Serum Creatinine > 1.5 mg/dL	Do not initiate
Bendamstine	CrCL < 40 mL/min	Do not use
Bleomycin	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 40–50 mL/min	70% of normal dose
	CrCl = 30–40 mL/min	60% of normal dose
	CrCl = 20–30 mL/min	55% of normal dose
	CrCl = 10–20 mL/min	45% of normal dose
	CrCl = 5–10 mL/min	40% of normal dose
Bosutinib (initial dosage adjustment)	CrCl > 50–80 mL/min	No dosage adjustments
	CrCl = 30–50	Initial: 400 mg once daily
	CrCl < 30 mL/min	Initial: 300 mg once daily
Brentuximab	CrCl ≥ 30 mL/min	Initial: no dosage adjustment
	CrCl < 30 mL/min	Avoid use
Cabazitaxel	CrCl > 30 mL/min	No dosage adjustment
	CrCl < 30 mL/min	Use caution; monitor closely
Capecitabine (initial dosage adjustment)	CrCl > 51 mL/min	Initial: no dosage adjustment
	CrCl = 30–50 mL/min	Initial: 75% of normal dose
	CrCl < 30 mL/min	Contraindicated
Carboplatin (initial dosage adjustment)	CrCl equal to 41–59 mL/min	Initiate at 250 mg/m^2 and adjust subsequent doses based on bone marrow toxicity
	CrCl = 16–40 mL/min	Initiate at 200 mg/m^2 and adjust subsequent doses based on bone marrow toxicity
	CrCl < 15 mL/min	No dosage adjustments provided in the manufacturer's labeling (has not been studied)
Carmustine	CrCl = 46–60 mL/min	80% of normal dose
	CrCl = 31–45 mL/min	75% of normal dose
	CrCl < 30 mL/min	Consider use of alternative drug
Cisplatin	CrCl = 10–50 mL/min	75% of normal dose
	CrCl < 10 mL/min	50% of dose
Cladribine	CrCl = 10–50 mL/min	75% of normal dose
	CrCl < 10 mL/min	60% of normal dose
Clofarabine (initial dosage adjustment)	CrCl > 60 mL/min	No dosage adjustment
	CrCl = 30–60 mL/min	50% of normal dose
	CrCl < 30 mL/min	No dosage adjustments provided in the manufacturer's labeling (has not been studied)
Crizotinib	CrCl = 30–89 mL/min	Do dosage adjustment
	CrCl < 30 mL/min	Decrease dose to 250 mg once daily
Cyclophosphamide	CrCl > 10	No dosage adjustment
	CrCl < 10	75% of normal dose
Cytarabine	CrCl = 46–60 mL/min	60% of normal dose
	CrCl = 31–45 mL/min	50% of dose
	CrCl < 30 mL/min	Consider use of alternative drug
Dacarbazine	CrCl = 46–60 mL/min	80% of normal dose
	CrCl = 31–45 mL/min	75% of normal dose
	CrCl < 30 mL/min	70% of normal dose
Daunorubicin	SCR > 3 mg/dL	50% of normal dose
Eribulin	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 15–49 mL/min	Reduce dose to eribulin mesylate 1.1 mg/m^2
Etoposide	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 15–50 mL/min	75% of dose
	CrCl < 15 mL/min	Data not available; consider further dose reductions
Fludarabine	CrCl > 80 mL/min	No dosage adjustment
	CrCl = 50–79 mL/min	Reduce dose to 20 mg/m^2
	CrCl = 30–49 mL/min	Reduce dose to 15 mg/m^2
	CrCl < 30 mL/min	Do not use
Gemcitabine	Mild-to-severe renal impairment	No dosage adjustment
Hydroxyurea	CrCl > 60 mL/min	No dosage adjustment
	CrCl < 60 mL/min	50% of normal dose, titrate to response/avoidance of toxicity
Idarubicin	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 10–50 mL/min	75% of normal dose
	CrCl < 10 mL/min	50% of normal dose
Ifosfamide	CrCl > 10 mL/min	No dosage adjustment
	CrCl < 10 mL/min	75% of normal dose

(*Continued*)

Table 88–8

Empiric Dose Modifications in Patients with Renal Dysfunction (*Continued*)

Agent	Organ Dysfunction	Dose Modification
Ixazomib (initial dosage adjustment)	CrCl > 30 mL/min	No dosage adjustment
	CrCl < 30 mL/min	Reduce initial dose to 3 mg once weekly
Lenalidomide (initial dosage adjustment)	CrCl > 60 mL/min	No dosage adjustment
	CrCl = 30–60 mL/min	10 mg once daily (for multiple myeloma, may increase to 15 mg once daily after 2 cycles if nonresponsive but tolerating treatment)
	CrCl < 30 mL/min	15 mg every 48 hours
Lomustine	CrCl = 10–50 mL/min	75% of normal dose
	CrCl < 10 mL/min	25%–50% of normal dose
Methotrexate[a]	CrCl = 10–50 mL/min	50% of normal dose
	CrCl < 10 mL/min	Do not use
Mercaptopurine	eGFR < 50 mL/min/1.73 m^2	Administer every 48 hours
Mitomycin	CrCl < 10 mL/min	75% of normal dose
Oxaliplatin	CrCl > 30 mL/min	No dosage adjustment
	CrCl < 30 mL/min	Reuce dose from 85 mg/m^2 to 65 mg/m^2
Pralatrexate	eGFR > 30 mL/min/1.73m^2	No dosage adjustment
	eGFR = 15–30 mL/min/1.73m^2	Reduce dose to 15 mg/m^2
Peginterferon alpha-2b	CrCl = 30–50 mL/min	Reduce dose by 25%
	CrCl = 10–29 mL/min	Reduce dose by 50%
Pemetrexed	CrCl > 45 mL/min	No dosage adjustment
	CrCl < 45 mL/min	Do not use
Pentostatin	CrCl = 46–60 mL/min	70% of normal dose
	CrCl = 31–45 mL/min	60% of normal dose
	CrCl < 30 mL/min	Consider use of alternative drug
Pomalidomide	CrCl > 45 mL/min	No dosage adjustment
	CrCl < 45 mL/min	Insufficient data to make determination
Streptozocin	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 10–50 mL/min	75% of normal dose
	CrCl < 10 mL/min	50% of normal dose
Topotecan (IV)	CrCl > 40 mL/min	No dosage adjustment
	CrCl = 20–39 mL/min	Reduce dose to 0.75 mg/m^2/dose
	CrCl < 20 mL/min	No dosage adjustments provided in manufacturer's labeling (insufficient data)
Topotecan (oral)	CrCl > 50 mL/min	No dosage adjustment
	CrCl = 30–49 mL/min	Reduce dose to 1.5/mg/m^2/day; may increase after 1st cycle by 0.4 mg/m^2/day if no severe hematologic or gastrointestinal toxicities occur
	CrCl < 30 mL/min	Reduce dose to 0.6 mg/m^2/day; may increase after 1st cycle by 0.4 mg/m^2/day if no severe hematologic or gastrointestinal toxicities occur
Vandetanib	CrCl > 50 mL/min	No dosage adjustment
	CrCl < 50 mL/min	Reduce initial dose to 200 mg once daily

[a]Monitor levels closely in all patients receiving high-dose therapy (eg, 150 mg/m^2 or greater).

this area and identified that increased efforts were needed to raising awareness. In addition to facing a risk of a cancer recurrence, secondary malignancy, and an increased risk of developing other health conditions, cancer survivors often face physical, emotional, financial, and social challenges as a result of the cancer diagnosis and treatment.[45] The American Cancer Society (ACS), Centers for Disease Control (CDC), American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) all have guidelines that describe strategies to meet the needs of these individuals who experience the long-term effects of cancer and its treatment.[46-49]

OUTCOME EVALUATION

Once a pathologic diagnosis of cancer is made, the patient may be evaluated by a radiation oncologist, a surgical oncologist, and a medical oncologist. Options for treatment are presented that may include surgery, radiation, pharmacologic therapy, or some combination of these modalities. The goals of treatment vary by the cancer and the stage of disease. For example, the patient who has metastatic kidney cancer could be presented with several options. They may have a possible cure with high-dose aldesleukin or receive palliative therapy with pazopanib or sunitinib, or the patient may decline any therapy because of fears of significant toxicity that would decrease quality of life. In this case, if the patient's performance status is poor, such as an ECOG performance status 3, then the patient would not be a candidate for aldesleukin therapy because of significant toxicity or even death from treatment. The patient with the poor performance status will receive palliative therapy to control symptoms of the disease to improve the quality of life at the end of life. For the patient with a poor performance status and extensive metastatic disease, no treatment of the cancer may be appropriate, and the patient may be enrolled in a hospice program or provided comfort care.

Table 88–9

Empiric Dose Modifications for Patients with Hepatic Dysfunction

Agent	Organ Dysfunction	Dose Modification
Abiraterone (initial dosage adjustment)	Child-Pugh Class A	No dosage adjustment
	Child-Pugh Class B	Decrease dose to 250 mg daily
	Child-Pugh Class C	Do not give
Asparaginase (dose modifications during treatment)	ALT/AST > 3–5 × ULN	Continue therapy
	ALT/AST > 5–20 × ULN	Delay next dose until transaminases < 3 × ULN
	ALT/AST > 20 × ULN	Discontinue therapy if it takes > 1 week for transaminases to return to < 3× ULN
	Direct bilirubin < 3 mg/dL	Continue therapy
	Direct bilirubin = 3.1–5 mg/dL	Hold asparaginase and resume when direct bilirubin < 2 mg/dL
	Direct bilirubin > 5 mg/dL	Discontinue
Axitinib	Child-Pugh Class A	No modification needed
	Child-Pugh Class B	Reduce starting dose by 50%
	Child-Pugh Class C	Has not been studied
Bendamustine	Mild impairment	Use with caution
	Bilirubin > 1.5 × ULN and/or AST/ALT 2.5 × ULN	Do not use
Bortezomib	Bilirubin > 1.5 × ULN	Reduce initial dose to 0.7 mg/m^2 in the first cycle
Cabazitaxel	Mild impairment	Reduce dose to 20 mg/m^2
	Moderate impairment	Reduce dose to 15 mg/m^2
	Severe impairment	Contraindicated
Cabozantinib	Mild or moderate impairment	40 mg daily (Cabometyx); 80 mg daily (Cometriq)
	Severe impairment	Do not use
Carfilzomib	Mild or moderate impairment	75% of normal dose
	Severe impairment	Has not been studied
Crizotinib (during treatment)	Grade 3/4 ALT/AST elevation (> 5 × ULN) or bilirubin ≥ 1.5× ULN	200 mg twice daily
	Recurrent grade 3/4 ALT/AST elevation	250 mg once daily
	Recurrent grade 3/4 ALT/AST elevation at 250 mg	Permanently discontinue
Daunorubicin	Serum bilirubin 1.2–3 mg/dL	75% of normal dose
	Serum bilirubin > 3 mg/dL	50% of normal dose
Docetaxel	Total bilirubin > ULN, or AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN	Do not give
	AST/ALT > 2.5 but 5 × or less ULN and alkaline phosphate 2.5 × ULN or less	Decrease dose by 20%
	AST/ALT > 1.5 but 5 × ULN or less and alkaline phosphate > 2.5 but ≤ 5 × ULN	Decrease dose by 20%
	AST/ALT > 5 × ULN and/or alkaline phosphate > 5 × ULN	Discontinue use
Doxorubicin	Serum bilirubin 1.2–3 mg/dL	50% of normal dose
	Serum bilirubin 3.1–5 mg/dL	25% of normal dose
	Child-Pugh Class C or bilirubin > 5 mg/dL	Use is contraindicated
Epirubicin	Bilirubin 1.2–3 mg/dL or AST 2 to 4 × ULN	50% of normal dose
	Bilirubin > 3 mg/dL or AST > 4 × ULN	25% of normal dose
	Severe hepatic impairment	Do not use
Eribulin	Child-Pugh A	Reduce dose to 1.1 mg/m^2
	Child-Pugh Class B	Reduce dose to 0.7 mg/m^2
	Child-Pugh Class C	Do not use
Etoposide	Bilirubin 1.5–3 mg/dL or AST > 3 × ULN	50% of normal dose
Everolimus (for breast cancer)	Child-Pugh Class A	Reduce to 7.5 mg once daily
	Child-Pugh Class B	Reduce dose to 5 mg once daily
	Child-Pugh Class C	Reduce dose to 2.5 mg once daily
Fluorouracil	Bilirubin > 5 mg/dL	Do not use
Flutamide	Mild to moderate impairment	No dosing adjustments in manufacturer's labeling
	Severe impairment	Contraindicated
Idarubicin	Bilirubin 2.6–5 mg/dL	50% of normal dose
	Bilirubin > 5 mg/dL	Do not use
Imatinib	Mild-to-moderate impairment	No dosage adjustment
	Severe impairment	75% of normal dose
	During therapy, if elevations of bilirubin > 3 × ULN or transaminases > 5 × ULN	Withhold treatment until bilirubin < 1.5 × ULN and transaminases < 2.5 × ULN

(*Continued*)

Table 88–9

Empiric Dose Modifications for Patients with Hepatic Dysfunction (*Continued*)

Agent	Organ Dysfunction	Dose Modification
Irinotecan	Bilirubin > ULN but < 2 mg/dL	Consider reducing initial dose
	Bilirubin > 2 mg/dL	Do not use
Ixabepilone	AST&ALT ≤ 2.5 × ULN and bilirubin ≤ 1 × ULN	No dosage adjustments
	AST&ALT > 2.5 but ≤ 10 × ULN and bilirubin ≥ 1.5, but ≤3 × ULN	Reduce dose to 32 mg/m^2
	AST&ALT ≤ 10 × ULN and bilirubin > 1.5 but ≤ 3 × ULN	Reduce dose 20–32 mg/m^2
	AST or ALT > 10 × ULN or bilirubin > 3 × ULN	Do not use
Ixazomib	Mild impairment	No dosage adjustment
	Moderate impairment	Reduce initial dose to 3 mg once weekly
Lapatinib	Child-Pugh Classes A or B	No dosage adjustment
	Child-Pugh Class C	In combination with capecitabine—reduce dose from 1250 mg once daily to 750 mg once daily; In combination with letrozole—reduce dose from 1500 mg once daily to 1000 mg once daily
Paclitaxel	Hepatic impairment	Adjustments vary depending on diagnosis/regimen
Albumin-bound paclitaxel (Abraxane)	Hepatic impairment	Adjustments vary depending on diagnosis/regimen
Pralatrexate	AST or ALT > 5–20 × ULN or bilirubin > 3–10 × ULN	Omit dose; decrease to 20 mg/m^2 when recovery to grade 2 or better
	AST or ALT > 20 × ULN or bilirubin > 10 × ULN	Discontinue treatment
Pazopanib	Mild impairment	No dosage adjustment
	Moderate impairment	Consider alternative therapy or reduce to 200 mg once daily
	Severe impairment	Do not use
Pemetrexed	Grade 3 or 4 elevation during treatment	Reduce dose to 75% of previous dose (and cisplatin)
Pomalidomide	Mild or moderate impairment	Initial: 3 mg once daily
	Severe impairment	Initial: 2 mg once daily
	Impairment during treatment	Stop and evaluate; after liver enzymes return to baseline, may consider restarting at lower dose
Ponatinib	Mild-to-severe impairment	Initial: 30 mg once daily; monitor closely for toxicity
Ramucirumab	Mild-to-moderate impairment	No dosage adjustment
	Severe impairment	Has not been studied
Ribociclib	Mild impairment	No dosage adjustment
	Moderate-to-severe impairment	Reduce initial dose to 400 mg/day
Temsiroliumus	Mild impairment	Reduce dose to 15 mg once weekly
	Moderate-to-severe impairment	Contraindicated
Thiotepa	Hepatic impairment	No dosage adjustments in labeling; use with caution; thiotepa is extensively hepatically metabolized
Trabectedin	Mild impairment	No dosage adjustment
	Moderate impairment	Reduce dose from 1.5 mg/m^2 to 0.9 mg/m^2
	Severe impairment	Do not give
Vandetanib	Mild impairment	No dosage adjustments provided in manufacturer's labeling
	Moderate-to-severe impairment	Do not use
Vinblastine	Serum bilirubin 1.5–3 mg/dL or transaminases 2–3 × ULN	50% of normal dose
	Serum bilirubin > 3 × ULN	Do not use
Vincristine	Serum bilirubin 1.5–3 mg/dL or transaminases 2–3 × ULN or alkaline phosphatase increased	50% of normal dose
	Serum bilirubin > 3 mg/dL	Do not use
Vinorelbine	Serum bilirubin > 2.1–2 mg/dL	50% of normal dose
	Serum bilirubin > 3 mg/dL	25% of normal dose
Vorinostat	Mild-to-moderate impairment	300 mg once daily
	Severe impairment	Not studied

Mild preexisting impairment: Bilirubin > 1 to 1.5 × ULN or AST > ULN

Moderate preexisting impairment: Bilirubin > 1.5 but 3 × ULN or less, or AST or ALT 2.5 to 10 × ULN

Severe preexisting impairment: Bilirubin > 3 × ULN

AST, aspartate transaminase; ALT, alanine transaminase; ULN, upper limit of normal.

Table 88–10

Oral Chemotherapy Administration with Respect to Food

	With Food	Empty Stomach	With or Without Food
Abiraterone		X	
Afatinib		X	
Alectinib	X		
Altretamine	X (and at bedtime)		
Anastrozole			X
Axitinib			X
Bexarotene	X		
Bicalutamide			X
Brigatinib			X
Bosutinib	X		
Cabozantinib		X	
Capecitabine	X		
Ceritinib		X	
Crizotinib			X
Cobimetinib			X
Dabrafenib		X	
Dasatinib			X
Enzalutamide			X
Erlotinib		X	
Estramustine		X	
Etoposide		X	
Everolimus			X
Exemestane	X		
Flutamide			X
Ibrutinib			X
Idelalisib			X
Imatinib	X		
Lapatinib		X	
Lenalidomide			X
Lenvatinib			X
Letrozole			X
Lomustine		X	
Midostaurin	X		
Neratinib	X		
Nilotinib		X	
Nilutamide			X
Niraparib			X
Olaparib			X
Palbociclib	X		
Panobinostat			X
Pazopanib		X	
Pomalidomide			X
Ponatinib			X
Procarbazine			X (avoid tyramine-containing foods)
Regorafenib	X (low fat meal)		
Rolapitant			X
Rucaparib			X
Sonidegib		X	
Sorafenib		X	
Sunitinib			X
Tamoxifen			X
Temozolamide			X (must be consistent)
Thalidomide		X	
Toremifene			X
Trametinib		X	
Tretinoin	X		
Trifluridine/Tipiracil	X		
Vandetanib			X
Vemurafenib			X
Venetoclax	X		
Vismodegib			X
Vorinostat	X		

LO 7

Patient Care Process

Collect Information:

- Patient characteristics (eg, age, race, sex, patient preferences)
- Patient history (lifestyle factors—alcohol use, tobacco use, diet, physical activity)
- Patient medical and family history (eg, ECOG performance status, concurrent disease states)
- Clinical presentation signs and symptoms (eg, changes in bowel habits, unusual bleeding, weight loss, recurrent fevers)
- Current medications (prescription, over-the-counter, and complimentary alternative, medical marijuana)
- Objective data
  - BP, heart rate (HR), height, weight, and BSA
  - Labs (eg, serum electrolytes, renal function, liver chemistries, complete blood count, coagulation studies, tumor markers)
  - Other diagnostic test (eg, left ventricular ejection fraction)
  - Physical examination data (eg, hepatomegaly, lymphadenopathy)
  - Cancer staging
  - Colorectal tumor genomics (eg, *BRAF, HER-2, PIK3CA, RAS*)

Assess the Information:

- Risk factors for treatment-related toxicities (eg, *UGT1A1*28* genotype, poor nutritional intake, uncontrolled blood pressure or hypertension, baseline peripheral neuropathy)
- Type of and response to prior treatments
- Potential for disease responsiveness to specific agents and risk factors for disease recurrence
- Patient characteristics (eg, social history/situation, insurance coverage, pregnancy) and treatment preferences
- Potential problems with medication adherence to oral treatment regimens
- Goals of treatment
- Need for drug dose reductions or supportive care

Develop a Care Plan*:

- Drug therapy regimen including specific anticancer agent(s), dose (calculated correctly for patient characteristics and disease), route, frequency, and duration
- Supportive care plan (eg, antiemetics, prophylactic antidiarrheals, infusion reaction prophylaxis)
- Monitoring parameters including efficacy (eg, cancer imaging studies-chest, abdominal, and/or pelvic CT scans and radiographs, tumor markers if previously elevated, symptoms of recurrence), safety (medication-specific adverse effects, including major-dose limiting toxicities), and timeframe
- Patient education (eg, goals of treatment; expected and potential serious toxicities; drug therapy; monitoring and management plan; safe administration, storage, and disposal)

Implement the Care Plan*:

- Provide patient education regarding all elements of treatment plan
- Survivorship care plan (eg, primary prevention of other diseases, such as infections, and other cancers, support systems for maintaining healthy lifestyle choices and BMI)

Follow-up: Monitor and Evaluate:

- Determine disease response to treatment and occurrence of disease progression or recurrence (cancer imaging studies, tumor markers previously elevated)
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information (eg, patient self-report, medication administration records or refill data)
- Patient's satisfaction with treatment, including understanding of adherence

*Collaborate with patient, caregivers, and other health professionals

Abbreviations Introduced in This Chapter

2-FLAA	2-Fluoro-Ara-AMP
5-FU	Fluorouracil
6-MP	6-Mercaptopurine
ACS	American Cancer Society
ADC	Antibody–drug conjugate
ADCC	Antibody-dependent cellular cytotoxicity
AI	Aromatase inhibitor
ALK	Anaplastic lymphoma kinase gene
ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
AR	Androgen receptor
ASCO	American Society of Clinical Oncology
ATRA	All-trans-retinoic acid
AUC	Area under the curve
BSA	Body surface area
BCNU	Carmustine
c-MET	Mesenchymal epithelial transition growth factor
CAR	Chimeric antigen receptor
CBC	Complete blood count
CCNU	Lomustine
CDC	Centers for Disease Control
CDK	Cyclin-dependent kinase
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CRS	Cytokine-release syndrome
CTC	Common toxicity criteria
CTLA-4	Cytotoxic T-lymphocytic-associated antigen 4
CNS	Central nervous system
DPD	Dihydropyrimidine dehydrogenase
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FDA	Food and Drug Administration
FdUMP	Fluorodeoxyuridine monophosphate
G-CSF	Granulocyte–colony stimulating factor
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor

GnRH	Gonadotropin-releasing hormone receptor
HDAC	Histone deacetylase
HER-2	Human epidermal receptor-2
HFS	Hand–foot syndrome
HFSR	Hand–foot–skin reaction
HPV	Human papillomavirus
HSCT	Hematopoietic stem cell transplantation
IL	Interleukin
INR	International normalization ratio
IV	Intravenous
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone–releasing hormone
MEK	Mitogen-activated extracellular kinases
MM	Multiple myeloma
MMAE	Monomethyl auristatin E
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NSCLC	Non–small cell lung cancer
PARP	Poly ADP ribose polymerase
PCR	Polymerase chain reaction
PD	Programmed cell death
PD-L	Programmed cell death ligand
PET	Position emission tomography
PI3-K	Phosphoinositide 3-kinase
PSA	Prostate-specific antigen
RECIST	Response evaluation criteria in solid tumors
SERDs	Selective estrogen-receptor downregulators
SERMs	Selective estrogen receptor modulator
SPF	Sun protection factor
TKI	Tyrosine kinase inhibitor
TNM	Tumor, nodes, metastases
TPMT	Thiopurine *S*-methyltransferase
TS	Thymidylate synthase
UGT1A1* 28	Uridine diphosphate–glucuronosyltransferease 1A1 enzyme
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

REFERENCES

1. Cancer Facts & Figures 2017. American Cancer Society. Atlanta: American Cancer Society, 2017.
2. Sessions J, Valgus J, Barbour S, Iacovelli I. Role of oncology clinical pharmacists in light of the oncology workforce study. J Oncol Pract. 2010;6(5):270–272.
3. Holle LM, Michaud LB. Oncology pharmacists in health care delivery: vital members of the cancer care team. J Oncol Pract. 2014;10:e142–e145.
4. Schottenfeld D, Searle JG. The etiology and epidemiology of lung cancer. In: Pass HI, Carbone DP, Johnson DH, Minna JD, Turrisi AT, eds. Lung Cancer: Principles and Practice, 3rd ed. Philadelphia: Lippincott, Williams & Wilkins; 2005:3–24.
5. Blagosklonny MV. Molecular theory of cancer. Cancer Biol Ther. 2005;4(6):621–627.
6. DiPiro JT, Talbert RL, Yee GC, et al. (eds). Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York: McGraw-Hill; 2011: Table 135–2.
7. Buick RN. Cellular basis of chemotherapy. In: Dorr RT, Von Hoff DD, eds. Cancer Chemotherapy Handbook, 2nd ed. New York: Elsevier, 1994:3–14.
8. Folkman J. Angiogenesis. Annu Rev Med. 2006;57:1–18.
9. Mountford CE, Doran S, Lean CL, Russell P. Cancer pathology in the year 2000. Biophys Chem. 1997;68(1–3):127.
10. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The Eighth Edition Lung Cancer Stage Classification. Chest. 2017;151(1): 193–203.
11. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology Practice Guideline Update. J Clin Oncol. 2017;35: 96–112.
12. Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–247.
13. Innocenti F, Schilsky RL, Ramirez J, et al. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. J Clin Oncol. 2014;32(22):2328–2334.
14. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. U.S. Department of Health and Human Services. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed August 1, 2018.
15. Chabner BA. General Principles of Chemotherapy. In: Brunton LL, Chabner BA, Knollman BC (eds). Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 12th ed. New York: McGraw-Hill, 2010.
16. Baker J, Royer G, Weiss R. Cytarabine and neurological toxicity. J Clin Oncol. 1991;9(4):679–693.
17. Villela LR, Stanford BL, Shah SR. Pemetrexed, a novel antifolate therapeutic alternative for cancer chemotherapy. Pharmacotherapy. 2006;26(5):641–654.
18. American Society of Health-System Pharmacists. ASHP guidelines on preventing medication errors with antineoplastic agents. Am J Health Syst Pharm. 2002;59:1648–1668.
19. Sparreboom A, Scripture CD, Trieu V, et al. Comparative preclinical and clinical pharmacokinetics of a Cremophor-free, nanoparticle albumin-bound paclitaxel (ABI-007) and paclitaxel formulated in Cremophor (Taxol). Clin Cancer Res. 2005;11(11): 4136–4143.
20. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377(9769):914–923.
21. Hensley M, Hagerty K, Kewalramani T, et al. American Society of Clinical Oncology clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009;27(1):127–145.
22. Faulds D, Balfour JA, Chrisp P, Langtry HD. Mitoxantrone: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. Drugs. 1991;41(3):400–449.
23. Rudek MA, Donehower RC, Statkevich P, et al. Temozolomide in patients with advanced cancer: phase I and pharmacokinetic study. Pharmacotherapy. 2004;24(1):16–25.
24. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol. 1989;7(11):1748–1756.
25. Dorr RT. Bleomycin pharmacology: mechanism of action and resistance, and clinical pharmacokinetics. Semin Oncol. 1992;19(2 suppl 5):3–8.
26. Zhi-Xiang S, Chen, G, Ni J, et al. Use of arsenic trioxide in the treatment of acute promyelocytic leukemia: II. Clinical efficacy and pharmacokinetics in relapsed patients. Blood. 1997;89(9):3354–3360.
27. Cancer-Associated Venous Thromboembolic Disease. Version 1.2018. NCCN Clinical Practice Guidelines in Oncology. Available from: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed July 20, 2018.
28. Dokmanovic M, Clarke C, Marks P. Histone deacetylase inhibitors: overview and perspectives. Mol Cancer Res. 2007;5:981–989.
29. Tisagenlecleucel (Kymriah) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2017.

30. Programme on International Nonproprietary Names (INN) Division of Drug Management and Policies, World Health Organization, Geneva. 1997.
31. Adcetris (Brentuximab) package insert. Bothell, WA: Seattle Genetics, 2011.
32. Leyland-Jones B, Gelman K, Ayoub J, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J Clin Oncol. 2003;21:3965–3971.
33. West HJ. Immune checkpoint inhibitors. JAMA Oncology. 2015;1:115.
34. Hamilton M, Wolf JL, Rusk J, et al. Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res. 2006;12: 2166–2171.
35. Firmagon (Degarelix) package insert. Parsippany, NJ: Ferring Pharmaceuticals, 2009.
36. Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Eng J Med. 2011;364(21):1995–2005.
37. Goetz MP, Knox SK, Suman VJ, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat. 2007;101:113–121.
38. Gonzalez ID, Saez RS, Rodilla EM, Yges EL, Toledano FL. Hypersensitivity reactions to chemotherapy drugs. Allerg Immunol Clin. 2000;15:151–181.
39. Neuss MN, Gilmore TR, Belderson KM, et al. 2016 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards, including statements for pediatric oncology. Oncol Nurs Form. 2017;44:31–43.
40. Ensuring healthcare worker safety when handling hazardous drugs. Oncology Nursing Society/American Society of Clinical Oncology/Hematology/Oncology Pharmacy Association. Available from: https://www.ons.org/sites/default/files/Safe%20Handling.pdf. Accessed July 20, 2018.
41. Goldspiel B, Hoffman JM, Griffith N, et al. ASHP guidelines on preventing medication errors with chemotherapy and biotherapy. Am J Health-Syst Pharm. 2015;72:e6–e35.
42. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; September 30, 2017.
43. Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer. J Clin Oncol. 2012;30:1553–1561.
44. Goodin S, Griffith N, Chen B, et al. Safe handling of oral chemotherapeutic agents in clinical practice: reommendations from an international pharmacy panel. J Oncol Pract. 2011; 7(1):7–12.
45. Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington DC: National Academies Press; 2006.
46. Resnick MJ, Lacchetti C, Bergman J, et al. Prostate cancer survivorship care guideline: American Society of Clinical Oncology Clinical Practice Guideline Endorsement. J Clin Oncol. 2015;33:1078–1085.
47. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guidelines. J Clin Oncol. 2016;34:611–635.
48. Survivorship. Version 3.2017. NCCN Clinical Practice Guidelines in Oncology. Available from: https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Accessed July 20, 2018.
49. A national action plan for cancer survivorship: advancing public health strategies. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/cancer/survivorship/pdf/plan.pdf. Accessed July 20, 2018.

89 Breast Cancer

Gerald Higa

LEARNING OBJECTIVES

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

1. Explain the relative importance of various risk factors.
2. Summarize the surrogate definitions of the intrinsic breast cancer subtypes.
3. Articulate some of the reasons for improved patient survival.
4. Recognize signs and symptoms related to early and late stages of the disease.
5. Distinguish between good and poor prognostic factors.
6. Determine treatment goals for early stage, locally advanced, and metastatic breast cancers.
7. State the rationale for inclusion of adjuvant and neoadjuvant therapies.
8. Describe the relevance of hormone and HER2 receptors.
9. Discuss the benefits and risks associated with various endocrine therapies.

INTRODUCTION

The increasing prevalence of breast cancer in the United States is related to a number of factors including the predominance of early stage disease at diagnosis, better understanding of tumor biology, improvements in treatment outcomes and survival, and the relatively high incidence rate. Of note, the incidence, which has been increasing slightly over the past decade, appears to be driven almost exclusively by new breast cancer diagnoses in nonwhite women.

EPIDEMIOLOGY AND ETIOLOGY

Breast cancer is the most common type of cancer and second only to lung cancer as a cause of cancer death in American women. In 2018, female breast cancer will account for 99% of the projected 269,000 new cases; the median age at diagnosis will be 62 years; and approximately 41,000 deaths will occur as a result of the disease.[1] KEY CONCEPT Even though the disease occurs more frequently in white women than any other ethnic group, the mortality rate is highest among African Americans.

Tumor size of most breast cancers at diagnosis is usually small (< 2 cm); and localized disease predominates in all racial and ethnic groups. However, African American women have proportionally more cases of advanced disease compared with white women. It has been suggested that reduced access to proper medical care, including breast cancer screening programs, as well as certain biological factors, contribute to late diagnoses.

KEY CONCEPT The etiology of breast cancer remains largely unknown though a number of factors have been associated with risk of developing the disease. Evidence also strongly suggests that breast cancer biology involves complex interactions between sex hormones, genetic factors, environment, and lifestyle. The intrinsic and extrinsic components associated with the disease are discussed further.

Intrinsic Components

LO 1

Aside from gender, the variable most strongly associated with breast cancer is age as disease risk and incidence increase with age. One of the most frequently quoted breast cancer statistic is the probability that one in eight females will develop the disease sometime in their lifetime. The probability of developing breast cancer is presented in Table 89–1. Although the probability of developing breast cancer increases with age, more than half the risk occurs after 60 years of age.

Both personal and family history can influence the risk of developing breast cancer. For example, a woman who has a history of breast cancer has a fivefold increase in risk of developing contralateral breast cancer. Prior histories of cancers involving the uterus and ovary also appear to be associated with an increased risk of developing breast cancer. Even though family history is often linked to disease risk, the percentage of familial breast cancer is quite low (ie, ~10%). KEY CONCEPT The following key elements describe family history-associated breast cancer risk factors:

- A first-degree relative (ie, mother or sister) with breast cancer is associated with a threefold increase in risk.
- Multiple first-degree relatives with breast cancer have not been consistently shown to be associated with risk greater than one first-degree relative.
- A second-degree relative with breast cancer is associated with a 1.5-fold increase in risk.
- Family members on the paternal side contribute to risk similar to the maternal side.

KEY CONCEPT The endocrine factor most closely linked to breast cancer is estrogen. The risk is partially related to duration of exposure to the hormone. Hence, early menarche and late menopause and long-term use of hormone replacement therapy appear to contribute to breast cancer risk.

Table 89–1

Risk of Developing Breast Cancer: SEER Areas, Women, All Races, 2008–2010

Age Interval (years)	Probability (%) of Developing Invasive Breast Cancer during the Interval
30–40	0.44 or 1 in 227
40–50	1.45 or 1 in 69
50–60	2.31 or 1 in 43
60–70	3.49 or 1 in 29
From birth to death	12.15 or 1 in 8

SEER, Surveillance, Epidemiology, and End Results.

Probability derived by Devcan 6.7.0, June 2013 (http://surveillance.cancer.gov/devcan).

Use of postmenopausal estrogen replacement therapy in women with a history of breast cancer is generally contraindicated. However, most experts believe that the safety and benefits of low-dose oral contraceptives currently outweigh the potential risks and that changes in the prescribing practice for the use of oral contraceptives are not warranted. Moreover, oral contraceptives are known to reduce the risk of ovarian cancer by about 40% and the risk of endometrial cancer by about 60%.

KEY CONCEPT In the early 1990s, the *BRCA1* gene (locus 17q21) was found to be mutated in a large percentage of hereditary breast and ovarian cancer patients. A second breast cancer gene, called *BRCA2*, has been mapped to chromosome 13. Since *BRCA1* and *BRCA2* are tumor suppressor genes, mutations or functional aberrations result in loss of key inhibitory activities of both proteins.[2] Compelling evidence of their critical importance is the observation that women who carry germline mutations of *BRCA1* have a lifetime risk of breast cancer between 65% and 90%; the 10-year risk of contralateral breast cancer is approximately 25% to 30%. Carriers of the mutated *BRCA2* have a similar risk for breast cancer. Jewish people of Eastern European descent (Ashkenazi Jews) have an unusually high (2.5%) carrier rate of germline mutations in *BRCA1* and *BRCA2* compared with the rest of the US population. Women with strong family histories of breast cancer are candidates for *BRCA1* and *BRCA2* mutation analysis. If being considered, genetic testing should be done under the guidance of a professional genetic counselor.

Extrinsic Components

KEY CONCEPT Experimental and epidemiologic evidence suggest an association between breast cancer and a diet high in calories, fat, and cooked meats. Obesity in postmenopausal women and distribution of body fat around the abdominal region also appear to increase the risk of breast cancer. This risk factor may be related, in part, to peripheral conversion of androgens to estrogens in adipose tissue. Interestingly, obesity may not impact only disease risk. A recent review provides compelling evidence of the negative effect of obesity on distant disease-free and overall survival (OS) in patients with hormone receptor-positive breast cancer.[3] Data also indicate a modest ingestion-dependent relationship between alcohol and breast cancer. While exercise may have a modest protective effect against breast cancer, neither cigarette smoking nor breast augmentation appears to modify disease risk.

Radiation is also associated with an increased risk of breast cancer. Although the risk appears to be dosage-related, the minimal level of exposure is not well defined. Even therapeutic doses of radiation administered in the management of patients with postpartum mastitis, tuberculosis, and certain hematologic malignancies appear to increase breast cancer risk. Notably, this risk appears to be confined to exposure before 40 years of age, which suggests that a "window of initiation" for breast cancer occurs relatively early. On the other hand, it is currently accepted that exposure to radiation doses utilized in diagnostic x-rays, including screening mammography, are not of clinical concern.

Despite what is known to confer risk, the majority of women diagnosed with breast cancer do not have any of the identified factors (other than age). A number of calculators now accessible through the Internet can be used to estimate breast cancer risk. The National Cancer Institute (NCI) has an online version of the Breast Cancer Risk Assessment Tool that is considered to be the most authoritative and accurate (www.cancer.gov/bcrisk-tool). This tool was designed for health professionals to project individualized 5-year and lifetime risks for invasive breast cancer.

Prevention of Breast Cancer

Even though breast cancer is not the most lethal malignancy, disease-related morbidity and mortality is still significant. Current efforts at breast cancer prevention are directed toward the identification and removal of risk factors. Unfortunately, a number of risk factors such as age and family or personal history of the disease or other gynecologic malignancies cannot be modified.

The idea that prevention can be achieved pharmacologically was based on clinical trials of tamoxifen, a selective estrogen receptor modulator (SERM), as **adjuvant therapy** for women with early, **hormone receptor-positive** breast cancer. These trials demonstrated a reduction of contralateral breast cancer events as well as a survival advantage of patients who received the drug for 2 to 5 years following mastectomy.[4] Several clinical trials conducted with SERMs provided proof of principle that breast cancer risk reduction in premenopausal and postmenopausal women could be achieved through **chemoprevention**.[5-7]

In addition, a class of drugs known as the aromatase inhibitors (AIs) has been shown to be more effective than tamoxifen as adjuvant breast cancer therapy in postmenopausal women. This finding suggested that the AIs could also reduce the risk of developing breast cancer in postmenopausal women at high risk for the disease. Indeed, results of the International Breast Cancer Intervention (IBIS)-II study demonstrated a 53% reduction in new breast cancer diagnoses with anastrozole compared to placebo.[8] Similar findings have been reported with the steroidal AI, exemestane, in high-risk postmenopausal women.[9]

These positive findings are accompanied by a number of caveats. First, chemoprevention effectively reduces the incidence without a significant proven benefit in OS. Second, risk reduction appears to apply to hormone-dependent breast cancer only. Third, results of these trials confirmed the increased incidence of thromboembolic and gynecological adverse events of tamoxifen but not raloxifene. Fourth, if approved, the AIs would be indicated only for postmenopausal women at increased risk

for breast cancer. And though better tolerated, musculoskeletal events, asthenia, and hot flushes associated with the AIs can still be troublesome. Fifth, the role of tamoxifen in *BRCA* mutation carriers is still not clear. In women with familial breast cancer bilateral mastectomy remains the best, though not absolute, risk-reducing option.

It should be noted that even though the side-effect profiles of the SERMs and AIs can have a negative impact on patient acceptance, pharmacologic prevention could spare some patients from surgery-, radiation- and even chemotherapy-related morbidity.

PATHOPHYSIOLOGY

Histologic evaluation of breast lesions serves to establish a pathologic diagnosis and confirm the presence or absence of other factors believed to influence prognosis. These prognostic factors are discussed later.

Invasive Breast Cancer

LO 2

Breast cancers typically arise in the ducts or lobules of the mammary gland. When tumor cells infiltrate surrounding breast tissue, a diagnosis of invasive breast cancer is made. Even though the vast majority of tumors are adenocarcinomas, this does not imply that breast cancer is one disease. Furthermore, breast cancers can be grouped in one of four intrinsic subtypes with luminal B having two distinct surrogate features. When defined by clinical and pathological features, this classification system can be used for prognositication as well as a guide to treatment (Table 89–2).

Noninvasive Carcinoma

Notably, the annual breast cancer incidence does not include thousands of cases of carcinomas in situ (ie, noninfiltrating tumors confined to the ducts and lobules). Ductal carcinoma in situ (DCIS) accounts for approximately 85% of all in-situ breast cancers; while lobular neoplasia may not be a true cancer, but rather a high-risk premalignant lesion that does not always require active treatment. The overwhelming majority of cases can be cured by surgery followed by whole breast radiation therapy (after breast conserving surgery). Although there is no proven role for the application of cytotoxic chemotherapy, patients with hormone receptor-positive tumors may benefit from the addition of tamoxifen.

Patient Encounter Part 1

At a gathering of women who have been friends since high school, a 42-year-old mother of two expresses that one of her greatest fears is being diagnosed with breast cancer. Although there is no family history of breast or gynecological cancers, she mentions a younger aged friend who died recently of the disease. She has never had a mammogram but has been thinking about participating in a breast cancer screening program.

Discuss integral aspects women should know about screening mammography.

CLINICAL PRESENTATION AND DIAGNOSIS

Early Detection

LO 3

The rationale for early detection of breast cancer is based on the clear relationship between early stage disease at diagnosis and greater probability of long-term survival. KEY CONCEPT Screening guidelines for early detection of breast cancer have been put forward by the American Cancer Society, the United States Preventive Services Task Force (USPSTF), and the NCI (Table 89–3). All include recommendations for women at average risk, with some general statements regarding screening for high-risk women as well. Regular screening mammography contributes to reduction in breast cancer mortality by 20% to 40%, primarily in postmenopausal women.

Controversy regarding the use of screening mammography is largely confined to women 50 years of age or younger. After many years of debate, three organizations recommended

Table 89–2

Intrinsic Subtypes of Breast Cancer

Subtype	Tumor Features	Treatment Approach	Added Comment
Luminal A	All of the following: ER and PR positive, HER2 negative, and low Ki-67 (proliferation marker)	Endocrine only (usually)	May add chemotherapy if 4 or more positive nodes, grade 3 disease, Oncotype Dx recurrence score higher than 25, or age younger than 35 years
Luminal B (HER2 negative)	ER positive, HER2 negative, and either high Ki-67 or PR negative	Endocrine and chemotherapy (for most cases)	Add chemotherapy for most patients
Luminal B (HER2 positive)	ER positive, HER2 positive	Endocrine, HER2 targeted therapy and chemotherapy	
HER2 amplified or overexpressed (nonluminal)	HER2 positive	HER2 targeted and chemotherapy	Opinion differs regarding use of anti-HER2 therapy in tumors
Basal (triple-negative)	ER, PR, and HER2 negative	Chemotherapy only	Less than 5 mm

Adapted with permission from Oxford University Press. Coates AS, Winer EP, Goldhirsch A et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015, Annals of Oncology, 2015, 26:1533–1546.

Table 89–3

Guidelines for Early Detection of Breast Cancer in Average Risk Individuals

	American Cancer Society	U.S. Preventive Services Task Force	National Cancer Institute
BSE	Age ≥ 20 years: Risk-to-benefit discussion	NR	NR
CBE	Age 20–30 years: Every 3 years Age ≥ 40 years: Every year	Not specifically addressed	All ages: Every year
Mammography	Annual beginning at age 40 years	Age 50–74 years: Every 2 years (with or without CBE)	Age 40–49: Every 1–2 years Age ≥ 50 years: Every 1–2 years

BSE, breast self-examination; CBE, clinical breast examination; NR, not recommended.

mammograms in this age group of women every 1 to 2 years except for the USPSTF, which modified its recommendation in 2009.[10]

Diagnosis

LO 4

Unless following up on abnormalities found during screening, the initial workup for women presenting with signs or symptoms (see Clinical Presentation and Diagnosis) suggestive of breast cancer should include a careful history, physical examination of the breast, three-dimensional mammography, and possibly other imaging techniques such as magnetic resonance imaging. Most (80%–85%) breast cancers are visualized on a mammogram as a mass, a cluster of calcifications, or a combination of both. A breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination.

Clinical Staging

Stage is determined by the tumor, node, metastasis (TNM) system (see Table 88–2 for an example). Aside from carcinoma in situ (stage 0) multiple combinations of T and N are possible within a given stage. Simplistically, stage I disease is represented by tumors less than 2 cm in diameter and usually no lymph node involvement. KEY CONCEPT Stages I and II are referred to as early breast cancer, which carries a relatively good prognosis and correlates with the highest probability of cure (Table 89–4). Stage III, or locally advanced breast cancer, has poorer disease features, including larger tumor size, positive node involvement, and tumor invasion of the chest wall. Stage IV disease is characterized by the presence of metastases to organs or tissue distant from the primary tumor and is often referred to as advanced or metastatic breast cancer.

Patient Encounter Part 2

Since the woman in the previous encounter is deemed to be of "average risk," she decided against having a screening mammogram. Five years later, she discovers a lump in her left breast. She is seen by her primary care physician who confirms the abnormality and one palpable ipsilateral axillary lymph node. Bilateral mammography indicated showed a large mass in the upper outer quadrant of the left breast. A core needle biopsy of the suspicious breast lesion and regional node was performed; pathology confirmed a diagnosis of invasive breast cancer with node involvement. The patient continues to have menses.

Briefly discuss the relevance of several intrinsic tumor characteristics that should be assessed and integrated in the final pathological report.

Clinical Presentation and Diagnosis of Breast Cancer

Common early signs and symptoms include:

Painless lump (90% of cases) that is:

- Solitary
- Unilateral
- Solid
- Irregular
- Nontender

Stabbing or aching pain (10% of cases) as the first symptom

Uncommon early signs and symptoms include:

Nipple discharge (3% of women and 20% of men), retraction, or dimpling

- Eczema appearance of the nipple (Paget carcinoma)
- Prominent skin edema, redness, warmth, and induration of the underlying tissue (inflammatory carcinoma)

Signs and symptoms associated with metastasis—tissues most commonly involved with are lymph nodes (other than axillary or internal mammary), skin, bone, liver, lungs, and brain. The following symptoms of metastases will be present in about 10% of patients when they first seek treatment:

- Bone pain
- Difficulty breathing
- Jaundice
- Mental status changes

Table 89–4

Estimated Stage at Presentation and 5-Year Disease-Free Survival (DFS): Breast Cancer

	Percentage of Total Cases	5-Year DFS[a] (%)
Stage I	40	70–90
Stage II	40	50–70
Stage III	15	20–30
Stage IV	5	0–10[b]

[a]With current conventional local and systemic therapy.

[b]Patients in stage IV are rarely free of disease; however, 10% to 20% of these patients may survive with minimal disease for 5 to 10 years.

LO 5

Prognostic Factors

Good prognostic factors include:

- Luminal A subtype (ER and PR highly positive, Ki67 low)
- Absence of tumor cells in regional nodes (node-negative)
- Tumors smaller than 2 cm
- Early stage (I and II)
- Well-differentiated tumor
- Normal tumor grade

Poor prognostic factors include:

- Age younger than 35 years
- High nuclear grade (correlates with tumor growth)
- Triple-negative disease (ie, absence of ER, PR, and HER2 receptors)
- Overexpression of HER2 alone

Patient Encounter Part 3

The pretreatment workup is summarized below.

Pathology: 47-year-old female with new diagnosis of infiltrating intraductal adenocarcinoma involving the left breast and regional node. Further tests on tumor samples indicated ER (8%), PR (negative), HER2 (negative), Ki-67 (72%), and grade (poorly differentiated). Intrinsic subtype (luminal B, HER2-negative).

Radiology: FDG-PET/CT indicated a 5.3 × 2.5 cm mass in the left breast which appeared to extend to the epidermis of the skin; one node in the left axilla was also involved with tumor. No other evidence of distant disease was visualized.

Laboratory: CBC, liver, and kidney function tests WNL, alkaline phosphatase and calcium are normal also.

Stage: IIIB (T_4, N_1, M_0)

List the most important prognostic factors in this patient with newly diagnosed breast cancer.

Assess the patient's level of risk for relapse.

EARLY BREAST CANCER TREATMENT

Desired Outcome

KEY CONCEPT Most patients presenting with invasive breast cancer today have small tumors with negative lymph nodes (stage I or II).

LO 6

The goal of therapy for early breast cancer is cure. While surgery alone may be able to cure approximately one-third to one-half of all patients with early stage breast cancer, certain tumor features warrant addition of systemic therapy.

Surgical procedures have changed significantly over the past 50 years. KEY CONCEPT Less aggressive surgical options for early invasive breast cancer include total mastectomy and breast conserving surgery (BCS) such as lumpectomy. The reason for favoring the latter is based on findings that BCS achieves similar survival outcomes as more extensive surgical procedures and is cosmetically superior.[11] Additionally, breast conservation aids in preserving the emotional and psychological well-being of the patient.[12] Only two contraindications to BSC considered absolute (or nearly absolute) include persistence of tumor on surgical margins and inability to perform postsurgery radiation, if indicated.

KEY CONCEPT Equally important is the issue related to complete axillary lymph node dissection (CALND). Because of the morbidity associated with the procedure, clinical trials were conducted to determine when biopsy of the sentinel lymph nodes was sufficient. Results of these studies indicated that CALND can be avoided in patients with microscopic disease in the sentinel nodes as well as in patients undergoing BCS with postsurgery radiation to the breast.[13,14]

Except for the elderly and patients with substantial comorbid medical conditions, radiation therapy is an integral adjunct to BCS. However, radiation therapy should also be considered in certain postmastectomy situations, especially in patients with more than three positive nodes or patients with positive sentinel nodes without CALND. What used to entail 4 to 6 weeks of external-beam radiation, newer clinical evidence supports the efficacy of a 3-week course of whole breast irradiation.[15] Complications associated with radiation therapy are usually minor and include erythema of the breast tissue and shrinkage of total breast mass beyond that predicted on the basis of surgical resection alone.

Systemic Adjuvant Therapy

LO 7

Breast cancer cells can spread by contiguity, lymphatic channels, and blood to distant sites. Tumor cells often metastasize early in cancer growth. Because these deposits cannot always be detected with current diagnostic techniques, they are referred to as occult metastases. Hence, administration of adjuvant therapy (at a time when the tumor burden is low) should theoretically increase the likelihood of cure and minimize the emergence of drug-resistant tumor cell clones. KEY CONCEPT Most published results confirm that chemotherapy (in selected patients), hormonal therapy (in patients with hormone receptor–positive disease), anti-HER2 therapy (in tumors with amplification or overexpression of HER2) or appropriate combinations of these therapies improved **disease-free survival** (DFS) and/or overall survival (OS) in patients with early-stage breast cancer (see Table 89–2).

Among the most influential groups that provide treatment recommendations is the St. Gallen International Expert Consensus panel (see Table 89–2).[16]

▶ *Adjuvant Chemotherapy*

Cytotoxic drugs that are used most frequently as adjuvant therapy of breast cancer include cyclophosphamide, anthracyclines, and taxanes. The most common chemotherapy regimens used in the adjuvant setting are listed in Table 89–5. Dose-limiting and other significant toxicities have been previously described in Chapter 88 and are discussed succinctly in Table 89–6.

Chemotherapy is usually initiated within 2 to 6 weeks from the surgical procedure; the efficacy of systemic therapy decreases if delayed more than 12 weeks following surgery. Currently, four to eight cycles of chemotherapy is administered for 12 to 24 weeks. Dose reduction for standard chemotherapy regimens should be avoided in the absence of severe acute toxicity because of the negative impact on DFS and OS.[17] Even though most patients are able to maintain a reasonable level of functional, emotional, and social well-being during treatment, there are some compelling data indicating that some toxicities can have chronic debilitating effects on quality of life.[18] Various forms of supportive therapy including antiemetics and hematopoietic growth factors for patients receiving systemic adjuvant chemotherapy are discussed in Chapter 99.

As mentioned previously, the usefulness of the intrinsic subtype classification also extends to treatment strategies (see Table 89–2). Since the magnitude of the 10-year survival benefit with cytotoxic agents appears to be only 5% and 10% for patients with negative and positive nodes, respectively, there has been intensive research to identify patients with low-risk disease that could avoid treatment with chemotherapy. One validated

Table 89–5

Common Chemotherapy Regimens for Breast Cancer

Adjuvant Chemotherapy Regimens

AC
Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for four cycles[a]

FAC[w]
Fluorouracil 500 mg/m^2 IV, days 1 and 4
Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours[w]
Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycles every 21–28 days for six cycles[c]

CAF
Cyclophosphamide 600 mg/m^2 IV, day 1
Doxorubicin 60 mg/m^2 IV bolus, day 1
Fluorouracil 600 mg/m^2 IV, day 1
Repeat cycles every 21–28 days for six cycles[e]

FEC
Fluorouracil 500 mg/m^2 IV, day 1
Epirubicin 100 mg/m^2 IV bolus, day 1
Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycle every 21 days for six cycles[g]

CEF
Cyclophosphamide 75 mg/m^2 orally on days 1–14
Epirubicin 60 mg/m^2 IV, days 1 and 8
Fluorouracil 500 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for six cycles (requires prophylactic antibiotics or growth factor support)[i,j]

AC → Paclitaxel (CALGB 9344)
Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 21 days for four cycles
Paclitaxel 175 mg/m^2 on day 1

TAC (BCIRG 001)
Docetaxel 75 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV bolus, day 1
Cyclophosphamide 500 mg/m^2 IV, day 1
(doxorubicin should be given first)
Repeat cycles every 21–28 days for six cycles[d]

Paclitaxel → FAC[f,w]
Paclitaxel 80 mg/m^2/week IV over 1 hour every week for 12 weeks
Followed by:
Fluorouracil 500 mg/m^2 IV, days 1 and 4
Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours
Cyclophosphamide 500 mg/m^2 IV, day 1
Repeat cycles every 21–28 days for four cycles[n]

CMF
Cyclophosphamide 100 mg/m^2/day orally, days 1–14
Methotrexate 40 mg/m^2 IV, days 1 and 8
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for six cycles[h,j]
or
Cyclophosphamide 600 mg/m^2 IV, day 1
Methotrexate 40 mg/m^2 IV, day 1
Fluorouracil 600 mg/m^2 IV, days 1 and 8
Repeat cycles every 28 days for six cycles[i]

Dose-Dense AC → Paclitaxel
Doxorubicin 60 mg/m^2 IV bolus, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 14 days for four cycles (must be given with growth factor support)
Followed by:
Paclitaxel 175 mg/m^2 IV over 3 hours[i]
Repeat cycles every 14 days for four cycles (must be given with growth factor support)[k]
Followed by:
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days for four cycles[b]

Metastatic Single-Agent Chemotherapy

Paclitaxel
Paclitaxel 175 mg/m^2 IV over 3 hours
Repeat cycles every 21 days
or
Paclitaxel 80 mg/m^2/week IV over 1 hour
Repeat dose every 7 days[m]

Vinorelbine
Vinorelbine 30 mg/m^2 IV, days 1 and 8
Repeat cycles every 21 days
or
Vinorelbine 25–30 mg/m^2/week IV
Repeat cycles every 7 days (adjust dose based on absolute neutrophilcount; see product information)[n]

(*Continued*)

Table 89–5

Common Chemotherapy Regimens for Breast Cancer (*Continued*)

Metastatic Single-Agent Chemotherapy

Docetaxel
Docetaxel 60–100 mg/m^2 IV over 1 hour
Repeat cycles every 21 days[o]
or
Docetaxel 30–35 mg/m^2/week IV over 30 minutes
Repeat dose every 7 days[p]

Capecitabine
Capecitabine 2000–2500 mg/m^2/day orally, divided twice daily for 14 days
Repeat cycles every 21 days[q,r]

Docetaxel + Capecitabine
Docetaxel 75 mg/m^2 IV over 1 hour, day 1
Capecitabine 2000–2500 mg/m^2/day orally divided twice daily for 14 days
Repeat cycles every 21 days[t]

Epirubicin + Docetaxel[x]
Epirubicin 70–90 mg/m^2 IV bolus
Followed by:
Docetaxel 70–90 mg/m^2 IV over 1 hour
Repeat cycles every 21 days[v]

Gemcitabine
Gemcitabine 600–1000 mg/m^2/week IV, days 1, 8, and 15
Repeat cycles every 28 days (may need to hold day-15 dose based on blood counts)[q]

Liposomal Doxorubicin
Liposomal doxorubicin 30–50 mg/m^2 IV over 90 minutes
Repeat cycles every 21–28 days[s]

Doxorubicin + Docetaxel[x]
Doxorubicin 50 mg/m^2 IV bolus, day 1
Followed by:
Docetaxel 75 mg/m^2 IV over 1 hour, day 1
Repeat cycles every 21 days[u]

[a]From Fisher B, et al. J Clin Oncol. 1990;8:1483. [b]From Henderson CI, et al. J Clin Oncol. 2003;21:976. [c]From Buzdar AU, et al. In: Salmon S, ed. Adjuvant Therapy of Cancer, VIII. Philadelphia: Lippincott-Raven; 1997:93–100. [d]From Martin, et al. San Antonio Breast Cancer Symposium. 2003;A43. [e]From Wood WC, et al. N Engl J Med. 1994;330:1253. [f]From Martin M, et al. N Engl J Med. 2005;325:2302. [g]From Green MC, et al. J Clin Oncol. 2005;23:5983. [h]From Bonadonna G, et al. N Engl J Med. 1976;294:405. [i]From Fisher B, et al. N Engl J Med. 1989;32:473. [j]From Levine MN, et al. J Clin Oncol. 1998;16:2651. [k]From Citron, et al. J Clin Oncol. 2003;21;1431. [l]From Taxol (paclitaxel) product information. Bristol-Myers Squibb, April 2003. [m]From Perez EA, et al. Clin Oncol. 2001;19:4216. [n]From Zelek L. Cancer. 2001;92:2267. [o]From Taxotere (docetaxel) product information. Aventis Pharmaceuticals Inc., April 2003. [p]From Hainsworth JD, et al. J Clin Oncol. 1998;16:2164. [q]From Carmichael J, et al. J Clin Oncol. 1995;13:2731. [r]From Michaud, et al. Proc Am Soc Clin Oncol. 2000; A402, and Xeloda product information. [s]From Ranson MR, et al. J Clin Oncol. 1997;15:3185. [t]From O'Shaughnessy, et al. J Clin Oncol. 2002;20:2812. [u]From Nabholtz JM, et al. J Clin Oncol. 2003;21:968. [v]From Levin MN, et al. J Clin Oncol. 1998;16:2651. [w]FAC may also be given with bolus doxorubicin administration, and the fluorouracil dose is then given on days 1 and 8. [x]Paclitaxel may also be given concurrently with doxorubicin or epirubicin as a combination regimen. Pharmacokinetic interactions make these regimens more difficult to give.

IV, intravenous.

Table 89–6

Toxicities of Common Chemotherapies Used for Breast Cancer

Class	Drug	Dose-Limiting Toxicities	Other Toxicities
Anthracyclines	Doxorubicin, epirubicin	Myelosuppression, cardiomyopathy	Alopecia, nausea, vomiting, stomatitis, ulceration, and necrosis with extravasation, red-colored urine, radiation-recall effect
	Liposomal doxorubicin	Myelosuppression, palmar-plantar erythrodysesthesia (hand–foot syndrome)	Alopecia, infusion reactions, stomatitis, fatigue, nausea, vomiting
Taxanes	Paclitaxel	Neutropenia, peripheral neuropathy, hypersensitivity reactions	Alopecia, fluid retention, myalgia, skin reactions, ulceration, and necrosis with extravasation, bradycardia, stomatitis
	Docetaxel	Myelosuppression, severe fluid retention	Alopecia, fatigue, stomatitis, nausea, vomiting, diarrhea, peripheral neuropathy, nail disorder, skin reactions, hypersensitivity reactions
Antimetabolites	Capecitabine	Diarrhea, palmar-plantar erythrodysesthesia (hand–foot syndrome)	Myelosuppression, stomatitis, nausea, vomiting
	Gemcitabine	Myelosuppression (especially thrombocytopenia)	Flulike syndrome (fever, chills, myalgias, and arthralgias), nausea
	Fluorouracil	Myelosuppression	Stomatitis, diarrhea, alopecia
	Methotrexate	Myelosuppression, stomatitis	Diarrhea, nausea, vomiting, renal toxicity
Vinca alkaloids	Vinorelbine	Neutropenia	Fatigue, nausea, vomiting, ulceration, and necrosis with extravasation
Alkylating agents	Cyclophosphamide	Myelosuppression, hemorrhagic cystitis	Alopecia, stomatitis, amenorrhea, aspermia

multigene assay known as Oncotype DX is used to identify patients with luminal A disease, regardless of nodal involvement, who can be treated with endocrine therapy alone.[19]

KEY CONCEPT It is generally agreed that patients with high-risk luminal B, HER2 overexpression, and basal-like subtypes should receive chemotherapy (both anthracycline and taxane) with hormonal and/or HER2-targeted therapy if indicated.[20]

▶ Adjuvant Anti-HER2 Therapy

LO 8

HER-2 amplification or overexpression is found in approximately 15% to 20% of all breast cancers. Because of its aggressive features, trastuzumab (plus chemotherapy) is usually indicated in this subset of patients, especially for tumors greater than or equal to 0.5 cm in size. Most experts also agree that HER2-positive tumors appear to derive greater benefit from anthracycline or taxane-based chemotherapy regimens.[21] When used with these agents, trastuzumab is given either following completion of the anthracycline or concurrently with the taxane. Current evidence indicates that the duration of trastuzumab therapy is 12 months.[22]

▶ Adjuvant Endocrine Therapy

LO 8

Hormone receptors are used clinically as indicators of prognosis, predictors of response to endocrine therapies, and more recently, discriminators of luminal breast cancer subtypes. Estrogen receptors (ERs) and progesterone receptors (PRs) are cytoplasmic proteins that bind to nuclear DNA and function as transcription factors. Approximately 50% to 70% of patients with primary and metastatic breast cancer have hormone receptor–positive tumors. However, receptor-positivity refers to tumors expressing both ER and PR, as well as either ER or PR alone. Furthermore, "ER-positive" tumors traditionally refer to ERα only. Although it is beyond the scope of this discussion, it is noteworthy to mention the existence, and accumulating data regarding the roles of ERβ and the ERα/ERβ heterodimer in breast cancer.[23,24] Tumors with high expression of both ER and PR (ie, luminal A subtype) are associated with favorable prognoses, superior responses to endocrine therapy, and longer disease-free intervals following initial treatment. Hormone receptor–positive tumors are more common in postmenopausal patients. Many experts also believe that postmenopausal breast cancer is biologically less aggressive than breast cancers diagnosed before menopause.

KEY CONCEPT Hormonal therapies that have been studied in the treatment of early breast cancer include tamoxifen, ovarian suppression (surgical and pharmacologic), and the AIs.

LO 9

Tamoxifen has been used in the adjuvant setting for nearly five decades. Analysis of long-term data indicates the drug's antagonist (anti-estrogen) effect was associated with a significant reduction in disease recurrence and mortality. This observation, coupled with evidence of the drug's beneficial agonist activity on the lipid profile and bone density, supported tamoxifen's role as standard endocrine therapy. However, the agonist properties are also associated with detrimental effects on endometrial tissue and blood coagulation.

In premenopausal women, tamoxifen alone is considered the adjuvant hormonal therapy of choice. Some disagreement exists among experts regarding the utility of combining ovarian function suppression with tamoxifen particularly in chemotherapy-treated patients and women 40 years of age or younger. Tamoxifen is initiated shortly after surgery or as soon as pathology results are known. However, when chemotherapy is also indicated, tamoxifen is given after all cytotoxic agents have been completed. The rationale for sequential therapy is supported by some data which show a small negative effect on DFS when tamoxifen and chemotherapy are given concurrently.

Treatment with adjuvant tamoxifen (20 mg/day) has historically been for 5 years. Several years ago, results of a well-designed clinical trial indicated a survival benefit associated with extending therapy to a total of 10 years.[25] These data were further supported by additional evidence in women who were premenopausal when starting, and postmenopausal at completion, of tamoxifen therapy. In this subset of women, continuation of endocrine therapy with an AI was associated with a significant improvement in breast cancer-related events, including new primaries in the contralateral breast, disease recurrence, and DFS.[26] Collectively, these findings led to new recommendations regarding the use of endocrine therapies in the adjuvant setting.

However, recent data from three clinical trials of extended endocrine therapy were presented at the 2016 San Antonio Breast Cancer Symposium. None of the trials achieved statistical significance with regards to DFS, the primary endpoint. Even before these results were publicized, drug-related toxicities and medication compliance associated with the longer duration of therapy made extended therapy less appealing. And while there may be a subset of patients likely to benefit, recommendations regarding extended adjuvant endocrine therapy is now even more uncertain.

Finally, the issue regarding the role of pharmacogenomics in tailoring tamoxifen therapy is both persuasive and controversial.[27,28] As such, routine screening for germline variants of *CYP2D6* has not been endorsed. Nonetheless, drugs that do inhibit the enzyme should be avoided if possible.

In postmenopausal women, the use of adjuvant AIs has been studied in three different ways: (a) direct comparison with tamoxifen, (b) after 5 years of tamoxifen therapy, and (c) sequentially after 2 to 3 years of tamoxifen.[29] Based on the positive results of several studies, expert panels strongly recommend AIs for postmenopausal women with hormone-dependent breast cancer.[30] Five years of adjuvant AI therapy is considered standard. Extended therapy can be considered after careful assessment of potential clinical benefits and risks related to tumor features and patient characteristics including comorbidities, bone mineral density, and prior tolerance with AI therapy. While these recommendations can be applied to most postmenopausal patients, tamoxifen can still be used first line or as an alternative in those who do not tolerate AI therapy.

LO 9

AI therapy is associated with several adverse effects, including hypercholesterolemia, atherosclerotic cardiovascular disease, and skeletal-related events. The three available AIs are anastrozole, letrozole, and exemestane (Table 89–7).

Patient Encounter Part 4

After extensive discussion of the multidisciplinary committee which included patient preferences, the choice of treatment strategy was systemic neoadjuvant followed by breast conserving surgery (BCS), if possible, followed by radiation and adjuvant therapy.

Discuss the rationale for each component of the planned treatment with a focus on selection of specific agents in the neoadjuvant and adjuvant settings for this patient.

Table 89–7

Endocrine Therapies Used for Metastatic Breast Cancer

Class	Drug	Dose	Side Effects
Aromatase inhibitors			
Nonsteroidal	Anastrozole	1 mg/day PO	Hot flashes, arthralgias, myalgias, headaches, diarrhea, mild nausea
	Letrozole	2.5 mg/day PO	
Steroidal	Exemestane	25 mg/day PO	
Antiestrogens			
SERMs	Tamoxifen	20 mg/day PO	Hot flashes, vaginal discharge, mild nausea, thromboembolism, endometrial cancer
	Toremifene	60 mg/day PO	
SERDs	Fulvestrant	250 mg IM every 28 days	Hot flashes, injection site reactions, possibly thromboembolism
LHRH analogues	Goserelin	3.6 mg SC every 28 days	Hot flashes, amenorrhea, menopausal symptoms, injection site reactions
	Leuprolide	7.5 mg IM every 28 days	
	Triptorelin	3.75 mg IM every 28 days	
Progestins	Megestrol acetate	40 mg PO 4 for a day	Weight gain, hot flashes, vaginal bleeding, edema, thromboembolism
	Medroxyprogesterone	400–1000 mg IM every week	
Androgens	Fluoxymesterone	10 mg PO twice a day	Deepening voice, alopecia, hirsutism, facial or truncal acne, fluid retention, menstrual irregularities, cholestatic jaundice

IM, intramuscular; LHRH, luteinizing hormone-releasing hormone; PO, oral; SC, subcutaneous; SERD, selective estrogen-receptor downregulator; SERM, selective estrogen receptor modulator.

LOCALLY ADVANCED BREAST CANCER TREATMENT

Desired Outcome

Locally advanced breast cancer is defined by tumors 5 cm or greater and a high likelihood of nodal involvement in the absence of demonstrable distant metastasis. A wide variety of clinical scenarios can be seen within this group of patients, including tumors that have been neglected for a period of time and inflammatory breast cancer, which is a unique clinical entity. Inflammatory breast cancer has, at times, been misdiagnosed as cellulitis.

LO 6 LO 7 Treatment of stage III breast cancer consists of all modalities used in the management of early breast cancer. The goal of therapy is to achieve optimal systemic control of the disease. However, despite treatment, systemic relapse and death are common even when local-regional control is accomplished. One major difference related to the systemic therapies is the use of chemotherapy plus anti-HER2 therapy (if indicated) before surgery; notably, endocrine therapy can be used in postmenopausal women but is not routinely recommended in premenopausal women. This approach, referred to as **neoadjuvant therapy**, can render initially inoperable tumors resectable, even with the possibility of BCS. It is also conceivable that earlier administration of systemic therapy could have therapeutic benefits beyond surgical resection. Other potential advantages include in vivo assessment of treatment response, and an opportunity to evaluate the biologic effects of the systemic therapy. However, nodal status will not be assessable.

Pharmacologic Therapy

For patients with inoperable breast cancer, including inflammatory breast cancer, one of the treatment objectives is to obtain tumor resectability. The guidelines for selection and duration of systemic neoadjuvant chemotherapy are similar to the adjuvant setting. Available data support the use of anthracycline-containing regimens, incorporation of the taxanes, and approaches to improve dose-density or dose-intensity. Neoadjuvant endocrine therapy may be an option for patients who have unresectable, strongly hormone receptor–positive tumors, low risk factors, or are unable to receive chemotherapy because of comorbid medical conditions. Endocrine therapy is usually given for 4 to 8 months or until maximal response. In September 2013, the FDA approved the use of pertuzumab in combination with trastuzumab and docetaxel as neoadjuvant therapy in patients with HER2-overexpressing tumors. Regardless of therapeutic approach, about two-thirds of the tumors can be downsized.

In terms of local therapy, the extent of surgery will be determined by tumor response to neoadjuvant therapy, patient wishes, and cosmetic results likely to be achieved. To minimize local recurrence, adjuvant radiation therapy should be administered to all patients with locally advanced breast cancer who undergo mastectomy or BCS. Inoperable tumors that are unresponsive to systemic chemotherapy may require radiation for local management; however, these tumors may be ineligible for subsequent surgical resection. This situation is associated with a very poor prognosis though not commonly seen.

METASTATIC BREAST CANCER (STAGE IV) TREATMENT

Desired Outcome

LO 6 The goals of therapy for patients with metastatic breast cancer (MBC) are maintaining or improving quality of life and prolonging survival. In order to achieve these goals, an important consideration is selecting therapy with good activity and tolerability.

General Approach to Treatment

LO 8 The choice of therapy for metastatic disease is based on receptor expression status (ie, hormone and HER2) and distant disease sites. In many instances, age and comorbid medical problems will also be considered. While the choice between endocrine and cytotoxic chemotherapy is usually the hormone receptor status of the tumor, sites of metastatic disease may also influence treatment

decisions. For example, in patients with ER-positive breast cancer with soft tissue or bone-only metastasis (without impending fracture), endocrine therapy alone is usually warranted. Hormonal therapy can even be considered in patients with asymptomatic visceral involvement. In contrast, chemotherapy is usually the initial treatment option for hormone-dependent breast cancer in patients who present with significant life-threatening metastasis to liver and/or lung. When used, chemotherapy is continued to maximal response. Patients with tumors responding initially to endocrine therapies are often treated with chemotherapy when endocrine options are exhausted or symptomatic visceral metastasis develops. Approximately 75% to 80% of tumors positive for both ER and PR respond to initial hormonal therapy; responses decrease to 50% to 60% for ER-positive/PR-negative tumors. The best predictor of response to second- and, possibly, third-line endocrine therapies is extent and duration of the initial response. Nevertheless, tumor responses are frequently lower and durations shorter with subsequent hormonal therapies.

KEY CONCEPT Endocrine therapy is not indicated for tumors that do not express at least one of the hormone receptors. Patients with receptor negative tumors should be treated with cytotoxic chemotherapy. Objective responses are achieved in 50% to 60% of patients who have not received prior chemotherapy though less than 20% of the responses are complete. The duration of response to first-line therapy is usually less than 12 months. Although very uncommon, responses to initial treatment can be extremely durable with patients living years without evidence of disease. The response rate to second- and third-line chemotherapy varies from 20% to 40%. Combinations of different hormonal therapies or chemotherapy plus endocrine therapy are not used in the metastatic disease setting because of increased toxicity without added benefit.

Even though incurable, it has been recently reported that the 5-year relative survival rate has increased twofold from 18% to 36%. Notably, the improvement was observed primarily in women 50 years of age or younger.

Pharmacologic Systemic Therapy

▶ *Endocrine Therapy*

The operative mode of all endocrine therapies is estrogen deprivation. The pharmacologic goals of treatment include decreasing the levels of circulating estrogen and/or preventing the effects of estrogen on tumor tissue through hormone receptor blockade or downregulating receptor expression. Achievement of these goals is independent of menopausal status. Many available endocrine therapies can accomplish these goals. Combined endocrine therapies also have been studied in an attempt to improve patient outcomes with negative results. As such, patients usually receive sequential endocrine therapies before chemotherapy is considered.

Until the turn of the century, evidence did not support the superiority of one type of endocrine therapy with regards to response or survival. Because of the similarity in efficacy, selection of endocrine therapy was based primarily on their toxicity prolife (see Table 89–7), which favored tamoxifen. The only exception to this choice of therapy occurred in patients who received adjuvant tamoxifen and subsequently developed metastatic disease within 1 year of drug cessation.

Over the past 15 years, accumulating evidence related to the AIs has changed the way postmenopausal women with hormone-dependent metastatic breast cancers are treated. After menopause, estrogens continue to be produced by extragonadal conversion of androstenedione and testosterone to estrone and estradiol. This biosynthetic process, which is dependent on aromatase, occurs in peripheral tissue, including muscle, adipose, and even the breast itself. Therefore, AIs effectively reduce the level of circulating estrogens, as well as estrogens in the target gland. Their toxicity profile has been described in Chapter 88 and Table 89–7. Anastrozole and letrozole are nonsteroidal compounds that competitively inhibit aromatase. Exemestane is a steroidal compound that binds irreversibly (by forming a covalent bond) to aromatase. However, this biochemical distinction does not translate into clinical superiority with exemestane.

LO 9 In general, the AIs are preferred as first-line therapy for ER-positive advanced breast cancer in postmenopausal women.[32] Results of large clinical trials comparing these agents against tamoxifen demonstrated improved **progression-free survival** (PFS) or time to progression (TTP) among patients receiving AI therapy. A consistent observation in these trials was a lower incidence of thromboembolic events, endometrial cancer, and vaginal bleeding in patients treated with an AI. Of note also, several small studies indicated that regardless of which subclass of AI used initially, approximately 50% of the patients will have further antitumor benefit after switching to the other subclass suggesting that cross-resistance is incomplete. Therefore, postmenopausal patients may receive two AIs as first- and second-line therapies.

While the therapeutic benefit of the AIs is well accepted, targeted interruption of the cell cycle has recently been investigated to further enhance the treatment of patients with hormone-dependent MBC. The biological rationale is based on the critical role cyclin dependent kinases (CDKs) have in regulating phase transition for cell cycle progression, cell division, and cell proliferation. Of the four stimulatory kinases, CDKs 4 and 6 are believed to be key promoters of tumor proliferation and hence, attractive targets for inhibition. Published results of two clinical trials demonstrating a significant reduction in risk of disease progression or death with combined CDK 4/6 inhibitor plus AI compared to the AI alone led to the recent approval of palbociclib with letrozole and ribociclib with any AI as first-line therapy for ER-positive MBC in postmenopausal women.[33,34] In February 2018, a third CDK 4/6 inhibitor, abemaciclib (in combination with an AI), was approved as front-line therapy.

The AIs are only used in postmenopausal women. Even though ovarian estrogen production relies on the same enzymatic pathway discussed earlier, premenopausal or perimenopausal women with functioning ovaries are not appropriate candidates for these therapies. The reason is physiologic as evidence indicates that negative endocrine feedback will overcome aromatase inhibition. Clinical data also suggested that the strategy of combining an AI with ovarian suppression (ie, oophorectomy or LHRH agonists) can also be considered in treatment-naïve premenopausal women.

The use of AIs in men with advanced breast cancer should be avoided. Available data suggest the use of these agents in men increases circulating levels of testosterone, which may negate the therapeutic effects of the drug.

Antiestrogens bind to ERs, preventing receptor-mediated gene transcription, and therefore are used to block the effect of estrogen on the end target. This class of agents is subdivided into two pharmacologic categories: SERMs and SERDs. SERMs like tamoxifen have tissue-specific estrogenic and antiestrogenic activities. The effort to minimize or eliminate the adverse estrogenic effects led to the development of SERDs, which are pure ER antagonists. The distinguishing feature of SERDs is their ability to degrade the ligand–ER complex.

Fulvestrant is the only SERD approved for clinical use in the United States. As a single agent, the drug is indicated as

second-line therapy for postmenopausal patients. However, results from clinical trials of fulvestrant plus an AI as first-line therapy demonstrated significant TTP and OS rates compared to the AI alone.[35,36] These data support offering the combination as initial treatment for patient with MBC who have not been exposed to adjuvant endocrine therapy. The side effect profile of fulvestrant is generally similar to the antiestrogens except for dermal reactions at the injection site. Even though fulvestrant is a good option for patients who are unable to take an oral medication, some patients may be averse to the drug because it must be given intramuscularly. There is no biological reason why fulvestrant should not produce similar outcomes in premenopausal women; however, safety or efficacy data are lacking.

Resistance to frontline therapy inevitably occurs in patients with advanced disease. One of the mechanisms of endocrine resistance appears to involve the mammalian target of rapamycin (mTOR), a protein downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway. Results of a clinical trial involving everolimus, an mTOR inhibitor, plus exemestane showed a 2.5-fold prolongation of PFS in postmenopausal women previously treated with nonsteroidal AIs.[37] As such, the combination is currently recommended as a second-line option for postmenopausal women (and premenopausal women with continued ovarian suppression).

Tamoxifen can be used in both premenopausal and postmenopausal women with ER positive, metastatic breast cancer. Toxicities associated with tamoxifen have been previously described. The only additional acute adverse effect, which occurs in about 5% of the patients with bone metastasis is tumor flare or hypercalcemia following initiation of tamoxifen. Generally, this acute reaction is not an indication to discontinue treatment. Conversely, this finding appears to correlate with subsequent response to endocrine therapy.

Ovarian ablation or suppression in premenopausal women can be effectively achieved surgically or pharmacologically. Even though the efficacy of oophorectomy and tamoxifen are comparatively similar, secondary response rates to oophorectomy after tamoxifen treatment were somewhat higher than response rates achieved with tamoxifen after oophorectomy (33% vs 11%). Interpretation of these findings suggests that tamoxifen does not completely antagonize available estrogen, particularly in premenopausal women. Ovarian ablation is still commonly performed in parts of the United States and is considered by some to be the endocrine therapy of choice in premenopausal women with advanced disease. The mortality rate with surgical oophorectomy is less than 3% in appropriately selected patients.

Castration can also be achieved pharmacologically with LHRH agonists. An initial surge in luteinizing hormone (LH) and estrogen production during the first few weeks of treatment can cause a tumor flare reaction similar to tamoxifen. With continued therapy, this strategy induces remission in about one-third of unselected patients. LHRH agonists purportedly downregulates LHRH receptors in the pituitary resulting in decreased LH release and castrate levels of estrogens. Of the three agents available in the United States (ie, leuprolide, goserelin, and triptorelin), only goserelin is approved for the treatment of metastatic breast cancer.

Although tamoxifen alone can be considered, guidelines developed by the American Society of Clinical Oncology recommend offering ovarian ablation or suppression in combination with antiestrogen or AI in premenopausal women with endocrine-responsive MBC.

In randomized trials, progestins such as megestrol acetate and medroxyprogesterone acetate have been shown to induce noninferior response rates when compared with tamoxifen. Megestrol acetate is used more frequently in the United States. Despite their efficacy, these agents have been relegated to third-line status. The most common side effects are listed in Table 89–7. One side effect, weight gain, occurs in 20% to 50% of patients. Patients experiencing weight gain may have fluid retention, but fluid retention is not responsible for all of the weight gain. In cachectic cancer patients, the weight gain may be desirable, but this is not uniformly true of all patients with metastatic breast cancer.

High-dose estrogens and androgens are rarely used because they are more toxic than other hormonal agents and in some cases less effective. About one-third of patients placed on high-dose estrogens will discontinue the use of these agents because of side effects, the most important of which are thromboembolic events, vomiting, and fluid retention.

▶ *Cytotoxic Chemotherapy*

Except for brain and spine (with impending cord compression), chemotherapy is given as initial treatment of metastasis in patients with hormone receptor–negative tumors. The median time to an objective response is 2 to 3 months, but this period depends largely on the site of measurable disease. For example, time to response is 3 to 6 weeks for disease localized primarily to skin and lymph nodes; 6 to 9 weeks lung lesions; 15 weeks for liver metastasis; and 18 weeks for bone involvement. Once chemotherapy has been initiated, it is usually continued until maximal response, disease progression, or intolerable toxicity.

Unlike endocrine therapy, no clinical characteristic or established test has been shown to predict benefit from chemotherapy. However, a number of factors are associated with likelihood of tumor response, including good performance status, limited number (one or two) of disease sites, treatment-naïve status, and previous response to chemotherapy with a long disease-free interval. Tumors that progress while being treated may respond to different agents. Importantly, tumors that do not respond to endocrine therapy are as likely to respond to chemotherapy as tumors treated with cytotoxic agents first. If not used initially, chemotherapy is eventually required in most patients with advanced breast cancer.

KEY CONCEPT The most active classes of chemotherapy in metastatic breast cancer are the anthracyclines and the taxanes with response rates as high as 50% to 60% in patients who have not received prior chemotherapy for metastatic disease. Although many chemotherapeutic agents have demonstrated activity in the treatment of breast cancer, the most frequently used agents include all of the agents used in the adjuvant setting. A brief discussion of the taxanes, capecitabine, and gemcitabine extends upon what is described in Chapter 88.

Taxanes

In the metastatic setting the most effective weekly dose of paclitaxel appears to be 80 mg/m^2/week with no breaks in therapy. With this approach, the toxicity profile of paclitaxel changes with less myelosuppression and delayed onset of peripheral neuropathy but slightly more fluid retention and skin and nail changes.

A dose-response relationship has been demonstrated with docetaxel. Dosages in the range of 60 mg/m^2 to 75 mg/m^2 can be given every 21 days in asymptomatic patients who may not require a rapid clinical response. While less neuropathy, myalgia, and hypersensitivity reactions are observed with docetaxel (compared to paclitaxel), the incidence of febrile neutropenia, fluid retention, and skin reactions is higher. A weekly schedule

of docetaxel, 35 mg/m^2, six doses of an 8-week cycle is also very active and more tolerable than the 3-weekly schedule.

Antimetabolites

Capecitabine has activity against tumors progressing on anthracycline- and taxane-containing regimens. Moreover, the drug exhibits somewhat selective activity against cancer cells. This belief is supported by the presence of higher tumor cell levels of thymidine phosphorylase, the enzyme which catalyzes the final step in the conversion of capecitabine to 5-FU. In previously treated patients, capecitabine produced response rates of about 25%, which was impressive compared with other tested chemotherapy agents.

Gemcitabine is another agent that is used frequently in patients with advanced breast cancer. This nucleotide analogue has a unique mechanism of action and a favorable toxicity profile. As a single agent, response rates of nearly 40% have been achieved in the first-line setting. However, overall response rates (ORRs) up to 90% have been obtained when gemcitabine was combined with doxorubicin or epirubicin and paclitaxel as first-line treatment. Response rates to gemcitabine monotherapy in the second- and third-line settings are approximately 18% to 26%. When combined with one other agent such as a taxane, vinorelbine, cisplatin, or an anthracycline, results of clinical studies consistently demonstrated higher efficacy than either single agent. In patients who have been exposed to an anthracycline and a taxane, gemcitabine appears to provide similar benefit to capecitabine.

General Comments

Combination chemotherapy regimens are usually associated with higher response rates than are single-agent therapies, but the higher response rates do not necessarily translate into significant differences in OS. The use of sequential single-agent therapy versus combination chemotherapy regimens has been debated widely for metastatic breast cancer.[39] In the metastatic setting, the least toxic approach is preferred when efficacy is considered equal. In clinical practice, patients who require a rapid response to chemotherapy (ie, those with symptomatic bulky metastases) often receive combination therapy despite the added toxicity. This decision is complex and should be made on an individual patient basis.

Because many patients receive adjuvant chemotherapy, regimens chosen for first-line use in the metastatic setting often are different from those used in the adjuvant setting with the following caveat. If the patient's cancer recurs more than 1 year after the end of adjuvant chemotherapy, the same agents may have activity in the metastatic disease setting.

▶ *Targeted Biologic Therapy*

LO 8

Anti-HER2 therapies are only indicated for breast cancers that meet the definition for HER2-positivity (ie, 3+ by immunohistochemistry and/or *HER2* gene/chromosome 17 ratio ≥ 2 by fluorescence in-situ hybridization).

Trastuzumab targets a specific extracellular epitope of HER2. Single-agent treatment with trastuzumab produces responses in approximately 15% to 20% of patients; the clinical benefit rate, which includes CRs, PRs, and stable disease, is nearly 40%. Trastuzumab has additive and perhaps synergistic activity with chemotherapeutic agents.[40] Because cardiac toxicity is associated with the antibody, trastuzumab is given after all cycles of the anthracyclines have been completed. A nonanthracycline-containing regimen with excellent activity is the combination of docetaxel and carboplatin with concurrent trastuzumab.[41] Other chemotherapy agents that are being evaluated in combination with trastuzumab include vinorelbine, gemcitabine, capecitabine, and cisplatin or carboplatin.

The most notable adverse effects associated with trastuzumab include cardiac dysfunction, first dose infusion-related chills, hypersensitivity, and pulmonary reactions.

Close monitoring for clinical signs and symptoms of heart failure is imperative. Although cardiac toxicity is usually reversible, some patients may require pharmacologic therapy. In addition, it is important to educate patients regarding the latter two adverse effects because they may occur up to 24 hours after the infusion and can be fatal if not treated promptly.

Lapatinib inhibits the intracellular kinase domains of HER2 and HER1 (epidermal growth factor receptor). A pivotal phase 3 clinical trial was conducted to assess the efficacy and safety of lapatinib plus capecitabine versus capecitabine alone in patients with disease progressing on trastuzumab. The trial was terminated early when a preplanned interim analysis indicated a significant reduction in risk of disease progression that favored the combination arm. Of note, the incidence of brain metastasis was significantly lower in the lapatinib-treated group.[42]

The side-effect profile of lapatinib is described in Chapter 88. A few side effects such as diarrhea, dyspepsia, and rash occurred more frequently when lapatinib was combined with capecitabine. Importantly, the lapatinib doublet was not associated with cardiac events resulting in subject withdrawal.

In May 2014, the American Society of Clinical Oncology (ASCO) issued two clinical practice guidelines related to lapatinib for the treatment of advanced, HER2-positive breast cancer. First, depending on hormone receptor status, third-line therapy may include hormonal therapy or chemotherapy with trastuzumab and in some cases with lapatinib or the combination of trastuzumab and lapatinib; and second, in patients with brain metastases systemic therapies with lapatinib and capecitabine is one option that can be considered for patients with a poor prognosis for survival.

An additional HER2-targeted agent called pertuzumab received FDA approval in June 2012. Although both pertuzumab and trastuzumab are monoclonal antibodies that inhibit HER2-mediated signaling, a number of differences exist. First, each agent recognizes different extracellular epitopes, a finding that could have important therapeutic ramifications. Second, the unique binding site of pertuzumab induces structural changes that hinder receptor dimerization. Theoretically, by inhibiting HER2 signaling initiated by ligand-activated HER1 or HER3, pertuzumab could provide even greater inhibition of HER2 than trastuzumab. However, this does not appear to be the case. In fact, compared to trastuzumab, pertuzumab has exhibited less activity. Based on the results of a phase 3 clinical trial, pertuzumab is indicated for use as first-line therapy (in combination with trastuzumab and docetaxel) for HER2-positive metastatic breast cancer.[43] The most frequently reported adverse effect observed in clinical trials involving pertuzumab was diarrhea; cardiac toxicity was similar to, but does not appear to be increased when used concurrently with, trastuzumab.

One of the most significant limitations of cytotoxic chemotherapy is the lack of tumor specificity. Coupling target selectivity with the observation that trastuzumab's modest antitumor effect was substantially improved by the addition of

chemotherapy led to the idea that antibodies could be used to deliver chemotherapy rather specifically to tumor cells. However, the efficacy of antibody-chemotherapy (drug) conjugates (ADCs) has historically been limited by variable expression of the target antigen, defective tumor cell uptake mechanisms, and unreliable linkers used in the conjugation process.

A novel therapeutic compound known as trastuzumab-DM1 (T-DM1, trastuzumab emtansine) has been developed that appears to have resolved all of the above issues. Because HER2 is overexpressed in approximately 20% of breast cancers, trastuzumab was identified as a reasonable vehicle for drug delivery. In order to improve the therapeutic index of the attached chemotherapeutic agent, a maytansine derivative was synthesized. The resulting maytansinoid, emtansine, was configured to have an easily cleavable linker to trastuzumab. The resulting ADC has the potential not only of retaining the antitumor properties of the individual agents but also maintaining a tolerable side-effect profile.

The most significant results were reported in a phase 3 clinical trial which compared T-DM1 against the combination of lapatinib plus capecitabine as second-line therapy for patients with HER2-positive breast cancer progressing on trastuzumab and a taxane.[44] Primary end points were PFS, OS, and tolerability. Compared to the capecitabine/lapatinib arm, T-DM1 significantly reduced the risk of disease progression or death by 35%. Median OS at the second interim analysis crossed the prespecified efficacy stopping boundary. The most common grade ≥ 3 toxicity observed in patients receiving T-DM1 arm was thrombocytopenia. Platelet nadirs occurred 7 days after drug administration and recovered within a week. Other frequently occurring side effects included liver function test abnormalities, hypokalemia, fatigue, nausea, and headache. However, none of these adverse events were greater than grade 2. Cardiac toxicity requiring treatment discontinuation was not observed. The results of this study led to FDA approval in February 2013.

Several other clinical trials involving TDM-1 are being conducted. One that has been recently completed is the TH3RESA trial. Final results of this trial demonstrated that compared to physician's choice of treatment, significantly longer PFS and OS rates were associated with TDM-1 in women with previously treated HER2-positive MBC.[45]

▶ *Bisphosphonates*

For women whose breast cancer has metastasized to bone, bisphosphonates are recommended, in addition to chemotherapy or endocrine therapy, to reduce bone pain and fractures. Zoledronic acid, a potent bisphosphonate, is used most frequently. Although usually dosed every 4 weeks, a 12 weekly schedule has been reported to be noninferior.[46] Supplemental calcium and vitamin D are usually prescribed.

Patient Encounter Part 5

The planned dose-dense chemotherapy regimen was completed with only a week delay in the schedule due to neutropenic fever. Other than fatigue, which was minimized by exercise and yoga, she tolerated the entire neoadjuvant and radiation therapies without additional treatment-limiting toxicities. Not only was a pCR achieved, but also downsizing of the primary tumor which allowed BCS to be performed. She is currently in her first year of tamoxifen therapy.

Discuss aims of follow-up and long-term implications.

Local-Regional Control

▶ *Radiation Therapy*

Radiation is an important modality in the treatment of symptomatic metastatic disease. The most common indication for treatment with radiation therapy is painful bone metastases or other localized sites of disease refractory to systemic therapy. Approximately 90% of patients who are treated for painful bone metastases experience significant pain relief with radiation therapy. Additionally, radiation is an important modality in the palliative treatment of metastatic brain lesions and spinal cord lesions, which respond poorly to systemic therapy.

OUTCOME EVALUATION

Early breast cancer is resected completely with curative intent and adjuvant chemotherapy and/or hormonal therapy with trastuzumab in selected patients are initiated to prevent recurrence. During adjuvant chemotherapy, laboratory values to monitor chemotherapy toxicity are obtained before each cycle of treatment. After completion of adjuvant therapy, patients are monitored every 3 months for the first few years after diagnosis, with intervals between examinations extended as time from diagnosis lengthens. Evaluation includes:

- Physical examination to detect breast cancer recurrence
- Annual mammography
- Symptom-directed workup

Patients with locally advanced breast cancer are often treated with neoadjuvant therapy to make the tumor surgically resectable. However, many believe that neoadjuvant therapy may have benefits that extend beyond downsizing. During neoadjuvant chemotherapy, laboratory values to monitor chemotherapy toxicity are obtained before each cycle and weekly thereafter while on treatment; physical and ultrasound examinations are conducted to determine the size of the tumor following a complete course of neoadjuvant therapy. Surgical resection is then performed. Although no further chemotherapy is given following surgery, a recent study demonstrated a DFS and OS benefit with adjuvant capecitabine in patients with pathologically assessed residual tumor cells after preoperative chemotherapy.[47] Metastatic breast cancer is not curable, and therapy is intended to palliate symptoms and prolong survival. In most cases, hormonal therapy is the mainstay for tumors that are ER positive. While on therapy, patients are monitored monthly for signs of disease progression or metastasis to common sites, such as the bones, brain, or liver. Evaluations include:

- Pain
- Mental status or other neurologic findings
- Laboratory tests
- Liver function tests
- Complete blood count
- Calcium, electrolytes

Patient Care Process

Collect Information:

- Review medical/medication history and current laboratory values
- Document components of the medical history related to risk factors, breast cancer screening and surveillance programs, menopausal status
- Discuss overall health and performance status with the patient
- Address issues related to quality of life, psychosocial support, and survivorship needs
- Gather information related to insurance coverage

Assess the Information:

- Detail key aspects of the patient's history related to breast cancer risk level (ie, age, family history of breast/ovarian and other cancers, exposure to estrogens and ionizing radiation, and atypia)
- Determine the circumstance(s) that led to the diagnosis
- Determine the intrinsic subtype and stage of the disease
- Evaluate overall prognosis for a patient with early breast cancer based on intrinsic subtype, stage, regional node status, proliferation markers, tumor grade

Develop a Care Plan:

- Provide sufficient time for patient to process and cope with the diagnosis
- Explore the appropriateness of testing for possible hereditary cancers and fertility-preservation in premenopausal women
- Assess treatment goals
- Formulate treatment strategy based on tumor burden, nodal involvement, tumor biology, health and menopausal status, and patient preference
- Identify key endpoints (especially with regards to quality of life issues) related to pharmacotherapeutic management of the patient
- Develop a supportive care plan

Implement the Care Plan:

- Ensure that the patient understands details related to the overall treatment plan (ie, timing and duration of systemic therapy relative to other treatment modalities)
- Assess pharmacologic treatment for drug interactions
- Address concerns and appraise comprehension and communication of drug-related side effects and possible adverse events (both acute and delayed)

Follow-up: Monitor and Evaluate:

- Reinforce compliance regarding clinic visit and medications prescribed
- Address acute therapy-related complications and recommend or modify therapy as appropriate
- Recommend treatment of delayed therapy-related complications (ie, menopausal symptoms, osteoporosis, etc)
- Reeducate patient regarding any change(s) in medication(s)
- Assess quality of life issues especially for women receiving long-term endocrine therapy

Abbreviations Introduced in This Chapter

AI	Aromatase inhibitor
DFS	Disease-free survival
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
LHRH	Luteinizing hormone-releasing hormone
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PR	Progesterone receptor
SERD	Selective estrogen-receptor downregulators
SERM	Selective estrogen receptor modulator
TNM	Tumor, node, metastasis (staging system)
TTP	Time to progression

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2015;67:7–30.
2. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;302:643–646.
3. Jiralerspong S, Goodwin PJ. Obesity and breast cancer prognosis: evidence, challenges, and opportunities. J Clin Oncol. 2016;34:4203–4216.
4. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687–1717.
5. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998; 90:1371–1388.
6. Powles TJ, Ashley S, Tidy A, et al. Twenty-year follow-up of the Royal Marsden randomized double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst. 2007;99:283–290.
7. Vogel VG, Costantino JP, Wickerham DL, et al. The study of tamoxifen and raloxifene (STAR): report of the National Surgical Adjuvant Breast and Bowel Project P-2 trial. JAMA. 2006;295:2727–2741.
8. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet. 2014;383(9922):1041–1048.
9. Barton MK. Exemestane is effective for the chemoprevention of breast cancer. CA Cancer J Clin. 2011;61(6):363–364.
10. U.S. Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151:716–726.
11. Veronesi U, Cascinelli N, Mariani MD, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347:1227–1232.

12. Markopoulos C, Tsaroucha AK, Kouskos E, Mantas D, Antonopoulou Z, Karvelis S. Impact of breast cancer surgery on the self-esteem and sexual life of female patients. J Int Med Res. 2009;37:182–188.
13. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14:297–305.
14. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection versus no axillary dissection in women with invasive breast cancer and sentinel node metastasis. JAMA. 2011;305: 569–575.
15. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Eng J Med. 2010;362:513–520.
16. Coates AS, Winer EP, Goldhirsch A, et al. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol. 2015;26:1533–1546.
17. Bonadonna G, Moliterni A, Zambetti M, et al. 30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: Cohort study. BMJ. 2005;330:217–222.
18. Azim Jr HA, de Azambuja E, Colozza M, Bines J, Piccart MJ. Long-term toxic effects of adjuvant chemotherapy in breast cancer. Ann Oncol. 2011;22:1939–1947.
19. Goldstein LJ, Gray R, Badve S, et al. Prognostic utility of the 21-gene assay in hormone receptor—positive operable breast cancer compared with classical clinicopathologic features. J Clin Oncol. 2008;26:4063–4071.
20. Cheang MCU, Voduc KD, Tu D, et al. Responsiveness of intrinsic subtypes to adjuvant anthracycline substitution in the NCIC.CTG MA.5 randomized trial. Clin Cancer Res. 2012;18:2402–2412.
21. Dhesy-Thind B, Pritchard KI, Messersmith H, et al. HER2/neu in systemic therapy for women with breast cancer: a systematic review. Breast Cancer Res Treat. 2008;109:209–229.
22. Goldhirsch A, Gelber R, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomized controlled trial. Lancet. 2013;382:1021–1028.
23. Skliris GP, Leygue E, Curtis-Snell L, Watson PH, Murphy LC. Expression of oestrogen receptor-β in oestrogen receptor-α negative human breast tumours. Br J Cancer. 2006;95: 616–626.
24. Papoutsi Z, Zhao C, Putnik M, Gustafsson J-A, Dahlman-Wright K. Binding of estrogen receptor α/β heterodimers to chromatin in MCF-7 cells. J Mol Endocrin. 2009;43:65–72.
25. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet. 2013;381:805–816.
26. Goss PE, Ingle JN, Martino S, et al. Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole. Ann Oncol. 2013;24:355–361.
27. Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA. 2009;302: 1429–1436.
28. Dezentjé VO, van Schaik RHN, Vletter-Bogaartz JM, et al. (2013). CYP2D6 genotype in relation to tamoxifen efficacy in a Dutch cohort of the tamoxifen exemestane adjuvant multinational (TEAM) trial. Breast Cancer Res Treat. 2013;140:363–373.
29. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med. 2009;361:766–776.
30. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol. 2010;28:509–518.
31. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M. Estimation of the number of women living with metastatic breast cancer in the United States. Cancer Epidemiol Biomarkers Prev. 2017; DOI:10.1158/1055-9965.EPI-16-0889.
32. Lønning PE. The potency and clinical efficacy of aromatase inhibitors across the breast cancer continuum. Ann Oncol. 2011;22:503–514.
33. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925–1936.
34. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. N Engl J Med. 2016; 375:1738–1748.
35. Robertson JF, Lindemann JP, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer. Follow-up analysis from the randomized "FIRST" study. Breast Cancer Res Treat. 2012;136:503–511.
36. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med. 2012;367:435–444.
37. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366:520–529.
38. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol. 2007;25:5210–5217.
39. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2014;32:3307–3329.
40. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–792.
41. Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC->T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC->TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients: BCIRG 006 Study. Cancer Res. 2010;69:62.
42. Lin NU, Diéras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res. 2009;15:1452–1459.
43. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366:109–119.
44. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367:1783–1791.
45. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomized open-label phase 3 trial. Lancet Oncol. 2017;18(6):743–754.
46. Hortobagyi GN, Van Poznak C, Harker WG, et al. Continued treatment effect of zoledronic acid dosing every 12 vs 4 weeks in women with breast cancer metastatic to bone. JAMA Oncol. 2017; doi:10.1001/jamaoncol.2016.6316.
47. Masuda N, Lee S-J, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 2017;376:2147–2169.

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90 Lung Cancer

Val Adams and Justin M. Balko

LEARNING OBJECTIVES

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

1. Identify major risk factors for the development of lung cancer.
2. Explain the pathologic progression of lung cancer and its relationship with signs and symptoms of the disease.
3. Make appropriate recommendations for screening and preventive measures in high-risk patients.
4. Understand staging of lung cancer patients and how it influences treatment decisions.
5. Explain how histology, biomarkers, and genetic mutational testing are used to select therapy.
6. List the rationale, advantages, and disadvantages for neoadjuvant and adjuvant chemotherapy in non–small cell lung cancer (NSCLC).
7. Identify the treatment of choice and treatment goals for limited and extensive small cell lung carcinoma.
8. Identify the treatment of choice and treatment goals for local, locally advanced, and advanced non–small cell lung carcinoma.

INTRODUCTION

Lung cancer continues to be one of the most commonly diagnosed cancers and the leading cause of cancer-related mortality. Although treatment can cure some patients, most therapies only prolong survival and improve symptoms. Recent advances in lung cancer research has provided a number of new therapies that provide significant benefit for some populations of patients; however, antismoking campaigns still appear to offer the best opportunity to reduce lung cancer incidence and mortality.

EPIDEMIOLOGY AND ETIOLOGY

Incidence and Mortality

Cancers of the lung and bronchus remain to be the second most common cancer diagnosis in the United States in 2018 (behind breast cancer). Lung cancer is the number one cause of cancer-related mortality, comprising more than 25% of cancer-related deaths in the United States. A close correlation exists between incidence and mortality of lung cancer, reflecting the reality that approximately 80% of lung cancer patients ultimately die of the disease.[1]

Clinical Risk Factors

▶ *Smoking*

LO 1 KEY CONCEPT The most important risk factor for the development of lung cancer is smoking. One of the most predictive factors of lung cancer incidence is cigarette smoking prevalence. Although rates of lung cancer have nearly doubled in never smokers over the past 25 years, this population still only represents about 15% of all cases and ~85% of cases occur in current or former smokers.[2] Correlation between smoking and lung cancer continues to drive antismoking and clean indoor air campaigns and should be considered an investment in the future health care of the nation. Furthermore, smoking cessation plays an important role in reducing lung cancer risk on a patient-to-patient basis, and appropriately guiding such therapy is a crucial part of preventing lung cancer in at-risk patients. Both total smoke exposure and current use correlate with the individual's risk of developing malignancy. The risk of lung cancer decreases to near-normal levels 10 to 15 years following successful smoking cessation. Total smoke exposure is reported as pack-years. One pack-year is equivalent of smoking one pack per day for 1 year. A patient who smokes 40 cigarettes per day (two packs) for 5 years would have a 10 pack-year history (2 packs/day for 5 years).

▶ *Other Air-Related Risks*

LO 1 In addition to direct inhalation of cigarette smoke, other environmental are risks for the development of primary lung tumors. Environmental tobacco smoke (ETS) presents a significant occupational hazard for nonsmokers working in environments that have a high-smoking population, such as bars or restaurants. Each year approximately 3000 cases of lung cancer in nonsmokers are caused by ETS. In response, the majority of states have enacted clean indoor air act, which are legislative ordinances restricting smoking in public places. Other environmental factors linked to lung cancer include **radon**, arsenic, nickel, and chloromethyl ethers. Those who live in an urban environment are also at an increased risk for lung cancer owing to exposure to high concentrations of combustion fumes.[3] Asbestos exposure increases the risk of developing a distinct but rare type of lung cancer called **mesothelioma**.

Hereditary or Genetic Risk Factors

Although smoking is a key risk factor for lung cancer, the majority of smokers never develop lung cancer. Genetic risk factors may predispose certain smokers to lung cancer. After adjustments for age, smoke exposure, occupation, and gender, relatives of a lung cancer patient have approximately a twofold risk of developing lung cancer. The degree of inherited risk inversely correlates with the age of the relative at the time of diagnosis. First-degree relatives of a lung cancer patient diagnosed between the ages of 40 and 59 years have a sixfold relative risk for lung cancer. Familial lung cancer that develops at an early age in nonsmokers fits a Mendelian codominant inheritance model. However, a lung cancer gene has not been identified.

Chemoprevention

LO 3

Many studies of potential **chemoprevention** agents, including nonsteroidal anti-inflammatory drugs, retinoids, inhaled glucocorticoids, vitamin E, selenium, and green tea extracts, have been conducted, but none have been successful. A large randomized trial testing the effects of selenium, previously considered a promising chemopreventative agent for lung cancer, was stopped early due to lack of any observable effect at its first interim analysis.[4]

Interestingly, data from a placebo-controlled, double blind study demonstrated that selective cyclooxygenase-2 (COX-2) inhibition with celecoxib reduces the proliferation of bronchial epithelial cells, lowers inflammatory markers, and may resolve benign or premalignant lung nodules in former smokers.[5] Existing data suggest that bronchial epithelial cell proliferation may be a surrogate endpoint for chemopreventative lung cancer trials. However, at this time, routine use of celecoxib as a chemopreventative agent is not warranted.

Screening and Early Detection

LO 3

Five-year survival is greater than 50% for patients diagnosed with localized lung cancer. Unfortunately, most patients have regional or advanced disease at the time of diagnosis, which negatively impacts survival (**Figure 90–1**). Screening and detecting lung cancer tumors when they are localized should improve overall survival which is the basis for lung cancer screening.

The landmark trial, the National Lung Screening Trial (NLST) randomized more than 53,000 patients at high risk for lung cancer to three annual low-dose spiral computed tomography (CT) scans or chest x-ray. Chest x-ray has been shown in large trials to be equivalent to no screening and can be considered a placebo control for mortality. In the CT arm 6.9% of patients were diagnosed with localized lung cancer with over 90% having surgery with curative intent. Screening by CT reduced lung cancer mortality by 20% and was subsequently approved and recommended for high-risk patients. High-risk patients are defined by all of the following criteria:

1. Age between 55 and 74 years old
2. If former smoker, had quit within the previous 15 years
3. Greater than or equal to a 30 pack-year history

While screening reduces lung cancer mortality, implementation has been slow. This is likely due to the small absolute change in mortality of 0.3% (1.3% vs 1.6%) combined with the high false positive findings. In the NLST, the CT screening arm had positive findings in 26% of scans and nearly 40% of all patients; meaning 96.4% of the lesions discovered were benign (false positives). Due to this high false positive rate, research continues to look for methods to lower the false positive rates.[7]

The United States Preventative Services Task Force guidelines provide lung cancer screening a grade B recommendation, which means the magnitude of benefit is moderate. The proposed action for grade B recommendations is to offer or provide this service for qualifying patients. The most rational addition is smoking cessation in combination with screening.[6]

PATHOPHYSIOLOGY

Histologic Classification

Most lung cancers arise from the respiratory epithelium and are classified as **carcinomas**.

Histologic classification of lung cancer involves determining the cellular origin of the tumor. Knowing the histology of the tumor influences treatment decisions as well as prognosis.

There are four major histologic types of lung cancer that are divided into different classes based on response to treatment and prognosis: small cell lung cancer (SCLC), squamous cell

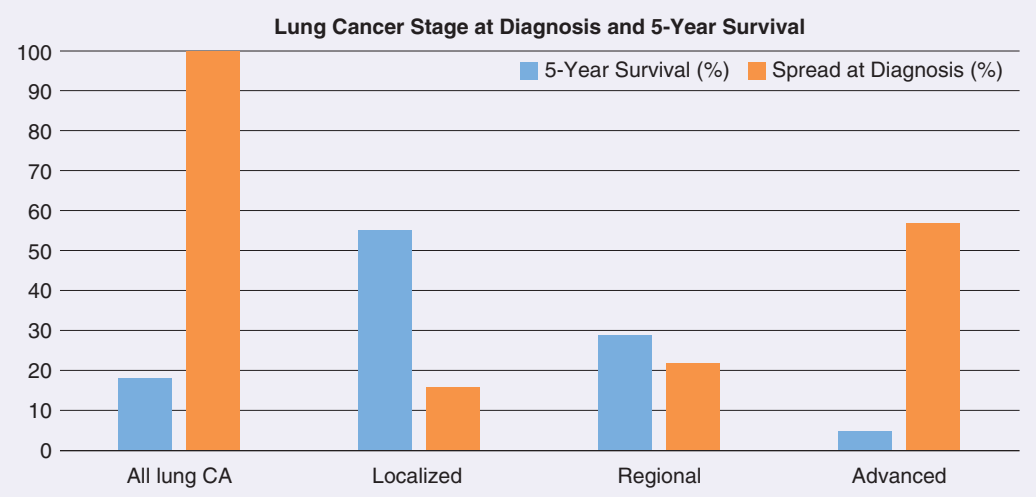

FIGURE 90–1. Spread of lung cancer disease at diagnosis and corresponding 5-year survival in the United States. Data from National Cancer Institute. SEER Database https://seer.cancer.gov/statfacts/html/lungb.html accessed 8/14/2017.

Table 90–1

Lung Tumor Histopathology[7]

Tumor Type	Percent of Tumors	Targetable Mutation	Frequency
Small cell	15–20	None	
Non–small cell			
Adenocarcinoma	35–40	*EGFR*	15%–20%
		ALK	5%
		BRAF	1%–3%
		ROS1	1%–2%
Squamous (epidermoid)	25–30	None	
Large cell (giant)	10	None	

non–small cell lung cancer (NSCLC), adenocarcinoma, and large cell lung cancer. These histology types of lung cancer are further divided by driver mutations or biomarkers as outlined by class in Table 90–1.[7] Mutation (genetic) and surface protein expression testing plays a key role in the treatment plan for NSCLC. Tumors where more than 50% of viable cells express programmed death ligand 1 (aka B7-H1 and CD274) (PD-L1) (TPS ≥ 50%, PD-L1+) and tumors with driver mutations or rearrangements of *ALK, BRAF, EGFR,* or *ROS1* have specific treatment options that offer improved response rates and survival compared to traditional cytotoxic therapies. PD-L1 testing should be performed on all patients, whereas, mutational testing should be performed on all nonsquamous histologies.[8]

However, it is important to note that certain other rare malignancies can be seen and many lung cancers may consist of multiple histologic subtypes. Furthermore, a recent phenomenon has been observed where pharmacologic treatments may selectively kill different components of the tumor, resulting in a conversion of the remaining tumor to a different subtype (ie, NSCLC becomes SCLC after treatment).

Clinical Staging

LO 4

Once the diagnosis of lung cancer is confirmed through visualization and biopsy, the extent of disease must be determined. Clinical staging serves two primary purposes: predicting prognosis and guiding therapy. Both NSCLC (squamous and nonsquamous subsets) and SCLC are staged using the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) staging system.[9]

Patient Encounter Part 1

A 68-year-old man presents at your clinic complaining of worsening cough with occasional hemoptysis. He has had 1 to 2 severe upper respiratory infections annually for the past 4 to 5 years and 1 last month. He smoked about a pack of cigarettes per day beginning since he was 15 years old. He lives in a small rural town where he worked as a coal miner. A year after retiring at age 62 he purchased a restaurant/bar where he now works.

What risk factors for lung cancer are present?

Calculate this patient's pack-year history.

▶ *Non–Small Cell Lung Cancer*

Clinical staging of NSCLC with the TNM system evaluates the size of the tumor (T), extent of nodal involvement (N), and presence of metastatic sites (M). The combination of these three evaluations determines the stage. Clinical stages are grouped together as localized, regional, or metastatic disease for real world prognosis by the National Cancer Institute Surveillance Epidemiology and End Results (SEER). Local disease (stages 1 and 2) includes tumors that are confined to a single hemithorax and those cancers which have spread to the ipsilateral hilar lymph nodes. Once malignancy invades the mediastinal lymph nodes or contralateral hilar nodes, the disease becomes locally advanced (regional, stage 3). When lung cancer is detected outside the pleural cavity, it is considered as advanced disease (metastatic, stage 4). Local disease is associated with the highest cure and survival rates, whereas those with advanced disease have a 5-year survival rate of less than 5%.

▶ *Small Cell Lung Cancer*

The most common system for staging SCLC was developed originally by the Veterans Administration Lung Cancer Study Group, and has now been incorporated into the TMN staging system.[10] This system categorizes SCLC into two classifications, limited and extensive disease.

- Limited disease: Stages I–III that can be safely treated with definitive radiation doses.
- Extensive disease: Stage IV or T3–T4 due to multiple nodules that are too extensive to be encompasses in a tolerable radiation plan.

CLINICAL PRESENTATION AND DIAGNOSIS

KEY CONCEPT Signs and symptoms of lung cancer can be classified into three subdivisions: pulmonary, extrapulmonary, and paraneoplastic syndromes. Distinguishing among these classes of symptoms is important because it can aid in determining the severity of the disease, guide treatment options, and affect prognosis.

TREATMENT

General Treatment Considerations

LO 5

The treatment of lung cancer depends on tumor histology, biomarkers (driver mutations, PD-L1 expression), stage of disease, patient characteristics, and performance status (PS). All these aspects must be assessed before appropriate treatment can be recommended. In the development of a patient care plan, keep in mind the ultimate goals of therapy. Treatment modality based on histology and stage is outlined in Figure 90–2. Some treatments may prolong survival by a few months, but at the expense of significant decreases in patient quality of life. Treatment decisions must include both the health care team and a well-informed patient. KEY CONCEPT In general patients with early stage disease, a definitive cure is the primary goal of treatment, although this end point is not always met. Additional goals of treating lung cancer patients include prolongation of survival and improvement of quality of life through alleviation of symptoms.

▶ *Performance Status*

The performance status (PS) of an individual patient predicts response and likelihood of toxicity to chemotherapy as well as

LO 2

Clinical Presentation and Diagnosis[11]

Pulmonary Symptoms

Symptoms related to the direct effects of the primary tumor often appear first and are the most common. These include the following:

- Cough
- Chest pain
- Shortness of breath
- Dysphagia
- Hemoptysis

Extrapulmonary Symptoms[11]

Once the tumor invades tissues outside the pleural cavity, it can produce a wide array of symptoms, including:

- General bone pain
- Adrenal insufficiency
- Confusion
- Personality changes
- Enlarged lymph nodes
- Weight loss
- Seizures
- Nausea and vomiting
- Focal neurologic symptoms
- Horner syndrome
- Fatigue
- Headache
- Pancoast syndrome
- Subcutaneous skin nodules

Paraneoplastic Syndromes[11]

Symptoms that are not a result of the direct effects of the tumor are termed paraneoplastic syndromes. They may be caused by substances secreted by the tumor or in response to the tumor and often occur in tissues far from the site of malignancy. Paraneoplastic syndromes are numerous and affect a wide variety of systems, including the endocrine, neurologic, skeletal, renal, metabolic, vascular, and hematologic systems.

Diagnosis

Diagnosis requires visualization of one or more lesions as well as biopsy of the lesion to confirm malignancy. Both visualization and sampling can be performed by invasive or noninvasive methods. These methods are summarized in Table 90–2.

overall survival. The PS evaluation system used most frequently was developed by the Eastern Cooperative Oncology Group (ECOG) (see Chapter 88). Patients with localized disease may be treated more aggressively in this scenario because the intent of treatment is curative. KEY CONCEPT Categorizing patients by their ECOG PS allows for a standardized approach to predict the capability to tolerate systemic therapies that may severely compromise the patient's health. Patients with a good PS 0 to 1 are more likely to tolerate intense therapy. PS 2 may receive chemotherapy, and PS 3 to 4 may receive supportive therapy or treatment with targeted therapies if they have targetable activating mutations.

Treatment Modality

▶ *Surgery (NSCLC)*

KEY CONCEPT Of all treatment modalities, surgical resection is associated with the greatest improvement in survival for patients with early stage NSCLC tumors (clinical stage IA, IB, or IIA). Surgery is not recommended in locally advanced and metastatic disease as it has not been proven to prolong survival. However, surgery for advanced disease is an important palliative treatment that can improve quality of life in some patients. In this respect, surgery is limited to local sites where the tumor is causing significant morbidity (eg, spinal cord compression).

▶ *Surgery (SCLC)*

Patients with SCLC are rarely treated with surgery because the results of a randomized trial published in 1969 showed that surgery did not result in any 5- or 10-year survivors in comparison to radiation which produced a 4% survival rate at 5 and 10 years.[12] With improved imaging and surgical techniques as well as the use of effective adjuvant therapy, some clinicians believe that surgery does have a role in early stage SCLC. However, this has yet to be proven in a clinical trial.

LO 5

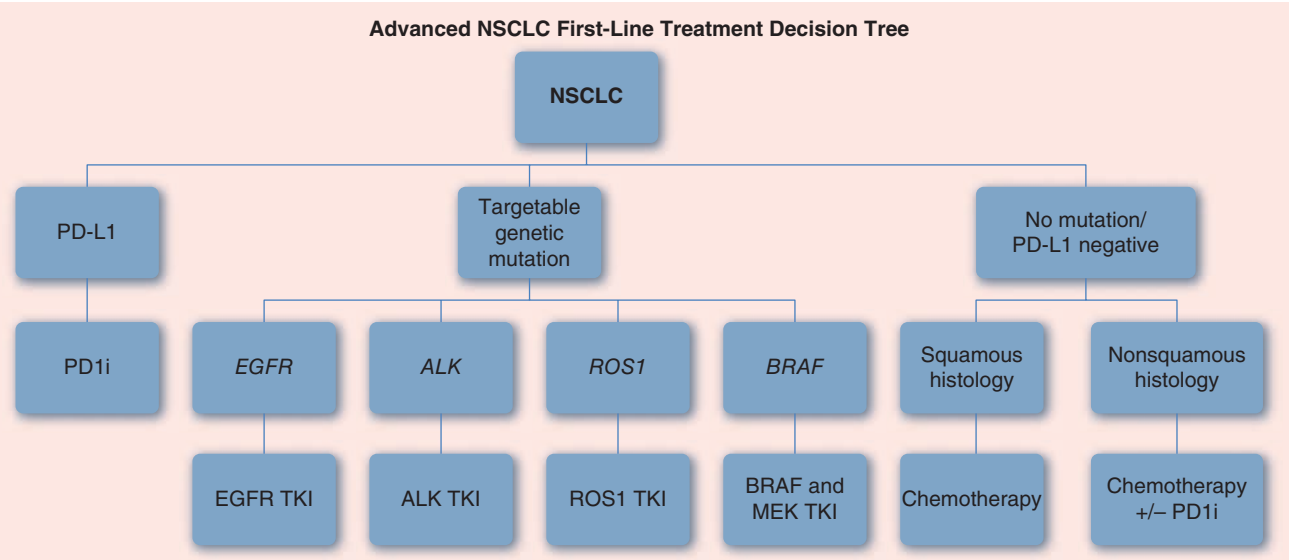

FIGURE 90–2. First-line treatment algorithm for advanced stage disease based on biomarkers, genetic mutations, and histology. (NSCLC, non–small cell lung cancer; PD1i, PD-1 targeting immunotherapy; TKI, tyrosine kinase inhibitor.)

Table 90–2

Diagnostic Tools[13,14]

	Technique	Description
Visualization	Chest x-ray	The least expensive visualization method in the diagnosis of lung cancer. Readily accessible and does not require systemic administration of contrast dye. However, it often detects lesions that are not cancerous and is not capable of assessing lymph node status.
	CT	More accurate when providing information on size, location, and invasion than chest radiography. It is recommended as part of the standard workup in most cases.
	PET scanning	Uses a substance called 5-FDG to produce a functional image of the lungs. Cells that are actively growing and dividing use greater amounts of glucose and therefore take up more 5-FDG. Focal regions of fluorescence can be visualized in cancerous lesions. PET scanning combined with a CT scan is more accurate than CT scan alone; however, the exact role of PET scanning in staging and monitoring is unclear. The apparent benefit and common role in staging is to evaluate mediastinal disease when it can influence the tumor resectability.
Tumor sampling	Fine-needle aspiration	A method of aspirating cells from the tumor via insertion of a small-bore needle into the lesion and aspirating. Commonly used to evaluate lymph nodes or other poorly accessible sites, it has the advantage of being faster and less invasive than other biopsy methods; however, it does not preserve the architecture of the tumor and may return cells that are undergoing cell death, which negates histologic analysis.
	Bronchoscopy	A fiberoptic camera is inserted through the airways to examine the site of the suspected lesion. Once the lesion is visualized, a tool attached to the camera allows for a tissue biopsy. Newer technologies incorporate fluorescence to differentiate malignant tissue from premalignant lesions.
	Core needle biopsy	A method of obtaining tissue and preserving the tumor architecture. A large-bore needle is inserted into a lesion, where it cuts a core of tissue out that then can be evaluated.
	Thoracentesis	Involves removal of fluid in the pleural cavity via a needle. The fluid then is assayed for the presence of cancerous cells. This procedure has low sensitivity and depends on the presence of a pleural effusion.
	Sputum cytology	Detects cancerous cells that become dislodged from the airways into the sputum. Sputum cytology is useful because it is not invasive, but it has much lower sensitivity for detecting cancer.

CT, computed tomography; 5-FDG, 5-fluorodeoxyglucose; PET, positron-emission tomography.

▶ *Radiotherapy (NSCLC)*

Patients with localized NSCLC are best treated with surgery; however, many of these patients are inoperable because of comorbidities (eg, lung disease from smoking). In these situations, radiation therapy can be used with curative intent in place of surgery, and the success rate is approximately 50% that of surgery.[15] Patients with locally advanced (stage IIIB, nonsurgically resectable) disease have prolonged survival with combined chemotherapy and radiotherapy. Patients with late stage NSCLC can receive radiation therapy to palliate symptomatic metastases. Although radiation is less invasive than surgery, it can have marked toxicity on normal tissue, and patients may experience esophagitis, pneumonitis, cardiac abnormalities, myelosuppression, and skin irritation. These adverse events can be decreased by using stereotactic radiation and/or hyperfractionated administration.[16]

Postoperative radiotherapy (PORT) is thought to eliminate remnants of the resected tumor that might be deposited in nearby tissue, but is only recommended for patients with positive margins after surgical resection when a local recurrence is of concern.[9]

Patient Encounter Part 2: Medical History, Physical Examination, and Diagnosis

PMH: Moderate hypertension (controlled)

FH: Father died from lung and colorectal cancer at age 62, mother is 85, alive, and living in a nursing home due to heart failure and dementia

Meds: Lisinopril 20 mg daily

ROS: (+) Chest pain, shortness of breath, hemoptysis; (–) recent weight loss

PE:

VS: BP 125/69 mm Hg, RR 26 breaths/min, P 80 beats/min, T 99°F (37.2°C)

CV: RRR

Labs: Slightly elevated LFTs and platelets, mild anemia (Hgb 11.8 gm/dL); all others WNL; CXR reveals a solitary nodule in right lobe; fine-needle aspiration confirms squamous cell carcinoma of the lung that stains positive for PD-L1; further evaluation with CT and PET scans reveal a 3-cm mass, with bilateral mediastinal lymph node involvement and a lesion on his adrenal gland.

What clinical stage is this patient's disease?

What is the estimated survival time for this stage of NSCLC?

Does this patient have any factors that may negatively or positively influence survival?

▶ *Radiotherapy (SCLC)*

Radiotherapy (concurrent with chemotherapy) is the treatment of choice for limited-stage SCLC. Limited- and extensive-stage SCLC patients who respond to therapy should also receive prophylactic cranial irradiation (PCI), which treats micrometastatic disease in the CNS. This improves cure rates for limited-stage disease and prolongs survival for extensive-stage disease.[17]

Cytotoxic Chemotherapy (NSCLC)

LO 6

Traditional chemotherapy remains the mainstay of lung cancer treatment, despite recent advances with immunotherapy and targeted therapy. While patients with PD-L1 positive, ROS1, EGFR, BRAF, and ALK mutations are treated with targeted therapies, the majority of patients do not have actionable mutations. Cisplatin and carboplatin are arguably the most effective traditional chemotherapy agents regardless of histology.[7,8] KEY CONCEPT Platinum doublet chemotherapy regimens offer superior response rates compared with single-agent chemotherapy regimens and should be used when the patient can tolerate the increased toxicity. Effective chemotherapy agents that are added to platinum include paclitaxel, albumin bound paclitaxel, docetaxel, gemcitabine, vinorelbine, and pemetrexed. Patients with squamous histology do not benefit from pemetrexed, while they seem to benefit more from gemcitabine (see Table 90–3 for regimen details). The duration of therapy has also been intently studied. Doublet therapy is generally given for four to six cycles; patients with nonsquamous histology receive benefit from maintenance therapy with pemetrexed with or without bevacizumab. Those with squamous histology can be treated with maintenance gemcitabine.[9]

Cytotoxic Chemotherapy (SCLC)

Cytotoxic chemotherapy with platinum and etoposide are the mainstay of treatment for SCLC. With limited-stage disease, cisplatin is thought to be slightly superior to carboplatin, but more toxic. Extensive-stage disease is treated with either agent, although most commonly carboplatin. Cisplatin combined with irinotecan, which was superior to cisplatin

Table 90–3

Select Chemotherapy Regimens and Their Efficacy

Regimen	Comparison	PFS	OS
	NSCLC Adjuvant Therapy[18]		
Cisplatin–vinorelbine (JBR.10)	Cisplatin 50 mg/m² IV day 1 and 8 every 4 weeks × 4 weeks Vinorelbine 25 mg/m² IV day 1 Every 3 weeks for 16 weeks vs Observation		Median 7.8 years vs 6.1 years (p = 0.05)
	NSCLC First Line for Advanced Disease[19-21]		
Cisplatin–paclitaxel	Paclitaxel 135 mg/m² CIV over 24 h day 1 + cisplatin, 75 mg/m² IV day 2 repeat q3week	Median 3.4 months vs	Median 7.8 months vs
Cisplatin–docetaxel	Cisplatin 75 mg/m² IV day 1 and docetaxel 75 mg/m² IV day 1 repeat q3week	3.7 months vs	7.4 months vs
Cisplatin–gemcitabine	Cisplatin 100 mg/m² IV day 1 and gemcitabine 1000 mg/m² IV days 1, 8, and 15 repeat q4week	4.2 months vs	8.1 months vs
Carboplatin paclitaxel (ECOG 1594)	Carboplatin, dosed to AUC of 6 IV day 1 and paclitaxel 225 mg/m² IV over 3 hours day 1 repeat q3week	3.1 months (p = NS)	8.1 months (p = NS)
Cisplatin–pemetrexed	Cisplatin 75 mg/m² IV day1 + Pemetrexed 500 mg/m² IV day 1 Repeat q3week × 6	Median 4.8 months vs	Median 10.3 months vs
Cisplatin–gemcitabine	Cisplatin 75 mg/m² IV day 1 + Gemcitabine 1250 mg/m² IV days 1 and 8 Repeat q3week × 6	5.1 months (p = NS)	10.3 months (p = NS)
Carboplatin–Paclitaxel +/– Bevacizumab (ECOG 4599)	Paclitaxel 200 mg/m² IV Day 1 + Carboplatin AUC 6 IV Day 1 Repeat q3week × 6 vs Paclitaxel 200 mg/m² IV Day 1 + Carboplatin AUC 6 IV Day 1 + Bevacizumab 15 mg/kg IV day 1 Repeat q3week × 6	Median 4.5 months vs 6.2 months (p < 0.001)	Median 10.3 months vs 12.3 months (p = 0.003)
	SCLC First-Line Regimens[17]		
Limited stage			
EP	Etoposide 100 mg/m²/d IV days 1–3 + Cisplatin 80 mg/m² IV day 2+ Radiation Repeat every 4 weeks vs	Median 1.1 year vs	Median 3.2 years vs
IP	Irinotecan 60 mg/m² IV days 1, 8, 15 + Cisplatin 60 mg/m² IV day 1 Repeat every 4 weeks	1.0 year (p = 0.74)	2.8 years (p = 0.70)
Limited and extensive stage			
EC	Etoposide 100 mg/m²/d IV days 1–3 + Carboplatin 300 mg/m² IV day 1 Repeat every 3 weeks		Median 12.5 months

and etoposide in a Japanese study, was found to be equivalent in the United States. Although it is not commonly used, it is a reasonable alternative.

Immunotherapy

Immunotherapy is considered a unique modality and is often referred to as the 4th cornerstone of treatment. Although it involves targeted monoclonal antibodies, it is separate because the goal is to activate the immune system. Programmed cell death protein 1 receptor (PD1) and PD-L1 inhibitors have become a mainstay in NSCLC and research is being done to determine if they have a role in SCLC. Pembrolizumab is currently approved for first-line therapy both as monotherapy in PD-L1 positive patients and in combination with chemotherapy regardless of PD-L1 positivity. Additionally, nivolumab, atezolizumab, and pembrolizumab are effective as second-line therapy. Key studies are shown in Table 90–4.

Targeted Therapy

Monoclonal antibodies targeting vascular endothelial growth factor (VEGF) signaling (bevacizumab and ramucirumab) and epidermal growth factor receptor (EGFR; necitumumab) have been combined with traditional chemotherapy to improve outcomes. Their use is currently limited to stage IV NSCLC; investigation in SCLC indicates no role at this time.

Tyrosine kinase inhibitors (TKIs) are the front-runners in precision medicine. Monotherapy with a TKI in genetically selected patients frequently outperforms cytotoxic chemotherapy. Multiple agents are approved for *EGFR* mutations, *ALK* mutations (generally a rearrangement), *ROS1* mutations, and *BRAF* mutations. The TKIs are all oral medications, which allow the pharmacist to play a more integral role in the patient's therapy. Consequently, optimizing outcomes requires pharmacists to obtain a complete medication history and be knowledgeable about preventing and managing therapy-induced toxicity (see Chapter 88). Everyone involved in this process should be adequately knowledgeable about toxicity prevention and management.[9,17] Results of key studies for targeted therapies are shown in Table 90–5.

Therapeutic decisions to start therapy must include the full consent and understanding of risks by the patient. Counseling on the therapeutic regimen and risk of toxicity is imperative before dosing. Refer to Chapter 88 for dosing recommendations in renal and hepatic failure.

Treatment of Small Cell Lung Cancer

LO 7

SCLC typically presents as an extensive disease (approximately 60%–70% of new cases) and progresses very quickly. SCLCs are very responsive to chemotherapy and radiation but have a short duration of response. Radiotherapy became the standard in 1969, when a randomized trial showed that it offered the potential for cure, whereas surgery did not.[22] In the vast majority of patients, chemotherapy with or without radiotherapy is the treatment of choice. Even after a complete response to therapy, the cancer usually recurs within 6 to 8 months, and the survival time following recurrence is typically short (~4 months). This yields an average survival rate of 14 to 20 months for limited disease and 8 to 13 months for extensive disease.[18]

Table 90–4

Select Clinical Trials in Advanced NSCLC with Immunotherapy

Regimen	Comparison	PFS	OS
	PD-L1 Positive First Line[23,24]		
Pembrolizumab (KEYNOTE-024)	Pembrolizumab 200 mg IV q3week vs Platinum Doublet	Median 10.3 months vs 6.0 months ($p < 0.001$)	6 month survival 80% vs 72% ($p = 0.005$)
Carboplatin – Pemetrexed – Pembrolizumab (KEYNOTE-021)	Pemetrexed 500 mg/m^2 IV + Carboplatin AUC 5 IV Pembrolizumab 200 mg IV Repeat q3week vs Pemetrexed 500 mg/m^2 IV + Carboplatin AUC 5 IV Repeat q3week	Median 13 months vs 8.9 months ($p < 0.0001$)	Not Reported
	Second Line[29-31]		
Atezolizumab (OAK)	Atezolizumab 1200 mg IV q3week vs Docetaxel 75 mg/m^2 IV q3week	Median 2.8 months vs 4 months	Median 13.8 months vs 9.6 months ($p = 0.0003$)
Nivolumab (CheckMate 017) Squamous Histology	Nivolumab 3mg/kg IV q2week vs Docetaxel 75 mg/m^2 IV q3week	Median 3.5 months vs 2.8 months	Median 9.2 months vs 6.0 months ($p < 0.001$)
Nivolumab (CheckMate 057) Nonsquamous	Nivolumab 3 mg/kg IV q2week vs Docetaxel 75 mg/m^2 IV q3week	Median 2.3 months vs 4.2 months	Median 12.2 months vs 9.4 months ($p = 0.002$)
Pembrolizumab (KEYNOTE-010)	Pembrolizumab 2 mg/kg IV q3week vs Docetaxel 75 mg/m^2 IV q3week	Median 3.9 months vs 4 months	Median 10.4 months vs 8.5 months ($p = 0.0008$)

Table 90–5

Select Clinical Trials in Advanced NSCLC with a Targetable Mutation

Agent	Comparison	PFS	OS
	EGFR Positive First Line[29-31]		
Gefitinib (IPASS)	Gefitinib 250 mg PO daily vs Paclitaxel 200 mg/m² IV + Carboplatin AUC 5-6 IV every 3 weeks	In EGFR+ patients: HR 0.48 (95% CI 0.34-0.67)	In EGFR+ patients: HR 1.00 (95% CI 0.76-1.33)
Erlotinib (EURTAC)	Erlotinib 150 mg PO daily vs Chemotherapy	9.7 months vs 5.2 months (p < 0.0001)	19.3 months vs 19.5 months (p = 0.87)
Afatinib (LUX-Lung 3)	Afatinib 40 mg PO daily vs Cisplatin 75 mg/m² IV + Pemetrexed 500 mg/m² IV every 3 weeks	Median 11.1 months vs 6.9 months (p = 0.001)	Median 28.2 months vs 28.2 months (p = 0.39)
	EGFR T790M Positive Second Line[32]		
Osimertinib (AURA3)	Osimertinib 80 mg PO daily vs Pemetrexed 500 mg/m² IV + Carboplatin AUC 5 IV or Cisplatin 75 mg/m² IV q3week	Median 10.1 months vs 4.4 months (p < 0.001)	Not reported
	ALK Positive First Line		
Crizotinib (PROFILE 1014)	Crizotinib 250 mg PO BID vs Pemetrexed 500 mg/m² IV + Cisplatin 75 mg/m² IV or Carboplatin AUC 5-6 IV every 3 weeks	Median 10.9 months vs 7.0 months (p < 0.001)	HR for death with crizotinib 0.82 (95% CI, 0.54–1.26; p = 0.36)
Alectinib vs Crizotinib (ALEX)	Alectinib 600 mg PO BID vs Crizotinib 250 mg PO BID	Median 25.7 months vs 10.4 months (p < 0.001)	Not mature
Ceritinib (ASCEND-4)	Ceritinib 750 mg PO daily vs Pemetrexed 500 mg/m² IV + Cisplatin 75 mg/m² IV or Carboplatin AUC 5-6 IV every 3 weeks	16.6 months vs 8.1 months (p < 0.00001)	Not reached ceritinib vs 26.2 months chemotherapy (p = 0.056)
	ALK Positive Second Line[36,37]		
Ceritinib (ASCEND-5)	Ceritinib 750 mg PO daily vs Pemetrexed 500 mg/m² IV OR Docetaxel 75 mg/m² IV every 3 weeks	5.4 months vs 1.6 months (p < 0.0001)	HR 1.0 (95% CI 0.67–1.49; p = 0.5)
Brigatinib (ALTA)	Brigatinib 90 mg PO daily OR 180 mg PO daily	9.2 months Arm A and 12.9 months Arm B	1 year OS probability 71% Arm A and 80% Arm B
	ROS1 Positive First Line[38]		
Crizotinib	Crizotinib 250 mg PO BID	Median 19.2 months	12 month OS = 85%
	***BRAF*V600E Positive First Line**[39]		
Dabrafenib and Trametinib (BRF113928)	Dabrafenib 150 mg PO BID + Trametinib 2 mg PO daily	Median 9.7 months	Not mature

Patient Encounter Part 3

The patient's condition has caused symptoms and periodic interruptions to his tasks, but he has been able to work and complete daily activities up to this point.

What is this patient's ECOG PS score?

Are there any nonpharmacologic interventions you would suggest?

Limited Disease

The regimen of choice for limited-stage disease SCLC is etoposide–cisplatin (EP). In patients who are able to tolerate combined modality therapy, concomitant chemoradiotherapy offers the greatest survival benefit. Carboplatin may be substituted for cisplatin in patients who cannot tolerate cisplatin toxicity. Cisplatin is associated with significantly more nephrotoxicity and more emetogenicity than carboplatin. Cisplatin is preferred over carboplatin because of a small study that randomized patients to

cisplatin or carboplatin plus etoposide. There was a numerically higher complete response rate with cisplatin, which is believed to be requisite for cure. Consequently, the guidelines recommend that the EP regimen be used with concurrent radiotherapy.[19]

Because patients with SCLC commonly have a recurrence in the CNS, trials have been performed to evaluate the benefit of PCI. A pivotal study showed that PCI reduces the incidence of brain metastasis and increases the 3-year survival rate from 15% to 21%.[40] Patients with limited-stage SCLC who achieve a complete response with treatment should be offered PCI.

▶ *Extensive Disease*

In the first line setting platinum regimens, particularly EP, are the treatment of choice in extensive disease. Carboplatin is commonly used in place of cisplatin because it is generally thought to have less toxic and demonstrated similar outcomes in progression-free survival and overall survival. Another regimen that is acceptable, albeit uncommonly used, is cisplatin–irinotecan. This regimen became relevant due to a Japanese study, where a combination of irinotecan and cisplatin demonstrated an increased median survival time by approximately 3 months over the EP regimen. This irinotecan–cisplatin regimen also had a lower incidence of severe neutropenic side effects but exhibited higher rates of moderate to severe diarrhea. However, this study was repeated in the United States and did not show an improvement over the EP regimen.[17] Therefore, EP remains the regimen of choice for treating extensive SCLC in the United States.

Concurrent radiotherapy is not used routinely in extensive disease; however, PCI provides significant benefit in patients responding to chemotherapy. A pivotal study demonstrated that median survival from the time of randomization increased from 5.4 to 6.7 months and 1-year survival rates increased from 13.3% to 27.1% with PCI. An additional benefit was a lower rate of brain metastases (14.6% vs 40.4%).[41]

▶ *Recurrent Disease*

The treatment of recurrent SCLC depends on the time to recurrence. If the time to recurrence is less than 6 months, second-line therapy should be considered if the patient has an acceptable PS (0–2) (see Patient Care Process). The most widely accepted second-line therapies in SCLC are topotecan alone or CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine). Relapses occurring more than 6 months after treatment warrant a repeat of the initial regimen. Patients with a poor PS (3–4) are typically managed with best supportive care, including palliative care therapies.[17]

Treatment of Non–Small Cell Lung Cancer

LO 8

The first step in treatment of NSCLC involves confirmation of the clinical stage and determination of likelihood of resection of the tumor. Tumors that are resectable require histology confirmation; while advanced (nonsurgically resectable) disease requires genetic and biomarker analysis. PD-L1 testing needs to be done on all tumors, while the genomic analysis of driver mutations is only required on nonsquamous histology (adenocarcinoma and large cell) tumors. Treatment options depend on the stage of disease (ie, eligibility for resection), PS, histology, PD-L1 expression, and genetic findings.[8]

▶ *Local Disease (Stages IA, IB, and IIA)*

Local disease encompasses stages IA through IIA and is associated with a favorable prognosis. Approximately 40% to 60% of these patients are expected to live more than 5 years from diagnosis. Goals of therapy are curative in local disease, and surgery is the mainstay of treatment regardless of histology or genetics. Stage IA tumors are rarely seen clinically and may be treated with surgery alone. If surgical margins are positive, radiotherapy or re-resection is recommended.[9] Stage IB, IIA, and locally advanced IIB NSCLC are treated with adjuvant chemotherapy. The rationale behind adjuvant chemotherapy is to eradicate micrometastases or other tumor cells that may have been missed during removal of the primary tumor. The recent results of five relatively large prospective trials suggest that there is benefit from adjuvant chemotherapy leading to a survival advantage of 4% to 15%.[42,43] Consequently, adjuvant therapy has become the standard of care in resectable NSCLC and should be offered to patients after resection, particularly those with stage II or III disease.

Although the regimen of choice is unclear, studies evaluating pemetrexed in squamous cell histology demonstrate that it has minimal to no activity in this histology. Thus, regimens containing pemetrexed should be avoided in patients with squamous cell histology. Cisplatin vinorelbine regimens appear to have the most evidence, regardless of histology or genetics. Carboplatin-based regimens may be used in patients unable to tolerate cisplatin or with comorbidities precluding cisplatin use.

▶ *Locally Advanced Disease (Stages IIB and IIIA)*

Patients with locally advanced disease should also be considered for surgery, which would be followed with adjuvant treatment as outlined in local disease. However, neoadjuvant chemotherapy could also be considered before surgery. The rationale behind neoadjuvant therapy is to decrease the size of the tumor so that it can be resected more easily with clean margins, as well as to eliminate distant micrometastases before invasive local treatment. Meta-analysis of neoadjuvant trials suggests that neoadjuvant chemotherapy in all early stages improves 5-year survival by 5%.[44] However, the methods used in many of these studies did not give adjuvant chemotherapy, which could also improve survival by about the same degree. One concern of giving neoadjuvant therapy is that the toxicity of regimens may delay surgery, and if the tumor does not respond to the treatment, there is a risk of disease progression. Nonetheless, current data suggest that more than 90% of patients who are treated with neoadjuvant therapy maintain their scheduled surgery.[45] The utilization of neoadjuvant chemotherapy is inconsistent, but is most common in patients with locally advanced tumors (stage III).[46] Neoadjuvant chemotherapy regimens are platinum-based doublets that do not include a targeted therapy. None of the large studies prospectively controlled or individualized therapy choices based on histology or genetics, which could improve results. Three cycles of carboplatin and paclitaxel administered on a 3-week schedule is a common and supported approach. The benefit of combining neoadjuvant therapy and surgery with additional adjuvant therapy is being investigated but is of unknown value at this time. Relatively small studies have compared using three treatment modalities (chemotherapy, radiation, and surgery) to two treatment modalities (chemotherapy and radiation). Improvements have been shown for progression-free survival, but not overall survival. Consequently, the value of trimodal therapy is unknown and does not have a clear role.

▶ *Advanced or Metastatic Disease (Stages IIIB and IV)*

Advanced disease is treated with systemic therapy if the patient has an acceptable ECOG PS score. The selection of

therapy is determined by the histology, biomarker, and patient characteristics. The most common first-line therapy still includes a platinum doublet, which represents those patients who are biomarker negative and do not benefit from targeted and immunotherapies. In some patients with stage IIIB disease, cisplatin and etoposide may be given concurrently with radiotherapy. However, treating unresectable stage III patients with a platinum-containing doublet regimen and omitting the radiation is common. A large randomized trial comparing four platinum doublets reported similar response rates and survival, although there were less life-threatening toxicity and treatment-related deaths associated with paclitaxel–carboplatin.[21] Consequently, some argued that paclitaxel–carboplatin was the treatment of choice. Guideline recommended platinum doublets that are considered generally equivalent; key trials are listed in Table 90–3.

This historic approach indicates use of a platinum-containing doublet given for four to six cycles. This approach produces an overall response rate of 25%–35% and 1-year survival rates of 30%–40%.

For nonsquamous histology patients who are PD-L1 negative and have no targetable mutational drivers, pembrolizumab or bevacizumab can be used in addition to a platinum doublet. The addition of bevacizumab to carboplatin and paclitaxel improves survival by about 2 months (median OS = 12.3 months); however, the survival curve still had the same shape (without plateau at the end of the curve) indicating that patients would have a lung cancer event it was just delayed. The addition of pembrolizumab to carboplatin and pemetrexed has recently been published and the overall survival data is not mature; however, the progression-free survival was 4 months longer when pembrolizumab was added to the chemotherapy regimen.

Patients who fail doublet therapy will benefit from second-line therapy. The choice of therapy depends on prior therapies, comorbidities, PS, PD-L1 status, and mutation status. For those treated without immunotherapy, the preferred therapy is a PD1 or PD-L1 inhibitor. If patients received immunotherapy in the first-line setting their options include docetaxel, pemetrexed, ramucirumab + docetaxel and gemcitabine. Second-line treatment with atezolizumab, nivolumab, or pembrolizumab improves overall survival by 2 to 4 months when compared to docetaxel (the prior standard).[9] For patients treated with chemoimmunotherapy second-line treatment with docetaxel would be the standard. This is the situation where adding ramucirumab should be considered. The pivotal study that led to FDA approval of ramucirumab reported an overall survival benefit (10.5 months vs 9.1 months); however, the clinical significance of this difference is questionable and this has not become a clear standard of care.[9]

Patients with ***squamous*** histology, who are PD-L1 negative, and have ***no targetable genetic driver mutation*** are treated with a platinum doublet. As mentioned earlier, pemetrexed does not provide benefit for this population and should be avoided. Based on secondary endpoints, it appears that a platinum-gemcitabine regimen is most effective. After failing doublet therapy, the preferred therapy is a PD1 or PD-L1 inhibitor. The historical standard was docetaxel, which is inferior to atezolizumab, nivolumab, and pembrolizumab. The pivotal studies for these three drugs showed an improved overall survival by 2 to 4 months, although crossover from docetaxel to immunotherapy may have diminished the survival impact. Although not formally tested, patients who progress or fail to respond to immunotherapy could be treated with additional therapy in the third-line setting.

First-line immunotherapy for patients with PD-L1 positive tumor score of greater than or equal to 50% provides a clinically significant improvement in response rate, progression-free survival and overall survival when compared to a platinum doublet.[24] Consequently PD-L1 assessment should be done on all advanced stage NSCLC and for those who are PD-L1 positive (50%) without a contraindication should be treated with pembrolizumab monotherapy. A similar trial comparing nivolumab to chemotherapy in the first-line setting did not find any improvement with nivolumab.[47] After patients progress on monotherapy pembrolizumab, they can be treated similarly to patients who are PD-L1 negative and no mutational driver tumors and combination chemotherapy plus pembrolizumab may be an option without prior adverse effects on pembrolizumab (see Figure 90–2).[9]

Patients whose tumor has a targetable mutation do significantly better with a targeted agent and traditional chemotherapy. Currently, there are four targetable mutations: (1) *EGFR*, (2) *ALK*, (3) *BRAF*, and (4) *ROS1*; they occur almost exclusively in nonsquamous histologies and are generally mutually exclusive. The *EGFR* activating mutations (most commonly exon 19 deletion and exon 21 substitution) are present in about 15% of nonsquamous tumors, *ALK* mutations (most commonly *ALK-EML4* rearrangement) are found in about 5% to 7% of nonsquamous histology tumors, while *BRAF* and *ROS1* mutated tumors are less common (~1% of nonsquamous histologies).[8] Once patients fail appropriate targeted therapies, treatment options are similar to first-line treatment for no driver mutation (consider PD-L1 status and histology). See Figure 90–2.[9]

EGFR mutation positive patients should be treated with osimertinib, afatinib, erlotinib, or gefitinib in the first-line setting. In large randomized trials they have all been shown to be superior to chemotherapy with a median PFS of about 11 months. Osimertinib was recently compared to erlotinib and gefitinib in the first-line setting of *EGFR*-mutated NSCLC. Osimertinib demonstrated superior progression-free survival (18.9 months vs 10.2 months; hazard ratio for disease progression or death, 0.46; 95% confidence interval [CI], 0.37–0.57; P<0.001) with fewer serious adverse effects.[48] Ultimately, all patients have a recurrence and the most common acquired mutation conveying resistance is *T790M*. Upon recurrence patients should be tested for this mutation with a tissue or liquid biopsy. A liquid biopsy refers to a PCR-based test that can detect this mutation in circulating cell-free DNA. Since a tissue biopsy is considered the gold standard, negative liquid biopsy results are generally followed up with a tissue biopsy. Those who are positive should be treated with osimertinib (a second-generation EGFR TKI) if they have not received it in the first-line setting. A prospective randomized trial compared second-line osimertinib to a platinum doublet. The results showed that osimertinib was superior in terms of ORR (71% vs 31%) and PFS (10.1 months vs 4.4 months); however, the overall survival data was not mature at the time of analysis.[32]

ALK mutation positive patients should be treated with alectinib. Recently second-generation alectinib was studied head to head with crizotinib showing superiority of alectinib over crizotinib. The median PFS with crizotinib was 10.4 months (similar to previous trials), which was inferior to alectinib (PFS 25.7 months).[33] Although the overall survival data is not mature, a 15-month improvement in PFS is unprecedented. Ceritinib, another second-generation ALK inhibitor was approved as first-line therapy based on a trial showing its superiority to chemotherapy. In that trial the ceritinib PFS was 16.6 months.[37]

Brigatinib is the most recently approved ALK inhibitor. It was approved as second-line therapy for patients who had failed crizotinib. *In vitro* studies suggest that it is active against resistance mutations, but the clinical significance of this is unknown. Ceritinib, alectinib, and brigatinib are all approved as second line and choice depends on what was received in first-line therapy.

According to the guidelines, patients whose tumor harbors an *ROS1* mutation should be treated with crizotinib. Since this mutation is only present in ~1% of tumors it is relatively uncommon and we do not have randomized controlled trial data. The approval for crizotinib in this subset population came from a single arm trial where 50 ROS1+ patients had a remarkable response (6% CR and 66% PR) and PFS (19.2 months).[38] Although other agents inhibit this pathway, none have been compared to crizotinib and are not indicated at this time. After progression on crizotinib, patients should be treated with systemic chemotherapy or clinical trial.

A small number of lung cancer patients harbor a mutation in *BRAF*, where dabrafenib and trametinib are indicated. A pivotal single arm, phase II trial enrolled 57 previously treated patients and reported an overall response rate of 63%. The progression-free survival for this trial was 9.7 months with a median duration of response of 9 months. Similar to the *ROS1* population, this mutation is rare (~1% of patients) and consequently we don't have large randomized trials. However, nonrandomized comparison of dabrafenib to dabrafenib plus trametinib support the combination based on ORR (27% vs 63%), and duration of response (9.9 months vs 12.6 months).[39] For this population, dabrafenib and trametinib are recommended to be used first line. The other BRAF and MEK inhibitors do not have enough data to be used in this setting at this time. When patients fail dabrafenib and trametinib, they should be treated into the no targetable mutation pathway (see Figure 90–2).

Special Populations

Patients who cannot tolerate platinum can be treated with gemcitabine–paclitaxel or gemcitabine–docetaxel. Randomized trials have produced response durations and survival times similar to the platinum-containing doublet regimens. However, these regimens are only recommended for patients who are unlikely to tolerate the toxicity of platinum regimens owing to comorbidities or other factors.[9]

Patients with poor PS, defined as those with a PS of 2, is a subject of debate. Although patients with a PS of 2 typically have inferior survival rates and higher toxicity to platinum chemotherapy than higher performing patients, low-toxicity single-agent regimens may offer a survival advantage in this subset. Use of these regimens also presents a method of providing symptomatic care for advanced stage patients. Agents such as pemetrexed, gemcitabine, and docetaxel may be used in this scenario. In patients with a PS of 3 or 4, chemotherapy typically results in high rates of toxicity and fails to convey a survival benefit. Consequently, treatment should be aimed at relief of symptoms instead of a definitive cure. Because targeted agents typically have lower rates of severe toxicity, they also have been used in appropriate subsets of patients with a poor PS (ECOG PS of 2 or 3). Unfortunately, we do not have adequate clinical trial data regarding the efficacy and toxicity of immunotherapy or targeted agents in these patients. In summary, debilitated patients should not be treated with combination chemotherapy with or without targeted agents because of historically high rates of toxicity without benefit. Single-agent therapy with less toxicity can be used to help palliate symptoms.[9]

Duration of Therapy

Because advanced stage lung cancer is not curable, an argument can be made that the goal is to extend the number of quality days, rather than just overall survival. With this goal in mind and an assumption that quality of life is lower during chemotherapy treatment, it is important to consider the duration of therapy. Over the last decade, treatment has moved toward fewer chemotherapy cycles. Typical cytotoxic doublet therapy regimens have decreased from planning eight cycles to six cycles, to four cycles; however, maintenance therapy with a single cytotoxic chemotherapy agent or with targeted therapies or immunotherapies has become the standard.

The duration of therapy for patients with SCLC is four to six cycles of cytotoxic chemotherapy with or without radiation. First-line treatment beyond six cycles has not been shown to be beneficial. This means the duration of therapy in the absences of dose delays would be 3 to 4 months (standard 21-day cycle). Second-line therapy is generally continued until progression or intolerable toxicity.

The duration of therapy for NSCLC depends on which pathway and agents you are treated with. For patients with a PD-L1 positive tumor or those with a targetable genetic mutation the duration is clearest. First-line pembrolizumab is continued for 35 cycles or until toxicity or progression. This duration of therapy is not proven to be the best, but is the result of the study design in the single positive pivotal trial. All of the targeted therapies (oral TKIs) for targetable mutational drivers are continued until progression. Some people believe they provide value after progression, but this belief has not been tested in well-controlled trials.

The population that are PD-L1 negative and have a tumor without a targetable genetic mutation have a variety of practices that can generally be described as continuation maintenance or switch maintenance. As mentioned previously, platinum doublets are the historical standard. These regimens have been improved by adding a monoclonal antibody (bevacizumab, pembrolizumab, necitumumab). In these pivotal trials the monoclonal antibody was continued until progression or toxicity, which is considered continuation maintenance. The pembrolizumab maintenance was only continued for 2 years, although few patients made it that long until progression. When the cisplatin and pemetrexed study was performed, the pemetrexed was continued as monotherapy after completing the doublet therapy. This is also considered continuation maintenance and led to switch maintenance; treating patients with pemetrexed after six cycles of a platinum doublet not including pemetrexed. Key studies regarding maintenance therapy included patients who had a response or stable disease after four cycles of a platinum-based doublet and then randomized them to placebo or treatment. The pemetrexed switch maintenance study reported a 3-month survival advantage with maintenance therapy. A subgroup analysis of this study demonstrated that patients with squamous histology did not benefit from therapy leaving an overall survival benefit of 5 months for the nonsquamous cell group. Similarly, an erlotinib maintenance study reported a 1-month overall survival advantage, which does not appear as robust; however, the subset analysis showed benefit was much more likely in nonsmokers and those with adenocarcinoma histology and particularly in patients who had an activating mutation (exon 19 or 21). Similar to the pemetrexed study, patients whose tumor was of squamous cell histology did not appear to benefit from maintenance. There is some data suggesting a benefit gemcitabine or docetaxel maintenance for squamous histology patients. The NCCN

Patient Encounter Part 4

The patient is treated with pembrolizumab 200 mg IV q3weeks as first-line treatment. Six weeks after starting therapy a repeat CT scan is performed, which shows that the primary 3 cm lesion is now 5 cm in diameter.

Does that mean he has progressed on this treatment?

Discuss how this influences assessments moving forward and propose a treatment and monitoring plan.

guidelines report the level of evidence as 2b, which means there is a low level of evidende, but concensus that the treatment is appropriate.[9] In summary, the duration of therapy depends highly on treatment pathway, histology, and therapy; doublet cyctotoxic chemotherapy rarely exceeds six cycles, while monotherapy is commonly administered until progression except in patients with squamous cell histology.[9]

OUTCOME EVALUATION

LO 8

Evaluating outcomes is a goal-oriented process and should begin from that perspective. Patients with localized disease are treated with localized therapy with or without systemic therapy with curative intent as the goal. Monitoring for toxicity and recurrence on a regular basis is essential.

Following surgery or pharmacologic treatment, the patient should be monitored regularly to detect recurrence or progression of disease. Methods include a physical examination and chest x-ray every 3 to 4 months for 2 years. If no disease is detected during this time, follow-up frequency can be prolonged to every 6 months for 3 years and then annually. Low-dose spiral CT scanning is also recommended annually.[9]

For patients who have advanced stage disease, response of target lesions is performed with a radiologic scan every 6 to 8 weeks. Response Criteria In Solid Tumors (RECIST) is then applied to classify response as follows: complete remission (CR) is complete disappearance of tumor, partial remission (PR) is a reduction target tumor unilateral diameters by 30% or more, progressive disease (PD) is defined as new lesions or a growth of the target lesion diameter by more than 20%, and stable disease (SD) is defined by not meeting the PR or PD criteria. These criteria have been altered for patients on immune therapy because the checkpoint inhibitors have a delayed time to effect, which correlates to the pharmacology. It takes time to activate an exhausted T-cell population, once activated they migrate to and infiltrate the tumor. Combining the increased cell burden and inflammatory-related edema, tumors can appear larger on radiologic evaluation prior to responding. The revised criterion most commonly used is the immune RECIST (iRECIST). The big difference is that the first progression based on RESIST v1.1 criterion is considered an immune Unconfirmed Progressive Disease (iUPD). The confirmatory radiology would then occur 4 to 8 weeks later. Progressive disease is confirmed if target lesions grow. If they do not grow or shrink to any degree it would become the new set point and future scans would again progress through iUPD prior to having confirmed progressive disease.[49]

Smoking cessation counseling with or without pharmacologic treatment should be a priority. Although studies have shown that patients who continue to smoke through treatment in NSCLC do not perform more poorly compared with those that quit before treatment, those who respond to treatment and continue to smoke probably have an increased risk of developing secondary malignancies.[2] In contrast to NSCLC, some data suggest that SCLC patients with limited-stage disease have poorer outcomes if they continue to smoke during treatment.[17]

Patient Care Process

Collect Information:

- Determine stage and histology of cancer.
- Perform PD-L1 expression and mutation analysis if clinically indicated.

Assess the Information:

- Comorbidities and organ and hematological function.
- Starting doses and schedules of planned chemotherapy.
- Need for supportive care therapies.

Develop a Care Plan:

- Ensure the patient has access and insurance coverage for chemotherapy and supportive therapies.
- Educate the patient on expected outcomes, potential adverse effects, and their management.

Implement the Care Plan:

- Evaluate the appropriateness of a patient's regimen at every visit (every week, 3 weeks, or 4 weeks).
- Inquire about toxicity or issues.
- Include a medication reconciliation process.
- Laboratory and/or radiology evaluations can be prompted by the initial assessment or at a scheduled interval for the treatment regimen.
- Findings of tumor growth or significant toxicity should prompt a change in the therapeutic plan.
- Grade and monitor toxicity—Grade 3 or 4 toxicity (see Chapter 88) requires a change in therapy with the next cycle of treatment. Common changes include a chemotherapy dose reduction or pharmacologic intervention to prevent or treat the toxicity.
- Manage toxicity—*Knowing when and how to treat adverse events from therapy is an important aspect of patient care. Unmanaged events may cause delays in therapy administration and reduced therapy doses and may contribute to treatment failure.* This includes managing neutropenic episodes (see Chapter 99) and chemotherapy-induced nausea and vomiting (see Chapter 99). The emetogenic potential of selected chemotherapy regimens is listed in Chapter 99. For patients on immunotherapy, they must be monitored for immune-related adverse events with early recognition and intervention (see Chapter 88).
- Counsel patients on appropriate use and adherence of oral medications.

Follow-up: Monitor and Evaluate:

- Monitor for recurrence. Follow recommendations of the NCCN, as outlined in Outcome Evaluation.
- Smoking cessation plans. For NSCLC patients, all long-term care plans should include options and recommendations for smoking cessation (see Chapter 36).

For those with advanced disease, the goal of treatment is to prolong the duration of life, particularly the number of quality days. Ultimately, most lung cancer patients succumb to their disease. Palliative care involves management of symptoms and improvement of quality of life when curative treatment options are no longer available. Often, problematic metastases can be removed by surgery (depending on location) or can be treated with radiotherapy to reduce tumor size. In selecting options at this point in treatment, it is important to keep the goals of therapy (ie, maximizing the duration and quality of life) in mind. Low-toxicity single-agent chemotherapy, targeted therapy, and best supportive care (including fatigue and pain management) are commonly the mainstays of palliative care.

Abbreviations Introduced in This Chapter

5-FDG	5-Fluorodeoxyglucose
ALK	Anaplastic lymphoma kinase
BRAF	A proto-oncogene kinase that is a sarcoma viral oncogene homolog B
CT	Computed tomography
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
EML4	Echinoderm microtubule-associated protein-like 4
EP	Etoposide–cisplatin
ETS	Environmental tobacco smoke
NSCLC	Non–small cell lung cancer
PCI	Prophylactic cranial irradiation
PD1	Programmed cell death protein 1 receptor
PD-L1	Programmed death ligand 1 (aka B7-H1 and CD274)
PET	Positron-emission tomography
PS	Performance status
ROS1	ROS Proto-Oncogene 1, Receptor Tyrosine Kinase
SCLC	Small cell lung cancer
TNM	Tumor, node, and metastasis staging
VEGF	Vascular endothelial-derived growth factor

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018 Jan;68(1):7–30.
2. Pelosof L, Ahn C, Gao A, et al. Proportion of never-smoker non-small cell lung cancer patients at three diverse institutions. J Natl Cancer Inst. 2017;109(7).
3. Stat bite: Causes of lung cancer in nonsmokers. J Natl Cancer Inst. 2006;98(10):664.
4. Karp DD, Lee SJ, Keller SM, et al. Randomized, double-blind, placebo-controlled, phase III chemoprevention trial of selenium supplementation in patients with resected stage I non-small-cell lung cancer: ECOG 5597. J Clin Oncol: official journal of the American Society of Clinical Oncology. 2013;31(33):4179–4187.
5. Mao JT, Roth MD, Fishbein MC, et al. Lung cancer chemoprevention with celecoxib in former smokers. Cancer Prev Res (Phila). 2011;4(7):984–993.
6. Hoffman RM, Sanchez R. Lung Cancer Screening. Med Clin North Am. 2017;101(4):769–785.
7. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer: current therapies and new targeted treatments. Lancet. 2017;389(10066):299–311.
8. Ernani V, Steuer CE, Jahanzeb M. The end of nihilism: systemic therapy of advanced non-small cell lung cancer. Annu Rev Med. 2017;68:153–168.
9. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(4):504–535.
10. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? Lung Cancer. 2002;37(3):271–276.
11. Overview of the risk factors, pathology, and clinical manifestations of lung cancer. UpToDate. Available from: https://www.uptodate.com/contents/overview-of-the-risk-factors-pathology-and-clinical-manifestations-of-lung-cancer. Accessed September 5, 2017.
12. Fox W, Scadding JG. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. Lancet. 1973;2(7820):63–65.
13. Dimou A, Sherman C, Wrangle J. Imaging in advanced non-small cell lung cancer: a medical oncology perspective. J Thorac Imaging. 2016;31(4):238–242.
14. Tochigi N, Dacic S, Ohori NP. Bronchoscopic and transthoracic cytology and biopsy for pulmonary nonsmall cell carcinomas: performance characteristics by procedure and tumor type. Diagn Cytopathol. 2012;40(8):659–663.
15. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Hyperfractionated radiotherapy for clinical stage II non-small cell lung cancer. Radiother Oncol. 1999;51(2):141–145.
16. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med. 2004;350(4):379–392.
17. Small Cell Lung Cancer v 3.2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf Accessed September 1, 2017.
18. Pepe C, Hasan B, Winton TL, et al. Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. J Clin Oncol. 2007;25(12):1553–1561.
19. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542–2550.
20. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543–3551.
21. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346(2):92–98.
22. Miller AB, Fox W, Tall R. Five-year follow-up of the Medical Research Council comparative trial of surgery and radiotherapy for the primary treatment of small-celled or oat-celled carcinoma of the bronchus. Lancet. 1969;2(7619):501–505.
23. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016;17(11):1497–1508.
24. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–1833.
25. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–1639.
26. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015;373(2):123–135.
27. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255–265.

28. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540–1550.
29. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361(10):947–957.
30. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13(3):239–246.
31. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327–3334.
32. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376(7):629–640.
33. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med. 2017;377(9):829–838.
34. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014;371(23):2167–2177.
35. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. Lancet. 2017;389(10072):917–929.
36. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncology. 2017;35(22):2490–2498.
37. Shaw AT, Kim TM, Crino L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017;18(7):874–886.
38. Shaw AT, Solomon BJ. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med. 2015;372(7):683–684.
39. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol. 2016;17(7):984–993.
40. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med. 1999;341(7):476–484.
41. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007;357(7):664–672.
42. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med. 2004;350(4):351–360.
43. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med. 2005;352(25):2589–2597.
44. Group NM-aC. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet. 2014;383(9928):1561–1571.
45. Belani CP. Adjuvant and neoadjuvant therapy in non-small cell lung cancer. Semin Oncol. 2005;32(2 Suppl 2):S9–S15.
46. De Marinis F, Gebbia V, De Petris L. Neoadjuvant chemotherapy for stage IIIA-N2 non-small cell lung cancer. Ann Oncol. 2005;16 Suppl 4:iv116–122.
47. Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. New Engl J Med. 2017;376(25):2415–2426.
48. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. N Engl J Med. 2018;378:113–125.
49. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143–e152.

91 Colorectal Cancer

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LEARNING OBJECTIVES

LO

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

1. Identify the risk factors for colorectal cancer.
2. Outline preventive and screening strategies for individuals at average and high risk for colorectal cancer.
3. Recognize the signs and symptoms of colorectal cancer.
4. Describe the treatment options for colorectal cancer based on patient-specific factors, such as stage of disease, age of patient, genetic mutations, and previous treatment received.
5. Outline the pharmacologic principles for agents used to treat colorectal cancer.
6. Develop a monitoring plan to assess the efficacy and toxicity of agents used in colorectal cancer.
7. Educate patients about the adverse effects of chemotherapy that require specific patient counseling.

INTRODUCTION

Colorectal cancer is one of the four most common cancers diagnosed in the United States and includes cancers of the colon and rectum. In 2018, an estimated 140,250 new cases of colorectal cancer are expected to be diagnosed, with an estimated 50,680 deaths expected, making colorectal cancer the second leading cause of cancer-related deaths in the United States.[1] The prognosis is primarily determined by the stage of disease with the majority of patients with early stage (I or II) disease cured. Treatment options for colorectal cancer include surgery, radiation, chemotherapy, and targeted molecular therapies.

EPIDEMIOLOGY AND ETIOLOGY

Colorectal cancer occurs more frequently in industrialized regions such as North America and Europe, while the lowest rates are seen in less-developed areas, suggesting that environmental and dietary factors influence the development of colorectal cancer. In addition to environmental factors, colorectal cancers develop more frequently in certain families, and genetic predisposition to this cancer is well known.

The incidence of colorectal cancer in men is approximately 1.3 times greater than observed in women. Overall, colon and rectal cancers make up approximately 12% of all cancer diagnoses in men and women in the United States. The median age at diagnosis is 67 years with very few cases occurring in individuals younger than 45 years of age.[2] KEY CONCEPT Age appears to be the biggest risk factor for the development of colorectal cancer with 57% of cases diagnosed in adults older than 65 years of age.

Although still the second leading cause of cancer death, mortality rates for colorectal cancer have declined over the past 30 years as a result of better and increasingly used screening modalities and more effective treatments.

RISK FACTORS

LO 1

In addition to age, dietary or environmental factors, inflammatory bowel disease, and genetic susceptibility increase the risk of colorectal cancer. Table 91–1 lists well-known risk factors for developing colorectal cancer.

KEY CONCEPT Diets high in fat and low in fiber are associated with increased colorectal cancer risk. While data is not entirely consistent, long-term consumption of red and processed meats is associated with an increased risk of colorectal cancer. A large pooled analysis of 13 prospective cohort studies found dietary fiber intake to be inversely associated with the risk of colorectal cancer; however, upon multivariate analysis for other dietary risk factors, the benefit was no longer observed.[3] This analysis does not consider the known benefits of a fiber-rich diet for noncancerous conditions such as diabetes and coronary artery disease.

Foods that are high in fiber include vegetables, fruit, and grains. The protective effects of fiber may be a result of reduced absorption of carcinogens in the bowel, reduced bowel transit time, or a reduction in dietary fat intake associated with high-fiber diets.[3]

Physical inactivity and elevated body mass index (BMI) are associated with up to a twofold increase in the risk of colorectal cancer. Decreased bowel transit time and exercise-induced alterations in body glucose, insulin levels, and other hormones may reduce tumor cell growth.[4,5] Type 2 diabetes mellitus, independent of body mass size and physical activity level, is also associated with an increased risk of colorectal cancer in women and supports a role for hyperinsulinemia as a possible link between obesity, sedentary lifestyle, diabetes mellitus, and colorectal cancer.[5] Additional lifestyle choices that increase the risk of colorectal cancer include alcohol consumption and smoking which may increase the risk of colorectal cancer by generating carcinogens with direct toxic effects on bowel tissue.[4]

Table 91–1

Risk Factors for Colorectal Cancer

General	
	Age is the primary risk factor
Dietary	
	High-fat, low-fiber diets
Lifestyle	
	Alcohol
	Smoking
	Obesity or physical inactivity
Comorbid Conditions	
	Inflammatory bowel disease (ulcerative colitis and Crohn disease)
Hereditary or Genetic	
	FAP and HNPCC
	Family history

FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer.

Inflammatory bowel diseases, such as chronic ulcerative colitis, particularly when it involves the entire large intestine, and to lesser extent Crohn disease, confer increased risk for colorectal cancer. Overall, individuals with inflammatory bowel disease account for about 1% to 2% of all new cases of colorectal cancer each year.

Finally, as many as 10% of cases are thought to be hereditary. The two most common forms of hereditary colorectal cancer are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). FAP is a rare autosomal dominant trait that is caused by mutations of the **adenomatous polyposis coli (*APC*)** gene and accounts for 1% of all colorectal cancers. The disease is manifested by hundreds to thousands of **polyps** arising during adolescence.[6] The risk of developing colorectal cancer for individuals with untreated FAP is virtually 100%, and patients require early screening for the disease and likely prophylactic total colectomy. HNPCC, also an autosomal dominant syndrome, accounts for up to 5% of colorectal cancer cases.[6] In contrast to FAP, juvenile polyps occur rarely, and the average age of colorectal cancer in these patients is closer to that of average risk patients, with most patients diagnosed in their 40s. Testing for HNPCC mutations is available but reserved for individuals who meet strict diagnostic criteria.

Up to 25% of patients who develop colorectal cancer have a family history of colorectal cancer unrelated to a mutation described earlier.[7] First-degree relatives of patients diagnosed with colorectal cancer have an increased risk of the disease that is at least two to four times that of persons in the general population without a family history.

Summary of Risk Factors

In summary, the true association between most dietary factors and the risk of colorectal cancer is unclear. The protective effects of fiber and a diet low in fat are not completely known at this time. Physical inactivity, alcohol use, and smoking appear to increase the risk of colorectal cancer. Clinical risk factors and genetic mutations are well-known risks for colorectal cancer.

SCREENING

LO 2

KEY CONCEPT Effective colorectal cancer screening programs incorporate annual fecal occult blood testing or regular examination of the entire colon starting at age 50 years for average-risk individuals and should be recommended by all health care providers. Appropriate screening of patients at normal and high risk for colorectal cancer leads to the detection of smaller, localized lesions and higher cure rates.[8] Screening techniques include fecal occult blood tests (FOBTs) and imaging of the colon. The use of FOBTs annually in combination with digital rectal examinations has led to diagnosis of early stages of disease and may reduce colorectal cancer mortality by up to one-third.[8] However, FOBT using a single stool sample collected during a digital rectal examination is not a recommended option for screening because this method has a decreased sensitivity for detecting advanced disease.[7] Recommendations for adequate FOBT require the patient to collect two stool samples from three consecutive specimens using at-home testing procedures.[8] Two main methods are available to detect occult blood in the feces: guaiac dye and immunochemical methods. The Hemoccult II is the most commonly used FOBT in the United States and is a guaiac-based test. Proper counseling by health care providers is required to receive accurate test results. Consumption of red meat, blood sausages, peroxidase-containing vegetables, iron products, or nonsteroidal anti-inflammatory drugs (NSAIDs) may result in false-positive results. Vitamin C and dehydrated samples may lead to false-negative results. These products should be avoided for 3 days prior to testing. Fecal immunochemical tests (FITs) (InSure and others), which use antibodies to detect hemoglobin, are also available for use. Though more expensive, an advantage of FITs is that they do not react with dietary factors or medications. Both FOBTs can be recommended in screening protocols for patients.

Imaging of the colon with a sigmoidoscopy, colonoscopy, or CT colonography is recommended every 5 to 10 years for most individuals. Colonoscopy is the preferred procedure as it allows for greater visualization of the entire colon and simultaneous removal of lesions found during screening.[8] A sigmoidoscopy only examines the lower half of the colon, and a double-contrast barium enema requires a supplemental colonoscopy to remove any lesions found during the screening process. Several revisions to the colorectal cancer screening guidelines have been made in an attempt to increase the compliance to screening guidelines. These include the use of computed tomographic colonography (CTC) and stool

Patient Encounter Part 1

A 68-year-old man presents to your clinic with a chief complaint of fatigue, abdominal discomfort, and occasional diarrhea and blood in his stool for 3 months. He has a medical history positive for chronic back pain, hyperlipidemia, hypertension, and obesity. He states that he consumes a moderate amount of alcohol (three to four beers most days of the week after work), is a previous smoker (quit over 20 years ago), and has tried to eat healthy the last month because his wife cooks and is concerned for his weight. Previously his diet mostly consisted of red meat and fried foods. Additionally he is unable to work or exercise due to back injury.

What risk factors does this patient have for colon cancer?

Does he have clinical symptoms suggestive of colon cancer?

What additional tests need to be ordered to diagnosis colon cancer?

Table 91–2

Colon Cancer Screening Guidelines

Average risk	Annual FOBT or FIT after age 50 years Stool DNA testing may be used as an alternative *or* One of the following after age 50 years: Sigmoidoscopy every 5 years Colonoscopy every 10 years CTC every 5 years
Family history	Screening at ages 40 years or 10 years before the youngest case in the immediate family, whichever is earlier
HNPCC	Screening at age 20–25 years or 10 years before the youngest case in the immediate family, whichever is earlier
FAP	Screening at ages 10–12 years
IBD	8 years after the onset of pancolitis; 12–15 years after onset of left-sided colitis

CTC, computed tomographic colonography; FAP, familial adenomatous polyposis; FIT, fecal immunochemical tests; FOBT, fecal occult blood tests; HNPCC, hereditary nonpolyposis colorectal cancer; IBD, inflammatory bowel disease.

DNA testing as acceptable screening methods. CTC, also known as "virtual colonoscopy," uses integrated two- and three-dimensional images to detect and characterize polyps. Although noninvasive compared with colonoscopy, adequate bowel preparation, which is often cited as the reason for noncompliance, is still required. In addition, any lesions found on examination require a follow-up colonoscopy.

Stool DNA testing detects molecular markers associated with advanced colorectal cancer. Because this test is not dependent on the detection of bleeding, which can be sporadic, it requires only a single stool collection. How often and what molecular markers to test for are undergoing further evaluation. KEY CONCEPT Table 91–2 is a summary of the current NCCN guidelines for screening and surveillance for early detection of colorectal polyps and cancer.[8]

COLORECTAL CANCER PREVENTION

There are currently no pharmacologic agents approved for colorectal cancer prevention. Strategies under investigation to prevent colorectal cancer include pharmacologic and surgical interventions and involve either preventing the initial development of colorectal cancer (primary prevention) or preventing cancer in patients who demonstrate early signs of colorectal cancer (secondary prevention).

The most widely studied agents for the chemoprevention of colorectal cancer are agents that inhibit cyclooxygenase-2 (COX-2) (aspirin, NSAIDs, and selective COX-2 inhibitors) and calcium supplementation.[9] Individual studies have demonstrated that regular (at least two doses per week) NSAID and aspirin use is associated with a 20% to 40% reduction in risk of colorectal cancer in individuals at average risk.[10,11] However, a meta-analysis of over 40 trials suggests the benefit of these agents may be limited to individuals at high risk for developing colorectal cancer.[12] Chronic use of aspirin and other NSAIDs are associated with significant potential adverse effects, including gastrointestinal (GI) and cardiovascular toxicities. These risks limit health care professionals from routine recommendations for use in patients of average risk for colorectal cancer.

The risk of colorectal cancer appears to be inversely related to calcium and folate intake. Calcium supplementation appears to be associated with a moderate reduction in risk of recurrent colorectal adenomas with prospective studies demonstrating a nonstatistical decrease in adenoma recurrence, its role as a chemoprevention agent in the average-risk patient remains under investigation.[9,12]

Additional agents, including selenium and folic acid, show promise as chemopreventive agents in colorectal cancer and preliminary, and confirmatory studies evaluating their effectiveness have been completed or are ongoing.[9] Exogenous hormone use, particularly postmenopausal hormone replacement therapy, is associated with a significant reduction in colorectal cancer risk in most studies with the greatest benefit in women who are on current hormone replacement therapy.[13] Unfortunately, the known risks of hormone replacement therapy outweigh this benefit, and routine use of hormone replacement therapy to prevent colorectal cancer is not recommended.

Surgical resection remains an option to prevent colorectal cancer in individuals at extremely high risk for its development such as patients diagnosed with FAP. Individuals with FAP who are found to have polyps on screening examinations require total abdominal colectomy. In addition, removal of noncancerous polyps detected during screening colonoscopy is considered the standard of care to prevent the progression of premalignant polyps to cancer.

PATHOPHYSIOLOGY

Anatomy and Bowel Function

The large intestine consists of the cecum; ascending, transverse, descending, and sigmoid colon; and rectum (Figure 91–1).

Four major tissue layers, from the lumen outward, form the large intestine: the mucosa, submucosa, muscularis externa, and serosa. Complete replacement of surface epithelial cells occurs every 7 to 10 days with the total number of epithelial cells remaining constant in normal colonic tissue. As patients age, abnormal cells accumulate on the surface epithelium and protrude into the stream

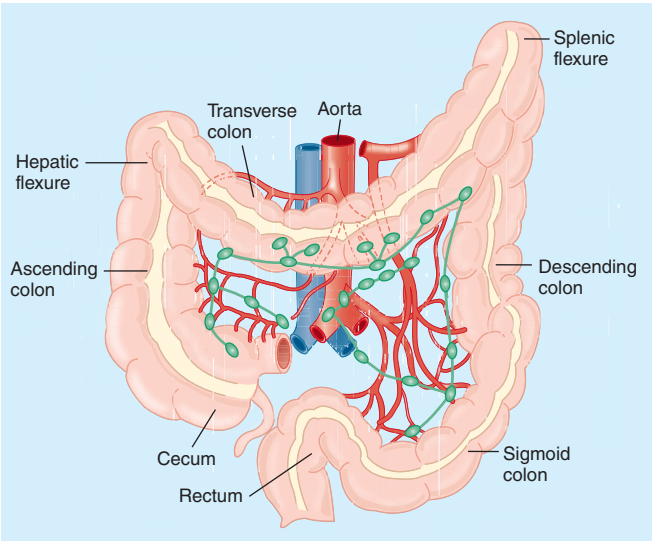

FIGURE 91–1. Colon and rectum anatomy. (From Davis LE, Sun W, Medina PJ. Colorectal Cancer. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York: McGraw-Hill, 2014; Figure 107–2.)

of fecal matter; their contact with fecal mutagens can lead to further cell mutations and eventual adenoma formation.[6]

Colorectal Tumorigenesis

The development of a colorectal neoplasm is a multistep process of several genetic and phenotypic alterations of normal bowel epithelium leading to unregulated cell growth, proliferation, and tumor development. A genetic model has been proposed for colorectal tumorigenesis that describes a process of transformation from adenoma to carcinoma. This model of tumor development reflects an accumulation of mutations within colonic epithelium that gives a selective growth advantage to the cancer cells.[6] Genetic changes include activating mutations of **oncogenes**, mutations of **tumor suppressor genes**, and defects in **DNA mismatch repair genes**.

Additional genes and protein receptors are believed important in colorectal tumorigenesis. COX-2, which is induced in colorectal cancer cells, influences apoptosis and other cellular functions in colon cells, and overexpression of the EGFR, a transmembrane glycoprotein involved in signaling pathways that affect cell growth, differentiation, proliferation, and angiogenesis, occurs in the majority of colon cancers.[14] These mechanisms are potentially important because of the availability of pharmacologic agents targeted to inhibit these processes.

CLINICAL PRESENTATION AND DIAGNOSIS

LO 3

The signs and symptoms associated with colorectal cancer can be extremely varied, subtle, and nonspecific. Most patients are asymptomatic but may develop changes in bowel or eating habits, fatigue, abdominal pain, and blood in the stool.

LO 3

Clinical Presentation and Diagnosis of Colorectal Cancer

General

Patients are often asymptomatic in early stages of disease

Symptoms

Changes in bowel habits, abdominal pain, anorexia, nausea and vomiting, weakness (if anemia is severe), and tenesmus

Signs

Blood in stool and weight loss

Laboratory Tests

- Patients may have a low-hemoglobin level from blood loss
- Positive FOBT
- Liver function tests (INR, activated partial thromboplastin time, and bilirubin) may be abnormal if disease has metastasized to the liver
- CEA level may be high; normal level is less than 2.5 ng/mL (2.5 mcg/L) in nonsmokers and less than 5 ng/mL (5 mcg/L) in smokers

Imaging Tests

Chest x-ray, CT scan, or PET scan results may be positive if cancer has spread to the lungs, liver, or peritoneal cavity

TREATMENT

Desired Outcomes

Patients are staged with the tumor, node, metastasis (TNM) classification system (see Chapter 88) to determine treatment options and assess prognosis. **Figure 91–2** depicts how the three categories are used in combination to determine the stage of disease. KEY CONCEPT The stage of colorectal cancer upon diagnosis is the most important prognostic factor for survival and disease recurrence. Stages I, II, and III disease are considered potentially curable and are aggressively treated in an attempt to cure these patients. Patients who develop stage IV disease are treated to reduce symptoms, avoid disease-related complications, and prolong survival.

General Approach to Treatment

LO 4

The treatment approaches for colorectal cancer reflect two primary treatment goals: curative therapy for localized disease (stages I–III) and palliative therapy for metastatic cancer (stage IV). Surgical resection of the primary tumor is the most important part of therapy for patients in whom cure is possible.[16] Depending on the stage of disease and whether the tumor originated in the colon or rectum, further **adjuvant** chemotherapy or chemotherapy plus radiation may be needed after surgery to cure these patients. In the metastatic setting, pharmacologic intervention is the main treatment option.

Pharmacogenetic and pharmacogenomic testing has become an integral component to designing the optimal pharmacologic intervention for patients with colorectal cancer. The choice of treatment agents is largely dictated by individualized patient and tumor-specific factors. For example, data have demonstrated specific tumor characteristics that may assist clinicians in predicting who will respond to EGFR inhibitors. Early immunohistochemical staining for EGFR status is not useful in predicting response because both EGFR-positive and EGFR-negative patients respond at the same rate. However, *RAS* gene mutation status has demonstrated predictive value. Patients should be tested for both *KRAS* and *NRAS*; patients with mutated *RAS* are unlikely to benefit from cetuximab or panitumumab therapy.[15] In particular, testing for *RAS* mutational status is now part of the disease workup to define patients who may derive benefit from cetuximab or panitumumab. Characteristics of the tumor are also vital in making treatment decisions for patients with stages II and III disease. The degree of **microsatellite instability (MSI)** within a tumor tells clinicians information about both prognosis and treatment options. More detail on specific pharmacogenetic and pharmacogenomic information is provided in the pertinent pharmacologic therapy sections.

Nonpharmacologic Therapy

▶ *Operable Disease (Stages I–III)*

Surgery Individuals with stages I to III colorectal cancer should undergo a complete surgical resection of the tumor mass with removal of regional lymph nodes as a curative approach for their disease.[16] Surgery for rectal cancer depends on the region of tumor involvement with attempts to retain rectal function as a goal of the surgical procedure. Overall, surgery for colorectal cancer is associated with low morbidity and mortality rates. Common complications include infection, anastomotic leakage, obstruction, adhesion formation, and malabsorption syndromes.

Radiation Therapy There is currently no role for adjuvant radiation in colon cancer. However, patients who receive surgery

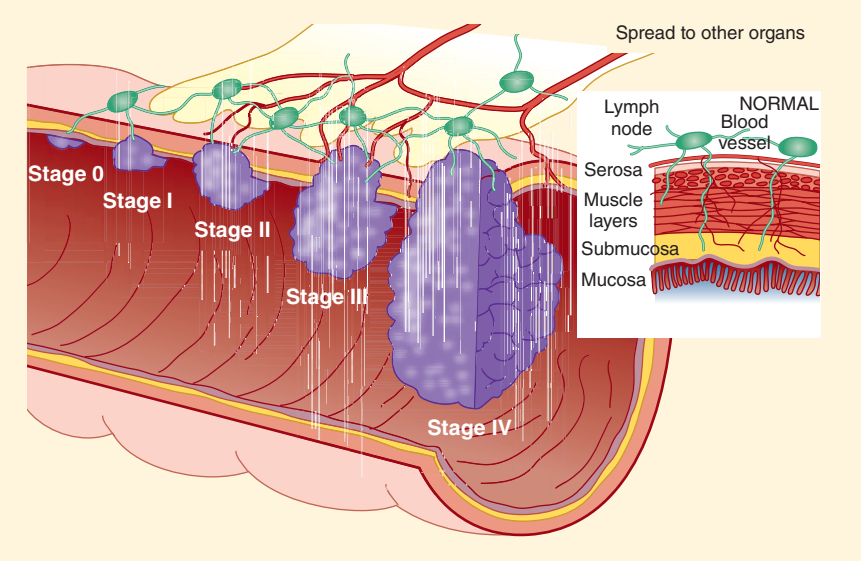

FIGURE 91–2. Stage I: cancer is confined to the lining of the colon. Stage II: cancer may penetrate the wall of the colon into the abdominal cavity but does not invade any local lymph nodes. Stage III: cancer invades one or more lymph nodes but has not spread to distant organs. Stage IV: cancer has spread to distant locations in the body, which may include the liver, lungs, or other sites. (From National Cancer Institute, Washington, DC.)

for rectal cancer receive radiation therapy to reduce local tumor recurrence. Adjuvant radiation plus chemotherapy is considered standard treatment for patients with stage II or III rectal cancer after the surgical procedure is complete.[17] Preoperative radiation may be used to reduce the initial size of rectal cancers to make the surgical procedure less extensive.

▶ *Metastatic Disease (Stage IV)*

Surgery Unlike stages I to III disease, the benefit of surgical resection in most patients with metastatic disease is limited to symptomatic improvement. Selected patients who have one to three small nodules isolated to the liver, lungs, or abdomen may have a prolongation of survival, although cure is rare. Five-year survival for patients who undergo surgical resection of metastases isolated to the liver is approximately double that of patients who are not surgical candidates with approximately 33% of patients alive at 5 years.[18] Alternatives to surgery include destroying the tumor through freezing and thawing (cryoablation), heat (radiofrequency), or alcohol injection, although these appear to be less successful than surgical resection.[16,18] Because the majority of these patients will relapse, many practitioners offer adjuvant chemotherapy to select patients following potentially curative resection, but further studies are needed to determine an optimal treatment regimen.[18]

Radiation Symptom reduction is the primary goal of radiation for patients with advanced or metastatic colorectal cancer.

Pharmacologic Therapy

Table 91–3 lists common chemotherapy regimens used in colorectal cancer and the abbreviations used in the literature to describe them.

▶ *Operable Disease (Stages I–III)*

KEY CONCEPT Adjuvant chemotherapy is administered after tumor resection to decrease relapse rates and improve survival in patients with colon cancer by eliminating micrometastatic disease that is undetected on imaging studies. Patients diagnosed with stage I colon or rectal cancer are usually cured by surgical resection,

Patient Encounter Part 2

PMH: Chronic back pain since 50 years, hyperlipidemia since 35 years, hypertension since age 36 years; obesity; the patient is 40% over his ideal body weight.

FH: Father died at age 78 years after a myocardial infarction; mother is living; older brother with testicular cancer; maternal uncle died at age 53 years from rectal cancer.

SH: Does not work. Previously an electrician. Married with two grown children.

Meds: Lisinopril/HCTZ 25 mg daily; amlodipine 10 mg daily; pravastatin 40 mg daily, tramadol 100 mg daily.

ROS: (+) Abdominal cramping, diarrhea, blood in stool, and fatigue.

PE:

VS: 138/84 mm Hg, P 80 beats/min, RR 18 breaths/min, T 37.1°C (98.8°F), Ht 187 cm (74 in), Wt 115 kg (253 lb).

Abd: Distended and tender to touch, (+) bowel sounds.

Labs: Positive hemoglobin 11.8 g/dL (118 g/L or 7.32 mmol/L) decreased from 13.4 g/dL (134 g/L or 8.32 mmol/L) last year. Positive lipid panel: triglycerides 250 mg/dL (13.9 mmol/L).

Imaging and Diagnostic Studies

- Colonoscopy revealed multiple polyps in his transverse colon.
- Biopsy revealed three polyps positive for adenocarcinoma of the colon.
- Staging CT scan negative for disease outside of the colon.
- Four lymph nodes positive for disease.

Because the patient has stage III colon cancer, how does this affect the goal of your treatment plan compared with stage IV disease?

What nonpharmacologic and pharmacologic options are available to this patient?

Table 91–3

Dosing Schedules of Chemotherapy Regimens for Colon Cancer[a]

Regimen	Dosing
5-FU + leucovorin (continuous infusion)	Leucovorin 200 mg/m^2 IV 5-FU 400 mg/m^2 IV bolus and then 600 mg/m^2 of 5-FU as a 22-hour continuous infusion on days 1 and 2; repeat every 2 weeks
FOLFIRI	Irinotecan 180 mg/m^2 IV day 1 Folinic acid (leucovorin) 400 mg/m^2 IV day 1 5-FU 400–500 mg/m^2 IV bolus after folinic acid; then 2400–3000 mg/m^2 of 5-FU IV over 46 hours Repeat every 14 days
FOLFOX4	Oxaliplatin 85 mg/m^2 IV + leucovorin 200 mg/m^2 IV followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV over 22 hours day 1 Leucovorin 200 mg/m^2 IV, followed by 5-FU 400 mg/m^2 IV bolus and then 5-FU 600 mg/m^2 IV over 22 hours day 2 Repeat every 2 weeks
mFOLFOX6	Oxaliplatin 85 mg/m^2 IV day 1 Leucovorin 400 mg/m^2 IV over 2 hours, followed by 5-FU 400 mg/m^2 IV bolus day 1 followed by 2400 mg/m^2 IV over 48 hours Repeat every 2 weeks
FOLFOXIRI	Irinotecan 165 mg/m^2 IV day 1 Oxaliplatin 85 mg/m^2 IV day 1 Leucovorin 200 mg/m^2 IV over 2 hours, followed by 5-FU 3200 mg/m^2 IV over 48 hours Repeat every 2 weeks
Bevacizumab + 5-FU regimen	Bevacizumab 5 mg/kg IV every 2 weeks + a 5-FU–containing regimen (FOLFOX, FOLFIRI, or 5-FU + leucovorin) Bevacizumab 7.5 mg/kg IV every 3 weeks with CapeOX
Cetuximab ± irinotecan	Cetuximab 400 mg/m^2 IV first infusion, then 250 mg/m^2 weekly ± irinotecan 125 mg/m^2 IV every week for 4 weeks Repeat irinotecan every 6 weeks (after a 2-week break)
Panitumumab	6 mg/kg IV every 2 weeks
Capecitabine	1250 mg/m^2 twice a day orally for 14 days Repeat every 3 weeks
CapeOX	Capecitabine 1000 mg/m^2 twice a day orally for 14 days Oxaliplatin 130 mg/m^2 IV on day 1 Repeat every 3 weeks

[a]Note that many variations exist, and current literature should be checked before administering any chemotherapy regimen.

5-FU, 5-fluorouracil; CapeOX, capecitabine–oxaliplatin; IV, intravenous.

and adjuvant chemotherapy is not indicated in these patients.[16] The role of adjuvant chemotherapy for stage II colon cancer is controversial but may benefit certain high-risk groups. Adjuvant chemotherapy is standard therapy for patients with stage III colon cancer. Table 91–4 lists adjuvant treatment regimens based on stage and performance status (PS). Adjuvant chemotherapy for patients with stage II disease has not been shown to be superior to surgery alone with the possible exception of high-risk patients, including those with inadequate nodes sampled for staging, bowel perforation upon diagnosis, T4 lesions, and those with unfavorable histology.[15] The risks and benefits of adjuvant chemotherapy should be discussed with medically fit patients who have stage II disease with high-risk features. However, the American Society of Clinical Oncology does not recommend the routine use of adjuvant chemotherapy in the general patient population unless part of a clinical trial.[19]

There is currently insufficient data to recommend the use of tumor gene profiling to determine need for adjuvant therapy in stage II disease, but it is an area of active research.[15] An additional consideration for deciding on adjuvant therapy is the status of MSI within the tumor. MSI results from defective DNA mismatch repair (dMMR) genes leading to damaged DNA. Patients with tumors that display high levels of MSI may have better prognosis than patients with microsatellite-stable (MSS) tumors. Despite being associated with a better prognosis, tumors that display high levels of MSI (MSI-H) do not respond as well to certain chemotherapy, including 5-fluorouracil (5-FU).[20] It is recommended that stage II patients should be tested for the status of MSI if 5-FU is being considered for therapy, and an

Table 91–4

Treatment Regimens for Adjuvant Colon Cancer

Stage II[a]	Stage III
High Risk • Capecitabine or 5-FU plus leucovorin • FOLFOX • CapeOx • FLOX	**Good Performance Status** • FOLFOX • CapeOX • FLOX • Capecitabine or 5-FU plus leucovorin
Low Risk[b] • Observation or clinical trial • Capecitabine or 5-FU plus leucovorin	**Poor Performance Status** • Capecitabine

[a]Individualized assessment of patient risk is necessary to determine if treatment is required. Clinical trials or observation may be an appropriate option.

[b]T3 lesions may be considered high risk by some clinicians.

5-FU, 5-fluorouracil.

alternative therapy should be considered if high levels of MSI are displayed.[15] In general, patients with stage II colon cancer should be enrolled into clinical trials to assess the impact of new agents and prognostic models.

Adjuvant chemotherapy is standard therapy for patients with stage III colon cancer. The presence of lymph node involvement in the resected specimen places patients with stage III colon cancer at high risk for relapse; the risk of death within 5 years of surgical resection alone is as high as 70%.[16] In this population of patients, adjuvant chemotherapy significantly decreases the risk of cancer recurrence and death and is considered the standard of care.

KEY CONCEPT 5-FU, leucovorin, and oxaliplatin (FOLFOX)–based chemotherapy is the standard regimen used in adjuvant colon cancer. It is usually given for 6 months. Refer to Tables 91–3 and 91–4 for recommended treatment regimens and schedules. 5-FU alone results in a small improvement in survival that can vary based on the method of 5-FU administration and the status of MSI.[20]

The combination of 5-FU plus leucovorin has undergone extensive study in the adjuvant setting with decreased rates of recurrence and improved survival seen in patients receiving 5-FU plus leucovorin compared with surgery alone. Though various schedules of 5-FU and leucovorin can be administered, continuous infusions may be less toxic and have improved response rates (although no survival advantage) compared with bolus regimens. Capecitabine is an oral prodrug of 5-FU that is also effective in the adjuvant setting and is being used as a replacement in certain regimens for 5-FU. Data suggest that capecitabine is at least equivalent to bolus 5-FU and leucovorin in efficacy and is better tolerated by patients in the adjuvant setting.[21] An increase in hand–foot syndrome and decreased mucositis and neutropenia are seen with capecitabine compared with bolus 5-FU.

More often, 5-FU or capecitabine is administered as part of a combination regimen with oxaliplatin and leucovorin (FOLFOX or CapeOx). FOLFOX is considered standard of care for patients with stage III disease unless their PS is so poor that clinicians do not believe the patients could tolerate intensive combination therapy. Every effort should be made to minimize adverse treatment effects and use this regimen in patients with stage III colon cancer because this is the only regimen demonstrated to improve overall survival in these patients.[16,22] Several variations on the original FOLFOX regimen have been studied with mFOLFOX6 being the most routinely used in clinical practice (refer to Table 91–4). CapeOx resulted in improved disease-free survival (DFS) compared with bolus 5-FU–leucovorin, but no overall survival benefit in stage III patients and is considered an acceptable adjuvant regimen in this patient population.[15,23]

Targeted therapies, including cetuximab and bevacizumab, have been evaluated for their role in their adjuvant treatment of colon cancer. At this time, no targeted agents are approved for use as adjuvant therapy in stage II or III colorectal cancer patients. Additionally, irinotecan should not be used in the adjuvant setting because its addition to 5-FU–based regimens has increased toxicity without therapeutic benefit.[15]

▶ *Metastatic Disease (Stage IV)*

Traditional chemotherapy and targeted biological therapies are the mainstay of treatment for metastatic colon or rectal cancer and have improved the median survival time of these patients to more than 2 years.[16] Most often, a combination of chemotherapy agents with biological therapies is administered to these patients. Currently, metastatic colorectal cancer is incurable, and treatment goals are to reduce patients' symptoms, improve quality of life, and extend survival. Combination chemotherapy regimens have been demonstrated to result in prolongation of survival with tolerable adverse effects. Similar to the adjuvant setting, 5-FU plus leucovorin continues to be in most first-line chemotherapy regimens used for metastatic colorectal cancer. A variety of continuous intravenous (IV) infusion 5-FU and bolus regimens can be used; however, compared with IV bolus 5-FU, response rates with continuous infusion 5-FU are approximately doubled. In a large meta-analysis of patients with advanced colorectal cancer, continuous infusions of 5-FU had a significantly higher tumor response rate, a small increase in survival, and lower incidence of myelosuppression, diarrhea, and mucositis when compared with bolus regimens.[24]

Additional agents including irinotecan and oxaliplatin have been added to the 5-FU and leucovorin regimen with superior response and survival rates compared to the two drugs used alone.[25,26] A large European study compared a combined bolus and infusional 5-FU regimen plus irinotecan (FOLFIRI) with the FOLFOX regimen (using a slightly different schedule) with crossover to the opposite arm upon relapse.[27] No difference in patient survival was seen with either regimen, and toxicity was as expected. Neuropathy and neutropenia were more common with FOLFOX, while diarrhea, nausea, vomiting, dehydration, and febrile neutropenia were more common with FOLFIRI. Based on improved survival data with the FOLFOX and FOLFIRI regimens, irinotecan-based regimens should only be administered outlined as described in Table 91–3.

Capecitabine also has activity in the metastatic setting. When combined with oxaliplatin in regimens known as CapeOx or XELOX, capecitabine appears to be as safe as 5-FU–based regimens.[15] Additionally, **progression-free survival** (PFS) with CapeOX is similar to that of FOLFOX and is considered noninferior to the FOLFOX regimen as first-line therapy in advanced disease.[28] This noninferiority with capecitabine may be specific to its use with oxaliplatin because capecitabine in combination with irinotecan (CAPIRI) demonstrated decreased PFS compared with FOLFIRI and the routine substitution of 5-FU with capecitabine in irinotecan-based regimens is not recommended.[15,29]

5-FU plus leucovorin, or capecitabine alone, are appropriate first-line treatment options for individuals for whom three-drug combination regimens are believed to be toxic. The site(s) of tumor involvement, history of prior chemotherapy, and patient-specific factors help define the appropriate management strategy. KEY CONCEPT The most important factor in patient survival is not the initial regimen but whether or not patients receive all three active chemotherapy drugs (5-FU, irinotecan, and oxaliplatin) at some point in their treatment course.[30] Some clinicians choose to use all three agents in combination in the first-line setting in a regimen termed FOLFOXIRI, although only in patients who are able to tolerate intensive therapy.

Targeted or biologic agents are approved for use in metastatic colorectal cancer. Bevacizumab in combination with IV 5-FU–based chemotherapy (either FOLFOX or FOLFIRI) is approved by the FDA for initial treatment of patients with metastatic colorectal cancer. Results from randomized trials show increased benefit compared with chemotherapy alone.[15] The efficacy of bevacizumab in this patient population shows the relevance of **angiogenesis** as an important target for the treatment of metastatic colorectal cancer. The addition of bevacizumab to first-line oxaliplatin-based chemotherapy has also been demonstrated to improve PFS but did not positively impact response rates

or overall survival.[31] Similar results were demonstrated with bevacizumab in combination with capecitabine and oxaliplatin.[42]

Based on these results, bevacizumab is recommended as part of 5-FU–based chemotherapy regimens used for the first-line treatment of metastatic colorectal cancer unless contraindicated. Bevacizumab is contraindicated in patients with GI perforation or fistulas involving a major organ, recent (within 28 days) major surgeries or open wounds, wound dehiscence requiring medical intervention, hypertensive crisis or uncontrolled severe hypertension, hypertensive encephalopathy—serious bleeding, a severe arterial thromboembolic event, moderate or severe proteinuria (urine protein excretion 2 g/24 hours or more), nephrotic syndrome, and reversible posterior leukoencephalopathy syndrome.

Monoclonal antibody EGFR inhibitors, cetuximab and panitumumab, demonstrate improved PFS as first-line therapy in the metastatic setting when individually combined with either the FOLFOX or FOLFIRI regimens in *KRAS* wild-type individuals.[32-35] KEY CONCEPT Before using these agents, testing for KRAS mutation status should occur. Extensive literature exists demonstrating poor response rates of EGFR inhibitors in patients whose tumors have a mutation in codon 12 or codon 13 of the *KRAS* gene.[15,36] Consequently, cetuximab or panitumumab may be used in the first-line setting in combination with traditional chemotherapy agents in *KRAS* WT patients only.[15]

Attempts to combine the vascular endothelial growth factor (VEGF) inhibitor bevacizumab with cetuximab and panitumumab as part of traditional chemotherapy regimens have resulted in inferior outcomes to regimens with bevacizumab alone.[37] Based on these results, the use of bevacizumab with either EGFR inhibitor is not recommended.[15]

KEY CONCEPT In summary, most practitioners select first-line treatment for metastatic colorectal cancer from among these treatments: oxaliplatin plus 5-FU plus leucovorin (FOLFOX); irinotecan plus 5-FU plus leucovorin (FOLFIRI); capecitabine plus oxaliplatin (CapeOx or XELOX); oxaliplatin plus irinotecan plus 5-FU plus leucovorin (FOLFOXIRI); bevacizumab plus 5-FU– or capecitabine-based chemotherapy (FOLFIRI or FOLFOX or CapeOx or FOLFOXIRI); or cetuximab or panitumumab plus 5-FU–based chemotherapy (FOLFOX or FOLFIRI) in *KRAS* WT patients.[15]

▶ *Second-Line Therapy*

KEY CONCEPT Treatment of relapsed or refractory metastatic disease uses agents not given in the first-line setting. Patients who receive all effective chemotherapy options have improved outcomes compared with those who do not. Because most patients will have received a combination of 5-FU or capecitabine with either irinotecan or oxaliplatin, second-line therapy with the alternate regimen should be considered.[15] For example, a patient who received FOLFOX plus bevacizumab as first-line therapy for metastatic disease should be offered FOLFIRI as part of their second-line regimen. EGFR inhibitors are an additional option for use in the second-line setting in patients with WT *KRAS* only. Patients who did not have an EGFR inhibitor in their first-line regimens are candidates for single-agent cetuximab or panitumumab or either agent in combination with 5-FU and irinotecan (FOLFIRI + EGFR inhibitor). Additionally cetuximab plus irinotecan can be used without the inclusion of 5-FU. The use of EGFR inhibitors may be beneficial as monotherapy, but response rates and PFS appear to be increased in combination with irinotecan-based chemotherapy.[38-42] The results appear to be best when irinotecan is continued because of synergy demonstrated between the two classes of agents.[15,38]

If targeted agents such as bevacizumab were not part of the initial regimen, addition to the second-line regimen should be strongly considered. The addition of bevacizumab to FOLFOX has been shown to increase overall survival.[43] Bevacizumab as monotherapy was shown to be inferior to FOLFOX4 in efficacy and should not be considered as a treatment option in the second-line setting. In patients receiving bevacizumab as part of first-line therapy, continuation of bevacizumab with second-line therapy is associated with increased survival.[44] Based on these findings, continuation of bevacizumab in combination with traditional second-line chemotherapy regimens (5-FU-irinotecan or 5-FU-oxaliplatin based) can be considered in patients treated with a first-line bevacizumab containing regimen. Additional agents targeting VEGF, ziv-aflibercept or ramucirumab, in combination with FOLFIRI can also be considered for use in the second-line setting in patients who have progressed following an oxaliplatin-based first-line regimen. A modest increase in overall and PFS was found in patients receiving FOLFIRI plus ziv-aflibercept compared to FOLFIRI alone.[45] In two separate clinical trials, the addition of ramucirumab or ziv-aflibercept to FOLFIRI led to a modest increase in overall and PFS when compared to FOLFIRI alone.[45,46] Adverse events and warnings for use with ziv-aflibercept or ramucirumab are similar to those with bevacizumab and described in the section of specific agents. Table 91–5 lists treatment options for first- and second-line treatment of metastatic colorectal cancer. Patients with good PS are treated more aggressively than those with poor PS because of their ability to better tolerate chemotherapy.

▶ *Salvage Therapy*

Several salvage therapy options exist for patients with colorectal cancer who have progressed beyond standard first- and second-line

Table 91–5

Treatment Options for Metastatic Colon Cancer[a]

First-Line Therapy	Second-Line Therapy
Good Performance Status	**If First-Line Irinotecan**
• FOLFOX or FOLFIRI with bevacizumab • FOLFOX or FOLFIRI with cetuximab or panitumumab[c] • FOLFOXIRI with or without bevacizumab • 5-FU + leucovorin or capecitabine with or without bevacizumab	• FOLFOX with or without bevacizumab[b] • Irinotecan with or without cetuximab[c,d] • Capecitabine or 5-FU plus leucovorin
Poor Performance Status	**If First-Line Oxaliplatin**
• Capecitabine or 5-FU plus leucovorin with or without bevacizumab	• FOLFIRI with or without bevacizumab • FOLFIRI with ziv-aflibercept • Irinotecan with ziv-aflibercept • FOLFIRI or irinotecan with or without cetuximab or panitumumab[c,d]

[a]CapeOX may replace FOLFOX in selected patients.

[b]Bevacizumab may be given if not part of the first-line therapy.

[c]If KRAS wild type.

[d]Cetuximab or panitumumab may be given if not part of first-line therapy.

5-FU, 5-fluorouracil.

Patient Encounter Part 3

Based on the information presented, create a care plan for this patient's colon cancer. Your plan should include:

(a) The patient's drug- and nondrug-related needs and problems.

(b) The goals of therapy.

(c) A treatment plan specific to this patient that includes strategies to prevent adverse effects of chemotherapy.

(d) A follow-up plan to determine whether the goals have been achieved and the adverse effects of chemotherapy have been minimized.

therapy. Panitumumab is approved for patients who have progressed after 5-FU, oxaliplatin, and irinotecan. Compared with best supportive care, it improves time to disease progression.[15] Based on improvement in PFS compared to best supportive care, the multiple tyrosine kinase inhibitor, regorafenib, was approved as a single agent for metastatic colorectal cancer in the third- or fourth-line setting.[47] Trifluridine and tipiracil is another oral treatment option for patients who have been previously treated with all standard therapies. This agent gained FDA approval after demonstrating improved overall survival when compared with placebo.[48]

A final option in patients with metastatic colorectal cancer and who also demonstrate high MSI or dMMR disease is pembrolizumab. Patients with these particular tumor characteristics have demonstrated notable clinical benefit in early clinical trial data, thus prompting FDA approval in this setting.[49] Although several salvage options exist, patients who fail standard treatment for metastatic colorectal cancer should be encouraged to participate in a clinical trial evaluating new treatment approaches for this incurable disease.

LO 5 SPECIFIC AGENTS USED IN COLORECTAL CANCER

Table 91–6 lists all FDA-approved drugs used in colorectal cancer along with their mechanisms of action, common toxicities, and recommended dose adjustments for hepatic and renal dysfunction as well as pharmacogenetic considerations.

5-Fluorouracil

5-Fluorouracil (5-FU) acts as a "false" pyrimidine inhibiting the formation of the DNA base thymidine as described in Chapter 88.[16]

5-FU is commonly used in the adjuvant and metastatic treatment of colon and rectal cancers with common regimens listed in Table 91–3. Clinical studies comparing efficacy of bolus and continuous infusion schedules generally favor continuous infusion of 5-FU. This is consistent with evidence that suggests that the duration of infusion may be an important determinant of the biologic activity of 5-FU, particularly because of its short plasma half-life, S-phase specificity, and relatively slow growth of colon tumors.[16,50]

Clinically significant differences in toxicity also differ based on the dose, route, and schedule of 5-FU administration. Leukopenia and mucositis are the primary dose-limiting toxicities of bolus 5-FU, whereas palmar-plantar erythrodysesthesia ("hand–foot syndrome") and diarrhea occur most frequently with continuous infusions of 5-FU.[16,50] Health care practitioners can offer valuable patient advice to decrease the impact of these adverse effects. Patients can be informed to suck on ice chips before and for up to 30 minutes after 5-FU boluses to decrease the incidence of mucositis. Hand–foot syndrome, characterized by painful swelling and redness of the soles of the feet and palms of the hand, can be minimized with loose-fitting clothing and keeping skin moist. Additional toxicities include moderate nausea and vomiting, skin discoloration, nail changes, photosensitivity, and neurologic toxicity.

An additional determinate of 5-FU toxicity, regardless of the method of administration, is related to its catabolism and **pharmacogenomic** factors. Dihydropyrimidine dehydrogenase (DPD) is the main enzyme responsible for the catabolism of 5-FU to inactive metabolites.[48] A number of polymorphisms in DPD have been identified in which patients have a complete or near-complete deficiency of this enzyme. This results in unusually severe toxicity, including death, after the administration of 5-FU. Approximately 3% of patients have a complete lack of DPD activity with other patients demonstrating a partial deficiency in enzyme activity. Although patients may be tested for level of DPD activity, it is not routinely done but may be considered in patients who develop severe toxicity after 5-FU administration. The response to 5-FU is also influenced by the status of MSI within the tumor. Tumors with high levels of MSI are generally more resistant to 5-FU despite being associated with better prognosis.

Leucovorin is commonly given with 5-FU. Leucovorin acts to increase the affinity of 5-FU to thymidine synthase, thus increasing the pharmacologic activity of 5-FU.[16] Leucovorin is most effective when administered before 5-FU and can be given by IV bolus or as a continuous infusion. 5-FU toxicities (leukopenia, mucositis, and diarrhea) are increased when leucovorin is given in combination with 5-FU.

Capecitabine

Capecitabine (Xeloda) is an oral prodrug of 5-FU that is designed to be selectively activated by tumor cells. Capecitabine undergoes a three-step conversion to 5-FU, the last step being phosphorylation by thymidine phosphorylase (TP). TP levels are reported to be higher in tumor cells than normal tissues; therefore, the systemic exposure of active drug is minimized, and tumor concentrations of the active drugs are optimized.[16,22] After the drug is converted to 5-FU, it has the same mechanism of action. The current FDA-approved indication for capecitabine is for use in metastatic and adjuvant colorectal cancer when monotherapy is desired, although it is actively being investigated as a replacement for 5-FU in most combinations of colon and rectal cancer regimens. Hand–foot syndrome and diarrhea are common with capecitabine because its toxicities (and pharmacologic activity) appear to mimic those of continuous infusions of 5-FU.

The dose of capecitabine ranges from 1000 to 1250 mg/m^2 twice a day when used by itself; lower doses are often used when it is given in combination with irinotecan or oxaliplatin or in patients with renal insufficiency. The dose should be taken on a full stomach with breakfast and dinner. Capecitabine administered with warfarin can result in significant increases in patients' international normalized ratio (INR) and requires close monitoring. The convenience of oral administration, potentially requiring fewer clinic visits, and an improvement in toxicity make capecitabine a useful alternative to IV 5-FU both by itself and incorporated into other regimens used in colorectal cancer.

LO 5

Table 91–6

FDA-Approved Drugs Used in Colon Cancer

Generic Name (Trade Name)	Mechanism of Action	LO 7 Common Toxicities	Dosing Adjustments for Renal or Hepatic Dysfunction or Pharmacogenetic Considerations
5-FU	Inhibition of the enzyme thymidylate synthase, the rate-limiting step in thymidine formation	*Dose limiting:* Myelosuppression and mucositis with bolus administration Diarrhea and hand–foot syndrome with continuous infusion *Additional toxicities:* Skin discoloration, nail changes, photosensitivity, and neurologic toxicity	Do not give if bilirubin greater than 5 mg/dL (86 μmol/L) DPD deficiency may result in increased toxicity. Testing not routine, but may be considered in those with excessive toxicity
Capecitabine (Xeloda)	Orally active prodrug of 5-FU. Once activated, the mechanism of action is the same	Similar to continuous infusion 5-FU	CrCl 30–50 mL/min (0.50–0.83 mL/s) decrease starting dose to 75% of the original dose Do not give if CrCl < 30 mL/min (0.50 mL/s)
Irinotecan (Camptosar)	Topoisomerase inhibitor that forms a complex with the covalently bound DNA topoisomerase enzyme and interferes with the DNA breakage-resealing process	*Dose limiting:* Early and late diarrhea *Additional toxicities:* Neutropenia, nausea, and vomiting	Decrease dose one level in patients with a homozygous UGT1A1*28 allele. Having this allele decreases the hepatic metabolism of irinotecan and increases the toxicity
Oxaliplatin (Eloxatin)	Similar to other platinum analogues (cisplatin) in that it binds to the N-7 position of guanine, which results in cross-linking of DNA and double-stranded DNA breaks	*Dose limiting:* Acute (within first 2 days) and persistent (> 14 days) neuropathies *Additional toxicities:* Anaphylactic-like reactions, dyspnea, nausea, vomiting	No formal dose adjustment, though use with caution in patients with mild to moderate renal dysfunction
Bevacizumab (Avastin)	Monoclonal antibody that binds to VEGF and inhibits angiogenesis	*Dose limiting:* Hypertension, bleeding episodes, thrombotic events *Additional toxicities:* Rare perforation of the bowel, proteinuria	None
Ziv-aflibercept (Zaltrap)	Recombinant fusion protein that binds to VEGF and inhibits angiogenesis	*Dose limiting:* Hypertension, bleeding episodes, thrombotic events, infection, diarrhea *Additional toxicities:* Rare perforation of the bowel, proteinuria	None
Ramucirumab (Cyramza)	Monoclonal antibody that binds to VEGF-2 and inhibits angiogenesis	*Dose limiting:* Hypertension, bleeding, thrombosis *Additional toxicities:* Gastrointestinal perforation, proteinuria, delayed wound healing	None
Regorafenib (Stivarga)	Multiple protein kinase inhibitor, including VEGF KIT, PDGFR, RET, FGFR, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, SAPK2, PTK5, and Abl	*Dose limiting:* Hypertension, hand–foot skin reaction *Additional toxicities:* GI perforation, impaired wound healing, hemorrhage, RPLS, fatigue, electrolyte imbalance, hepatotoxicity	Do not use if Child-Pugh Class C hepatic impairment Specific recommendations exist for hepatotoxicity developing while on therapy
Cetuximab (Erbitux)	Binds to the cell surface EGFR, preventing EGF and TGF-α binding. This decreased cell proliferation of cancer cells	*Dose limiting:* Infusion-related reactions, acneiform skin rash *Additional toxicities:* Diarrhea, hypomagnesemia, hypocalcemia, interstitial lung disease	*KRAS* WT only
Panitumumab (Vectibix)	Similar to cetuximab	*Dose limiting:* Acneiform skin rash *Additional toxicities:* Infusion-related reactions, diarrhea, hypomagnesemia, hypocalcemia, interstitial lung disease	*KRAS* WT only

(*Continued*)

Table 91–6

FDA-Approved Drugs Used in Colon Cancer (*Continued*)

Generic Name (Trade Name)	Mechanism of Action	LO 7 Common Toxicities	Dosing Adjustments for Renal or Hepatic Dysfunction or Pharmacogenetic Considerations
Trifluridine/tipiracil (Lonsurf)	Thymidine analog, inhibits DNA synthesis	*Dose limiting:* Myelosuppression *Additional toxicities:* Nausea, diarrhea, stomatitis	Do not initiate therapy in moderate or severe hepatic impairment
Pembrolizumab (Keytruda)	Monoclonal antibody that inhibits PD-1 receptor and prevents PD-1 pathway activation	*Toxicities:* Immune mediated colitis, dermatitis, hepatitis, etc	Indicated for MSI-H

5-FU, 5-fluorouracil; CrCl, creatinine clearance; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; PD, programmed death; RPLS, reversible posterior leukoencephalopathy syndrome; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; WT, wild type.

Irinotecan

Irinotecan (Camptosar) is a **topoisomerase-I** inhibitor that forms a complex with the covalently bound DNA topoisomerase I enzyme and interferes with the DNA breakage–resealing process. Binding permits uncoiling of the double-stranded DNA, but it prevents subsequent resealing of the DNA, resulting in double-stranded DNA breaks. Irinotecan is a prodrug that is converted by carboxylesterases to its active form, SN-38. Irinotecan is indicated for the first-line treatment of metastatic colorectal cancer in combination with 5-FU and leucovorin or as a single agent in patients who fail first-line therapies. Irinotecan is not recommended as part of the adjuvant treatment of colorectal cancer at this time.

The major toxicity of irinotecan is diarrhea, which can occur both early and late in therapy.[15,50] The early diarrhea is a cholinergic reaction that occurs in the first 24 hours (often during the infusion) in up to 10% of patients and responds to atropine 0.25 to 1 mg IV. The late diarrhea seen in a larger percent of patients occurs 7 to 14 days after the irinotecan infusion. Health care practitioners have to be diligent in counseling patients on this adverse reaction and counseling them on the proper use of antidiarrheals. At the first change in bowel habits, an intensive loperamide regimen should be started by patients (4 mg initially followed by 2 mg every 2 hours until diarrhea free for 12 hours). If diarrhea does not stop or if it worsens, patients should be instructed to call their health care provider immediately. Late-onset diarrhea may require hospitalization or discontinuation of therapy, and fatalities have been reported. Additional toxicities with irinotecan include leukopenia (including neutropenic fever) and moderate nausea and vomiting. Toxicities of irinotecan appear to be greater when the drug is given weekly compared with other administration schedules.

Similar to 5-FU, a pharmacogenomic abnormality is associated with irinotecan toxicity. UDP-glucuronosyltransferase (UGT1A1) is an enzyme that is responsible for the glucuronidation of SN-38 to inactive metabolites, and reduced or deficient levels of this enzyme correlate with irinotecan-induced diarrhea and neutropenia.[15,50] The FDA approved a blood test that detects variations in this gene. This test may assist health care providers in predicting which patients may develop severe toxicities from "normal" doses of irinotecan and can be ordered before patients receive irinotecan.[15] The package insert recommends dose reductions of one level in patients who are UGT1A1 homozygous variants. Irinotecan is administered as an IV bolus over 60 to 90 minutes in a variety of dosing schedules.

Oxaliplatin

Oxaliplatin (Eloxatin) is similar to other platinum analogues (cisplatin) in that it binds to the N-7 position of guanine that results in cross-linking of DNA and double-stranded DNA breaks.[50] Oxaliplatin differs from cisplatin in that the DNA damage induced by oxaliplatin may not be as easily recognized by DNA repair genes often seen in colorectal cancer. Oxaliplatin, in combination with 5-FU-based regimens, is indicated for the first- and second-line treatment of metastatic colorectal cancer as well as the adjuvant treatment of colorectal cancer.

The dose-limiting toxicity of oxaliplatin is acute and chronic neuropathy.[16] Acute neuropathies occur within 1 to 2 days of dosing, resolve within 2 weeks, and usually occur peripherally. These acute neuropathies occur in almost all patients to some degree and are exacerbated by exposure to cold temperature or cold objects. Health care providers should instruct patients to avoid cold drinks, avoid use of ice, and cover skin before exposure to cold or cold objects. In addition, carbamazepine, gabapentin, amifostine, and calcium and magnesium infusions have been used to both prevent and treat oxaliplatin-induced neuropathies, although use of these agents is not widely accepted.[16] Persistent neuropathies generally occur after eight cycles of oxaliplatin and are characterized by defects that can interfere with daily activities (eg, writing, buttoning, swallowing, and walking). Patients may receive predefined breaks from oxaliplatin to decrease the onset of these toxicities with reinitiation of therapy.[26] This strategy varies among protocols but involves administering a certain number of predefined oxaliplatin cycles and then stopping. Maintenance therapy with another agent is usually administered and then the oxaliplatin-based regimen is restarted based on the protocol. These neuropathies occur in up to half of patients receiving oxaliplatin but usually resolve with dosage reductions or after oxaliplatin is stopped.[16] Oxaliplatin has minimal renal, myelosuppressive effects, and nausea and vomiting when compared with other platinum drugs. Oxaliplatin is given IV in a variety of dosing schedules with a typical dose of 85 mg/m^2 IV every 2 weeks.

Bevacizumab

Bevacizumab (Avastin) is a recombinant, humanized monoclonal antibody that inhibits VEGF. VEGF is a proangiogenic growth factor found in many cancers, including colorectal, and is thought to promote blood vessel formation and metastasis of the tumor by binding to VEGF receptors on tumors. Bevacizumab inhibits circulating VEGF, preventing it from binding to receptors and

decreasing the formation of new blood vessels.[15,16] Additionally, bevacizumab may allow for increased concentrations of traditional chemotherapy such as irinotecan to reach the tumor to exert its pharmacologic effect. Bevacizumab is not effective alone and must be used in combination with other agents effective in colorectal cancer. It is indicated for first-line and second-line treatment of patients with metastatic colorectal cancer in combination with IV 5-FU–based regimens. Bevacizumab is also approved for use in combination with 5-FU-irinotecan or 5-FU-oxaliplatin–based chemotherapy for treatment of patients with metastatic colorectal cancer whose disease has progressed on a first-line bevacizumab-containing regimen.

Adverse effects associated with bevacizumab include hypertension, which is common but easily managed with oral antihypertensive agents. Thrombotic events (including myocardial infarctions, pulmonary embolisms, and deep vein thrombosis) occur more frequently in the elderly patients with cardiovascular risk factors and need to be monitored carefully. Because bevacizumab interferes with normal wound healing, it should not be given shortly before or after surgical procedures.[15] Initiation within 28 days of surgery is not recommended to allow for proper wound healing and decrease the risk of bleeding. The amount of time needed after bevacizumab discontinuation to perform elective surgical procedures is less clear, but health care providers should take into consideration bevacizumab's half-life of approximately 20 days when making clinical decisions.[33] Patients should have their urine checked for protein before each dose of bevacizumab to check for potential kidney damage. Patients who have developed 2+ protein on the urinalysis require additional testing before receiving therapy. These patients will have their 24-hour urine collected and assessed for protein. Therapy is interrupted if urine protein excretion exceeds 2 g/24 hours or more and resumed when urine protein excretion decreases to less than 2 g/24 hours.

Finally, there is a risk of GI perforation that is rare but potentially fatal. Patients complaining of abdominal pain associated with vomiting or constipation should be counseled to call their physician immediately. Bevacizumab is commonly given at a dose of 5 mg/kg IV every 14 days until disease progression. Once disease progresses and salvage chemotherapy is initiated, the benefit of continuing bevacizumab is unclear.

Ziv-aflibercept

Ziv-aflibercept (Zaltrap) is a soluble recombinant fusion protein developed by fusing sections of the VEGFR-1 and VEGFR-2 immunoglobulin domains to the F_c portion of human IgG1 antibody. This results in trapping the VEGF-A, VEGF-B, and PIGF ligands before they get to the native transmembrane receptors, and therefore, inhibiting the angiogenic process.[15,45] It is FDA approved for the treatment of metastatic colorectal cancer in combination with FOLFIRI after progression on an oxaliplatin-based regimen. The dose is 4 mg/kg as an IV infusion over 1 hour every 2 weeks in combination with FOLFIRI.

Toxicities include severe and potentially fatal hemorrhage, GI perforation, and compromised wound healing for which the FDA has given ziv-aflibercept a black-box warning. Other adverse effects common to VEGF inhibition (thromboembolic events, hypertension, proteinuria) are seen. As a result ziv-aflibercept shares similar monitoring parameters and warnings to those mentioned in the bevacizumab section. Finally additional warnings for neutropenia, diarrhea and dehydration, and reversible posterior leukoencephalopathy syndrome (RPLS) require monitoring patients for signs and symptoms of these toxicities.

Ramucirumab

Ramuricumab (Cyramza) is a fully human IgG-1 monoclonal antibody that targets and binds to the VEGFR-2, inhibiting ligand activation of the receptor and subsequent vascular tumor growth.[46] For the treatment of colorectal cancer ramucirumab is FDA-approved at a dose of 8 mg/kg IV in combination with FOLFIRI in patients who have progressed on or after therapy with 5-FU, oxaliplatin, and bevacizumab.

Ramucirumab shares an adverse effect profile similar to that of the previously discussed VEGF inhibitors bevacizumab and ziv-aflibercept, including black-box warnings for risk of hemorrhage, GI perforation, and impaired wound healing.

Regorafenib

Regorafenib (Stivarga) is an oral medication that inhibits multiple protein kinases. Its main mechanism of action in colorectal cancer appears to be related to inhibition of vascular endothelial receptors involved in angiogenesis. The importance of additional protein kinase inhibited by regorafenib is unknown in colorectal cancer. Regorafenib is FDA approved as a single agent for metastatic colorectal cancer in the third- or fourth-line setting.[47] The dose of regorafenib is 160 mg orally, once daily for the first 21 days of each 28-day cycle and it must be taken with a low-fat breakfast to improve absorption.

Adverse effects for regorafenib include those typical for VEGF inhibition (hemorrhage, hypertension, wound healing complications, GI perforation) mentioned with bevacizumab and ziv-aflibercept. Regorafenib has a black-box warning for hepatotoxicity that requires baseline liver function tests (ALT, AST, and bilirubin), then every 2 weeks during the first 2 months of therapy, and then monthly. In patients with elevated liver function tests holding doses, dose reductions, or permanent discontinuation of regorafenib may be necessary. Also, asthenia, fatigue, decreased appetite, hand–foot syndrome, diarrhea, mucositis, weight loss, infection, and dysphonia occurred in over 30% of patients. Refer to Chapter 99 on supportive care for management. Finally, regorafenib is a substrate of CYP3A4 and patients should be screened for potential drug interactions.

Cetuximab and Panitumumab

Cetuximab (Erbitux) and panitumumab (Vectibix) are monoclonal antibodies directed against the EGFR. Cetuximab is a chimeric antibody, whereas panitumumab is a fully human monoclonal antibody. EGFR is overexpressed in colorectal cancers and leads to an increase in tumor proliferation and growth. Cetuximab received FDA approval for use in EGFR-expressing metastatic colorectal cancer in irinotecan-relapsed or irinotecan-refractory patients. Cetuximab should be administered in combination with irinotecan but can be used as a single agent in patients who cannot tolerate irinotecan-based chemotherapy. Panitumumab is approved as monotherapy agent and as first-line therapy in combination with FOLFOX in metastatic colorectal cancer.

Both agents are well tolerated with infusion-related reactions being the dose-limiting toxicity of cetuximab and rash most commonly seen with panitumumab. Patients receiving cetuximab require premedication with diphenhydramine and may require modifications to their administration schedule or permanent discontinuation if they develop severe allergic toxicity. A skin rash and diarrhea are also commonly seen with both agents, and health care practitioners should provide counseling to patients about these adverse effects. Treatment options include common medications used to treat acne (doxycycline), topical

and systemic steroids, and general skin care. Patients may be offered these agents prophylactically, upon initiation of therapy, to decrease the potential impact the rash has on their quality of life. Development of rash may be a surrogate marker of response, and clinicians should attempt to minimize the complications of the rash before discontinuing therapy.[15] Other toxicities common to both agents include low magnesium, calcium, and potassium levels that require checking levels and replacement therapy as clinically indicated. A rare adverse effect (< 1%), interstitial lung disease is seen with all agents that inhibit EGFR, and patients should be instructed to report any new-onset shortness of breath. Cetuximab has an initial loading dose of 400 mg/m^2 IV infusion. Weekly doses of 250 mg/m^2 are then administered starting the following week. Panitumumab is given 6 mg/kg IV every 2 weeks.

Trifluridine and Tipiracil

Trifluridine/tipiracil (Lonsurf) is an oral agent which incorporates two components. The active component is trifluridine, a thymidine-based nucleic acid analog which is incorporated into DNA and interferes with DNA synthesis. Tipiracil hydrochloride inhibits TP and thereby prevents degradation of the active trifluridine and allows for adequate plasma concentration of active drug.[48] The FDA-approved dose of 35 mg/m^2 orally is based on the trifluridine component and is administered twice daily on days 1 to 5 and 8 to 12 of a 28-day treatment cycle. It is given as a single-agent in patients who have previously received 5-FU, oxaliplatin, irinotecan, anti-VEGF therapy and anti-EGFR therapy (if *KRAS* WT).

Adverse effects include myelosuppression (particularly neutropenia and anemia), fatigue, stomatitis, diarrhea, and nausea. Trifluridine/tipiracil has moderate emetic potential and pretreatment for nausea is recommended. Each dose should be taken within 1 hour of completion of the morning and evening meals. The unusual dosing schema of this agent may be difficult for some patients and negatively affect compliance, thus careful counseling and written dosing guidelines should be offered to all patients.

Pembrolizumab

Pembrolizumab is a humanized IgG4 monoclonal antibody which inhibits the programmed death 1 (PD-1) receptor to prevent ligand binding and subsequent pathway activation. The PD-1 pathway is an immune pathway that typically serves as a negative feedback system to suppress T-cell response. Many tumors upregulate the PD-1 pathway to encourage immune suppression and prevent host immune activity against tumor cells.[49] Pembrolizumab blocks this negative feedback mechanism to induce T-cell activation and subsequent antitumor immune response. Pembrolizumab is FDA approved in colon cancer patients with dMMR or MSI-H tumors after failure of standard chemotherapies. Patients with dMMR tumors typically have many mutations resulting in production of many abnormal proteins which serve as antigens to the immune system. Reactivation of the immune system by pembrolizumab is often an effective strategy in these patients. Pembrolizumab is given intravenously at a flat dose of 200 mg every 3 weeks for up to 24 months. Adverse effects are mainly related to overactivation of the immune system. Though most patients tolerate it quite well, patients may exhibit immune-mediated toxicity in nearly any organ in their body, particularly dermatitis, colitis, and endocrinopathies.[15,49] These and most other immune-mediated toxicities must be managed by temporary or permanent drug discontinuation and initiation of oral corticosteroids.

Patient Encounter Part 4

Despite completing six cycles of adjuvant chemotherapy, this patient's disease progresses, and a CT scan reveals metastases to his bone and liver. The tumor is sent for pharmacogenomic profiling and is found to have the mutated *KRAS* gene.

What pharmacologic treatment options are available for the treatment of his metastatic disease?

RECTAL CANCER

Although often treated similarly to colon cancer, there are some important differences in the treatment of rectal cancer, especially in the adjuvant setting. Rectal cancer involves tumors found in the distal 15 cm of the large bowel and, as such, is very distinct from colon cancer in that it has a propensity for both local and distant recurrence. The higher incidence of local failure and poorer overall prognosis associated with rectal cancer are attributable to limitations in surgical techniques. Therefore, multimodality therapies with a combination of chemotherapy, radiation, and surgery are at the forefront in the treatment of rectal cancer with the main goal of survival and quality of life by preserving the function of the anal sphincter. In addition, because treatment with surgery, radiation, or systemic chemotherapy at the time of the recurrence is often suboptimal, adjuvant therapy after tumor resection is an important aspect of treatment of the primary tumor. Similar to adjuvant therapy for colon cancer, 5-FU provides the basis for chemotherapy regimens for rectal cancer.

KEY CONCEPT Adjuvant therapy consisting of 5-FU–based chemotherapy in combination with radiation therapy should be offered to patients with stage II or III cancer of the rectum.[50] Radiation therapy decreases the rate of local recurrences, but 5-FU decreases the risk of distant tumor recurrence as well as acting as a radiosensitizer. Toxicities from combined modality therapy include severe hematologic toxicity, enteritis, and diarrhea. Additional trials have sought to determine optimal combinations of concurrent radiation and 5-FU. Similar to tumors in the colon, continuous infusions of 5-FU appear to be superior to bolus doses. However, leucovorin does not appear to improve efficacy of adjuvant treatment for rectal cancer. Use of oral alternatives to 5-FU that are also known to enhance radiation effects, such as capecitabine, are under investigation with preliminary data suggesting the combination of capecitabine and radiation is likely to be safe and effective. In addition, based on the efficacy in colon cancer, FOLFOX regimens have moved into clinical trials in the adjuvant setting.

Another unique aspect of rectal cancer is the use of neoadjuvant therapy. Preoperative radiation (with or without chemotherapy) is given to downstage the tumor before surgical resection to improve sphincter preservation.[50]

KEY CONCEPT Metastatic rectal cancer is treated with similar regimens as outlined in the colon cancer section that are used for palliation of symptoms.[50]

OUTCOME EVALUATION

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The goals of monitoring are to evaluate whether the patient is receiving any benefit from the management of the disease, detect recurrence, and minimize the adverse effects of treatment. During treatment for active disease, patients should undergo monitoring for measurable tumor response, progression, or new

metastases; these tests may include chest CT scans or x-rays, abdominal or pelvic CT scans or x-rays, depending on the site of disease being evaluated for response; and carcinoembryonic antigen (CEA) measurements every 3 months if the CEA level is or was previously elevated.[17] A positron emission tomography (PET) scan can be considered to identify localized sites of metastatic disease when a rising CEA level suggests metastatic disease but results of CT scans and other imaging studies are negative. Symptoms of recurrence such as pain, changes in bowel habits, rectal bleeding, pelvic masses, anorexia, and weight loss develop in fewer than 50% of patients. Patients who undergo curative surgical resection, with or without adjuvant therapy, require close follow-up because early detection and treatment of recurrence could still result in patient cures. In addition, early treatment for asymptomatic metastatic colorectal cancer appears superior to delayed therapy. Colorectal cancer surveillance guidelines published by the American Society of Clinical Oncology recommend against routinely monitoring liver function tests, complete blood count (CBC), FOBT, CT scans, annual chest x-rays, or pelvic imaging in asymptomatic patients.

In addition, a CBC should be obtained before each course of chemotherapy administration to ensure that hematologic values are adequate. In particular, white blood cell counts and absolute neutrophil counts can be decreased in patients receiving chemotherapy such as irinotecan and 5-FU. Baseline liver function tests and an assessment of renal function should be evaluated before and periodically during therapy. Other selected laboratory tests include checking for the presence of protein in the urine in patients receiving bevacizumab and monitoring of magnesium, calcium, and potassium in patients receiving cetuximab or panitumumab.

Patients should be evaluated during every treatment visit for the presence of anticipated side effects from their treatment, and health care practitioners should anticipate these adverse reactions and aggressively treat and prevent them from occurring. These generally include loose stools or diarrhea from irinotecan, 5-FU, and capecitabine; hand–foot syndrome from 5-FU and capecitabine; nausea or vomiting from irinotecan, 5-FU, and oxaliplatin; mouth sores from 5-FU; neuropathies from oxaliplatin; bleeding and hypertension from bevacizumab; and skin rash associated with cetuximab and panitumumab.

SUMMARY

Recent advances in the treatment of cancer of the colon and rectum now offer the potential to improve patient survival, but for many patients, improved DFS and PFS represent equally important therapeutic outcomes. In the absence of the ability of a specific treatment to demonstrate improved survival, important outcome measures should include the effects of the treatment on patient symptoms, daily activities, PS, and other quality-of-life indicators. Individualized patient care to balance the risks associated with treatment and benefits of a specific treatment regimen is necessary to optimize patient outcomes.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings. Identify the stage of malignancy.
- Review patient-specific factors, tumor-specific factors, and laboratory information that may influence chemotherapy selection and drug dosing.
- Speak with the patient and review records to identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and other aspects of care.
- Compile a list of appropriate chemotherapy treatment regimens.

Assess the Information:

- Determine the goal of therapy and prognosis based on stage of disease.
- Review the medication history (including prescription and OTC medications) to identify agents that may worsen the patient's symptoms of colon cancer. Identify agents that effect bowel function (resulting in diarrhea or constipation) or agents such as NSAIDs that may cause GI bleeding.
- Determine whether the patient is taking any substance that could potentiate chemotherapy toxicities or interact with prescribed medications.
- Based on the medical history, determine whether the patient has compelling indications or contraindications for specific chemotherapy.
- Review relevant laboratory tests (eg, CBC, electrolytes, complete metabolic panel to determine liver and hepatic function, tumor markers, tumor genetic profile) which might impact drug selection or dosing.
- Identify a list of the potential appropriate chemotherapy regimens and the related toxicities.
- Determine supportive care needs including nausea and vomiting control, pain management, prevention of infections, electrolyte supplementation, and toxicity management.
- Determine PS of the patient (see Chapter 88).

Develop a Care Plan:

- Review the chemotherapy order and assess efficacy, dosages, drug interactions, and possible adverse effects from the regimen (see Tables 91–3 and 91–5).

Implement the Care Plan:

- Discuss lifestyle modifications that may assist in symptom and disease management.
- Calculate the body surface area (BSA) and determine if doses are optimal and correct for this patient. Evaluate laboratory values to assist in this process.
- Review supportive care options to decrease the impact of adverse effects for this patient (see Chapters 88 and 99).

(*Continued*)

Patient Care Process (*Continued*)

- Determine whether the patient has insurance coverage or whether recommended agents are included on the institution's formulary.
- Counsel patient on potential adverse effects of the regimen.

Follow-up: Monitor and Evaluate:

- Follow-up when the patient is scheduled for their next round of chemotherapy. Assess the patient for adverse effects of the regimen or other supportive care measures that may need to be added (eg, pain management).
- Review medication history, physical examination, laboratory results, and other imaging and diagnostic tests to evaluate if the patient should continue on their current chemotherapy regimen.

Abbreviations Introduced in This Chapter

APC	Adenomatous polyposis coli
CapeOX	Capecitabine and oxaliplatin
CBC	Complete blood count
CEA	Carcinoembryonic antigen
COX-2	Cyclooxygenase-2
CTC	Computed tomographic colonography
dMMR	DNA mismatch repair
DFS	Disease-free survival
DPD	Dihydropyrimidine dehydrogenase
EGFR	Epidermal growth factor receptor
FAP	Familial adenomatous polyposis
FIT	Fecal immunochemical test
FOBT	Fecal occult blood test
FOLFIRI	Folinic acid, fluorouracil, and irinotecan
FOLFOX	Folinic acid, fluorouracil, and oxaliplatin
GI	Gastrointestinal
HNPCC	Hereditary nonpolyposis colorectal cancer
INR	International normalized ratio
MSI	Mircrosatellite instability
NSAID	Nonsteroidal anti-inflammatory drug
PET	Positron emission tomography
PFS	Progression-free survival
PS	Performance status
TNM	Tumor, node, metastasis
TP	Thymidine phosphorylase
UGT	UDP-glucuronosyltransferase
VEGF	Vascular endothelial growth factor

REFERENCES

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
2. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975–2014. Bethesda, MD: National Cancer Institute. Available from: http://seer.cancer.gov/csr/1975_2014. Accessed August 28, 2017.
3. Park Y, Hunter DJ, Spiegelman D, et al. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA. 2005;294:2849–2857.
4. Giovannucci E. Modifiable risk factors for colon cancer. Gastroenterol Clin North Am. 2002;31:925–943.
5. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J Clin Nutr. 2007;86(3):s836–s842.
6. Calvert PM, Frucht H. The genetics of colorectal cancer. Ann Intern Med. 2003;137:603–612.
7. NCCN Guidelines—Colorectal Cancer Screening v.1. 2014. Available from: http://www.nccn.org. Accessed October 5, 2017.
8. NCCN Guidelines—Colorectal Cancer Screening. Version 1. 2018. Available from: www.nccn.org. Accessed July 29, 2018.
9. Hawk ET, Levin B. Colorectal cancer prevention. J Clin Oncol. 2005;23:378–391.
10. Chan AT, Giovannucci EL, Meyerhardt JA, et al. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 2005;294:914–923.
11. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med. 2007;356:2131–2142.
12. Cooper K, Squires H, Carrol C, et al. Chemoprevention of colorectal cancer: systematic review and economic evaluation. Health Technol Assess. 2010;14:1–206.
13. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. JAMA. 2002; 288:872–881.
14. Grunwald V, Hidalgo M. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. J Natl Cancer Inst. 2003; 95:851–867.
15. NCCN Guidelines—Colon Cancer v.2. 2017. Available from: http://www.nccn.org. Accessed October 5, 2017.
16. Libutti SK, Saltz LB, Tepper JE. Colon cancer. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2011:1084–1126.
17. Libutti SK, Tepper JE, Saltz LB. Rectal cancer. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2011:1127–1141.
18. Simmonds PC, Primrose JN, Colquitt JL, et al. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer. 2006;94:982–999.
19. Benson AB, Schrag D, Somerfield MR, et al. American Society of Clinical Oncology recommendations of adjuvant chemotherapy for stage II colon cancer. J Clin Oncol. 2004;22:3408–3419.
20. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28:3219–3226.
21. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352:2696–2704.
22. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27:3109–3116.
23. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29:1465–1471.

24. Saltz LB, Cox JV, Blanke C, et al. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. Meta-analysis Group in Cancer. J Clin Oncol. 1998;16:301–308.
25. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med. 2000;343:905–914.
26. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol. 2004;22:23–30.
27. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22:229–237.
28. Cassidy J, Clarke S, Diaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008;26:2006–2012.
29. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: updated results from the BICC-C study. J Clin Oncol. 2008;26:689–690.
30. Grothey A, Sargent D, Goldberg RM, Schmoll H. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol. 2004;22:1204–1214.
31. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;20:2013–2019.
32. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27:663–671.
33. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360:1408–1417.
34. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28:4697–4705.
35. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360:563–572.
36. Amado RG, Wolf M, Peters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colotrectal cancer. J Clin Oncol. 2008;26:1626–1634.
37. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol. 2009;27:672–680.
38. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004;351:337–345.
39. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357:2040–2048.
40. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. *KRAS* mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359:1757–1765.
41. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28:4706–4713.
42. Sobrero AF, Maurel J, Febrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(14):2311–2319.
43. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25:1539–1544.
44. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013;14:29–37.
45. Van Cutsem E, Tabernero J, Lakomy R. Addition of aflibercept to fluorouracil, leucovorin and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30:3499–3506.
46. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and fluoropyrimidine (RAISE): a randomized, double-blind, multicenter, phase 3 study. Lancet Oncol. 2015;16:499–508.
47. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129:245–255.
48. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372:1909–1919.
49. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumor with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–2520.
50. NCCN Guidelines—Rectal Cancer v.1. 2017. Available from: http://www.nccn.org. Accessed October 12, 2017.

92 Prostate Cancer

Daniel J. Crona and Amber E. Proctor

LEARNING OBJECTIVES

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

1. Identify risk factors associated with prostate cancer development.
2. Discuss the benefits and risks associated with prostate cancer screening.
3. Appraise the prognostic- and patient-specific data needed to determine appropriate treatment options.
4. Evaluate pharmacotherapeutic treatment options for patients with prostate cancer.
5. Formulate a monitoring plan for patients receiving androgen deprivation therapy for prostate cancer based on patient-specific factors and the prescribed regimen.
6. Recognize the common adverse effects associated with androgen deprivation therapy.
7. Evaluate appropriate pharmacotherapeutic treatment options for patients with metastatic castration-resistant prostate cancer.
8. Formulate a monitoring plan for patients receiving treatment for metastatic castration-resistant prostate cancer based on patient-specific factors and the prescribed regimen.
9. Recognize the common adverse effects associated with pharmacotherapeutic treatments for metastatic castration-resistant prostate cancer.

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in the United States in men, and is the second leading cause of cancer-related death in men.[1] The disease course ranges from indolent, asymptomatic tumors that may not require treatment to rapidly progressing, aggressive tumors that result in distant metastases, morbidity, and mortality.

EPIDEMIOLOGY AND ETIOLOGY

KEY CONCEPT Prostate cancer is the most frequently diagnosed cancer among men in the United States, and represents the second leading cause of cancer-related deaths in all men. In the United States alone, it is estimated that 164,690 new cases of prostate cancer will be diagnosed, and more than 29,430 deaths will occur in 2018.[1] Although prostate cancer incidence increased during the late 1980s and early 1990s, due to widespread **prostate-specific antigen** (PSA) screening, prostate cancer-related deaths have declined since 1995.[2]

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Prostate cancer risk factors include age, race/ethnicity, and family history of prostate cancer (Table 92–1).[3] Age is the greatest predictor of risk, and while the disease is rare among men under age 40, the incidence sharply increases with each subsequent decade of life.[2] An evaluation of autopsies from men who died of unrelated causes revealed prostate cancer in 2%, 29%, 32%, 55%, and 64% of men in their third, fourth, fifth, sixth, and eighth decades of life, respectively.[4]

Race

The incidence of clinical prostate cancer varies across geographic regions. Scandinavian countries and the United States report the highest incidences of prostate cancer, while it remains relatively rare in Japan and other Asian countries.[2] African American men have the highest rate of prostate cancer in the world, and prostate cancer mortality among African Americans is approximately twice that observed among Caucasian patients. Hormonal, dietary, and genetic differences, as well as differences in access to health care, may contribute to the variability in prostate cancer incidence and mortality among different populations.[2] Testosterone, commonly implicated in the pathogenesis of prostate cancer, is 15% higher in African American men, when compared to Caucasian men. Japanese men demonstrate decreased activity of 5-α-reductase, when compared with African American and Caucasian men.[5,6] In addition, variations in the androgen receptor gene (*AR*) exist. *AR* transcription is inversely correlated with the length of trinucleotide (CAG) repeats in the *AR* transactivation domain. Shorter CAG repeat sequences have been found in African Americans, and thus a combination of increased testosterone and increased *AR* activation may account for the increased prostate cancer risk among African Americans.[5]

Family History

Men with a brother or father with prostate cancer have twice the risk for prostate cancer compared to the rest of the population, and 5% to 10% of all prostate cancers are thought to be inherited.[7] Genome-wide studies have identified potential prostate cancer susceptibility candidate genes, and there appears to be prostate cancer familial clustering. Carriers of germline mutations in one of 16 DNA repair genes (eg, *BRCA1*, *BRCA2*, and *CHEK2*) are known to have an increased risk for developing prostate cancer,[8] although currently gene sequencing is not routinely performed. Interestingly, early studies have also indicated that mutations

Table 92–1

Risk Factors Associated with Prostate Cancer

Factor	Possible Relationship
Probable Risk Factors	
Age	More than 70% of cases are diagnosed in men older than 65 years
Race	African Americans have a higher incidence and death rate
Genetic	Familial prostate cancer inherited in an autosomal dominant manner
	Germline mutations in one of 16 DNA repair genes (eg, *BRCA1*, *BRCA2*, *ATM*, and *CHEK2*) are associated with increased prostate cancer risk and severity
Possible Risk Factors	
Environmental	Clinical carcinoma incidence varies worldwide
	Latent carcinoma similar between regions
	Nationalized men adopt intermediate incidence rates between that of the United States and their native country
Occupational	Increased risk associated with cadmium exposure
Dietary	Mediterranean diet associated with reduced risk of prostate cancer
	Increased risk associated with high-meat and high-fat diets
	Decreased intake of 1,25-dihydroxyvitamin D, lycopene, and β-carotene increases risk
Hormonal	Does not occur in castrated men
	Low incidence in cirrhotic patients
	Up to 80% are hormonally dependent
	African Americans have 15% increased testosterone
	Japanese have decreased 5-α-reductase activity
	Polymorphic expression of the androgen receptor gene

in these DNA repair genes may be predictive of clinical benefit of poly-ADP ribose polymerase (PARP) inhibitors. Another analysis identified five single nucleotide polymorphisms (SNPs) at 8q24, 17q12, and 17q24.3 that associated with an increased risk of prostate cancer, particularly for those with a family history of the disease. Men harboring all five SNPs had a nearly 10-fold increased risk for prostate cancer.[9] Notably, inherited mutations in *HOX13B* at 17q21-22 have been implicated in hereditary prostate cancer.[7] Consideration of germline testing is now recommended for all men with metastatic, regional, or high to very high risk localized prostate cancer. Common exposure to environmental and other risk factors may also contribute to increased risk among patients with first-degree relatives with prostate cancer.[2]

Diet

The diet associated with the lowest risk of developing prostate cancer is the Mediterranean diet, which includes: high intake of fruits, vegetables, legumes, fish, olive oil, and red wine, combined with moderate intake of red meat, poultry, and dairy.[10] Dietary factors that have been investigated as potential protectors against prostate cancer include retinol, carotenoids, lycopene, calcium, and vitamin D. Studies have suggested that lycopenes, which are found in tomatoes, grapefruit, and watermelon, may lower prostate cancer risk, but prospective clinical trials are needed. Selenium and vitamin E supplementation have failed to yield benefit in prostate cancer risk reduction.[11]

Other Factors

Benign prostatic hyperplasia (BPH) is common among elderly men, affecting more than 40% of men older than 70 years. BPH results in urinary symptoms (eg, hesitancy and frequency). Because prostate cancer affects a similar age group and often has similar presenting symptoms, the presence of BPH often complicates the diagnosis of prostate cancer, although it does not appear to increase the risk of prostate cancer.[6] Smoking has not conclusively been associated with an increased risk of prostate cancer, but smokers with prostate cancer have an increased mortality from the disease, when compared with nonsmokers with prostate cancer.[6]

PATHOPHYSIOLOGY

The prostate gland is a solid, round, walnut-shaped organ positioned between the neck of the bladder and the urogenital diaphragm (Figure 92–1). More than 95% of prostate cancer cases are adenocarcinomas.[12] Rarer tumor types include small cell neuroendocrine cancers, sarcomas, and transitional cell carcinomas.

Prostate cancer can be graded systematically according to the histologic appearance of the malignant cell and then categorized into well-, moderately-, or poorly-differentiated grades.[12,13] Gland architecture is examined, and then rated on the Gleason scale of 1 (well differentiated) to 5 (poorly differentiated). At least two different specimens are examined, and the score for each specimen is added together. Groupings for total **Gleason score** are 2 to 4 for well-differentiated, 5 to 6 for moderately-differentiated, and 7 to 10 for poorly-differentiated tumors. Poorly-differentiated tumors grow rapidly (poor prognosis), while well-differentiated tumors grow slowly (better prognosis).

Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination.[12,13] Lymph node metastases are more common in patients with large, undifferentiated tumors that

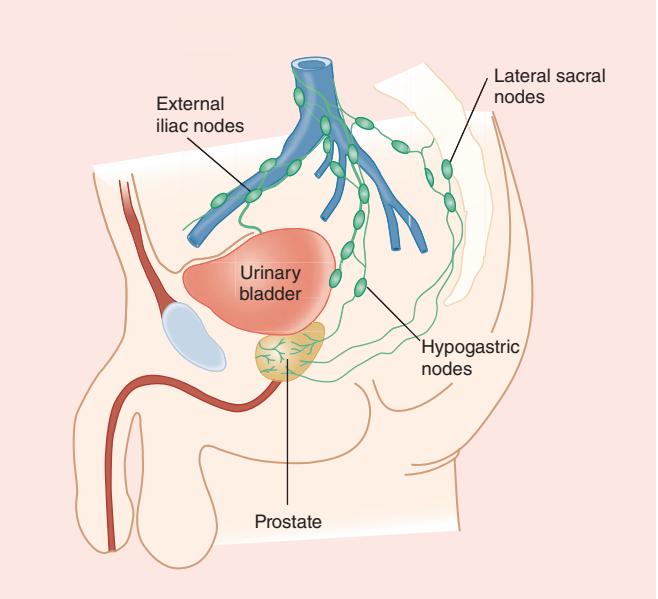

FIGURE 92–1. The prostate gland. (From DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed. New York, NY: McGraw-Hill, 2017:2168.)

invade the seminal vesicles. Pelvic and abdominal lymph nodes are the most common sites of lymph node involvement (see Figure 92–1). Osseous skeletal metastases from hematogenous spread are the most common sites of distant spread. Typically, the bone lesions are osteoblastic, or a combination of osteoblastic and osteolytic. The most common site of bone involvement is the lumbar spine. Other sites of bone involvement include the proximal femurs, pelvis, thoracic spine, ribs, sternum, skull, and humerus. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement; however, initial metastatic invasion does not occur in visceral organs, and the prostate is rarely a site for the metastatic spread of other solid tumors. About 25% to 35% of patients have evidence of lymphangitic or nodular pulmonary infiltrates at autopsy.

Normal growth and differentiation of the prostate depends on the presence of androgens, specifically dihydrotestosterone (DHT).[13,14] The testes and the adrenal glands are the major sources of circulating androgens. Hormonal regulation of androgen synthesis is mediated through a series of biochemical interactions among the hypothalamus, pituitary, adrenal glands, and testes (Figure 92–2).

Testosterone, the major androgenic hormone, accounts for 95% of the androgen concentration.[14] The primary source of testosterone is the testes; however, 3% to 5% of testosterone is derived from direct adrenal cortical secretion of testosterone or C19 steroids such as androstenedione.[13,15,16] In the prostate, 5-α-reductase converts testosterone to a more active form, DHT, and DHT is the active ligand that binds and activates the AR.

In early stage prostate cancers, aberrant tumor cell proliferation is promoted by DHT-induced activation of the AR signaling axis. Blockade and reduction of circulating androgens can induce tumor regression in most patients. Hormonal manipulations to reduce circulating androgens can occur through several mechanisms (Table 92–2).[15,16] The testes can be removed surgically (orchiectomy) to limit androgen production, or chemical interference of hormonal pathways that modulate prostatic growth can be accomplished at several steps using androgen deprivation therapy (ADT) (see Figure 92–2). Reduction in the release of luteinizing hormone (LH) and luteinizing hormone–releasing hormone (LHRH) (also known as gonadotropin-releasing hormone [GnRH]) by estrogens, LHRH agonists, direct GnRH antagonists, progesterones, and cyproterone acetate can also reduce testosterone secretion from the testes. Estrogen administration reduces androgens by directly inhibiting LH release, acting directly on the prostate cell, or decreasing free androgens by increasing steroid-binding globulin levels.[13,15,16]

The physiologic response to LHRH depends on both the dose and the mode of administration. Intermittent pulsed LHRH administration, which mimics the endogenous release pattern, results in sustained release of both LH and FSH; however, high dose or continuous infusions of LHRH inhibit gonadotropin release via receptor downregulation. Structural modification of the naturally occurring LHRH, combined with innovative delivery methods, has produced a series of LHRH agonists that cause a similar downregulation of pituitary receptors, and a decrease in testosterone production.[17]

Androgen synthesis can also be inhibited in the testes or adrenal gland. Aminoglutethimide inhibits the desmolase–enzyme complex in the adrenal gland, thereby preventing the conversion of cholesterol to pregnenolone. Pregnenolone is the precursor substrate for all adrenal-derived steroids, including: androgens, glucocorticoids, and mineralocorticoids. Abiraterone is a specific and potent inhibitor of CYP17A1, decreasing the conversion of pregnenolone to dehydroepiandrosterone (DHEA), a required precursor for testosterone. Ketoconazole, an imidazole antifungal agent, causes a dose-related reversible reduction in serum cortisol and testosterone concentration through a similar mechanism. Megestrol is a synthetic derivative of progesterone that also inhibits the synthesis of androgens. This inhibition appears to occur at the adrenal level, but circulating levels of testosterone are also reduced, suggesting that inhibition at the testicular level may also occur.[17]

Table 92–2

Hormonal Manipulations in Prostate Cancer

Androgen Source Ablation	Antiandrogens
Orchiectomy	Flutamide
Adrenalectomy	Bicalutamide
Hypophysectomy	Nilutamide
LHRH or LH inhibition	Enzalutamide
Estrogens	Cyproterone acetate[b]
LHRH agonists	Progesterones
Progesterones[a]	5-α-Reductase inhibition
Cyproterone acetate[b]	Finasteride[b]
Androgen synthesis inhibition	Dutasteride[b]
Abiraterone	GnRH antagonists
Aminoglutethimide	Degarelix
Ketoconazole	
Progesterones[a]	

[a]Minor mechanisms of action.

[b]Investigational compounds or use.

GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone.

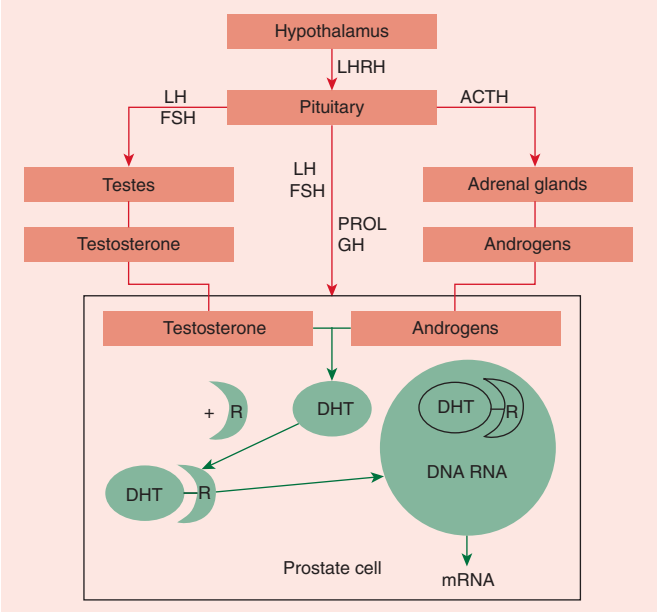

FIGURE 92–2. Hormonal regulation of the prostate gland. (ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; PROL, prolactin; R, receptor; RNA, ribonucleic acid.) (From DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach, 10th ed; New York, NY: McGraw-Hill, 2017:2168.)

Patient Encounter 1: Prevention and Screening

A 56-year-old Asian man with a past medical history significant for BPH presents to the pharmacy for a refill of his finasteride. He wants to know what he can do to reduce his risk of prostate cancer. He does not have a family history of prostate cancer, and he has never been screened for prostate cancer.

What do you recommend for prostate cancer screening?

What therapeutic options are available to the patient for prostate cancer chemoprevention?

The conversion of testosterone to DHT may be inhibited by 5-α-reductase inhibitors, but ultimately, it is the antiandrogens that inhibit the formation of the DHT–receptor complex, and thereby interfere with androgen-mediated action at the cellular level.[17]

In advanced stages of the disease, prostate cancer cells may be able to survive and proliferate without the growth signals normally provided by circulating androgens. When this occurs, these tumors are referred to as **castration-resistant prostate cancer (CRPC)** (previously described as "hormone-refractory" or "androgen-independent"). Because tumors remain amenable to secondary hormonal manipulations, and because the reintroduction of androgens can continue to promote tumor growth, the term castration-resistant more accurately reflects the clinical picture.

PREVENTION AND EARLY DETECTION

Screening

Early detection of potentially curable cancers is the goal of prostate cancer screening. For cancer screening to be beneficial, it must reliably detect cancer at an early stage, and identify those cancers that would benefit from an early intervention to decrease mortality. Whether prostate cancer screening fits these criteria has generated considerable controversy.[18,19] Digital rectal examination (DRE) has been a recommended prostate cancer screening method since the early 1900s. Primary advantages of DRE include specificity for detecting prostate cancer (> 85%), low cost, safety, and ease of performance. However, DRE has only moderate sensitivity (approximately 60%), and is subject to interclinician variability. LO 2

KEY CONCEPT Prostate-specific antigen (PSA) is a useful marker for detecting prostate cancer at early stages, predicting outcome for localized disease, monitoring disease-free status, and monitoring response to treatment of advanced-stage disease. PSA is a member of the human kallikrein gene family of serine proteases. PSA is produced by columnar secretory cells in the prostate, and plays a role in the liquefaction of seminal fluid. PSA levels are detected via a blood test, and levels greater than 10 ng/mL (mcg/L) are associated with prostate cancer. While the relative ease and noninvasive nature of the PSA test make it the preferred method for screening, the low specificity for prostate cancer detection is a significant limitation.[20,21] In addition to patients with prostate cancer, PSA may also be elevated in men who are smokers, cases of acute urinary retention, acute prostatitis, and prostatic ischemia or infarction, as well as in patients with BPH (an extremely common condition in men at risk for prostate cancer). PSA elevations between 4.1 and 10 ng/mL (mcg/L) cannot distinguish between BPH and prostate cancer, which limits the utility of PSA alone for the early detection of prostate cancer. Additionally, not all men with clinically significant prostate cancer have a serum PSA outside of the reference range.[18] LO 2

Chemoprevention

The use of 5-α-reductase inhibitors, such as finasteride and dutasteride, as chemopreventive strategies for prostate cancer has been debated for many years.[22,23] Both type I and II 5-α-reductase isoenzymes have been implicated in prostate cancer development. Finasteride selectively inhibits the 5-α-reductase type-II isoenzyme, whereas dutasteride inhibits both type I and type II.[13] Both finasteride and dutasteride can falsely lower PSA by approximately 50%, which should be a consideration for clinicians initiating these medications. Although no prospective studies have validated PSA monitoring thresholds in patients receiving 5-α-reductase inhibitors, the PSA threshold can be lowered by 50% (eg, a PSA of 4 ng/mL [mcg/L] for a patient receiving dutasteride which would be equivalent to a PSA of 8 ng/mL [mcg/L] for a patient not prescribed a 5-α-reductase inhibitor).

Data regarding the effectiveness of finasteride and dutasteride on reducing the risk of prostate cancer were assessed in individual studies, and then later evaluated in a comprehensive Cochran Review of 41,638 patients.[22] The use of 5-α-reductase inhibitors reduced the risk of prostate cancer by 25%, when compared to placebo; however, patients who were diagnosed with prostate cancer presented with higher-grade (Gleason 7–10) prostate tumors, when compared to those diagnosed from the placebo arm. Adverse effects observed more commonly in the 5-α-reductase inhibitor treatment arms included: decreased libido, erectile dysfunction, and gynecomastia.

Based on the risk of development of more aggressive prostate tumors, combined with a lack of overall survival benefit and increased risk of adverse effects, the use of 5-α-reductase inhibitors for prostate cancer prevention is not recommended. The American Society of Clinical Oncology and the American Urological Association (AUA) guidelines recommend that asymptomatic men who have a PSA of 3 ng/mL or less, and continue to be screened with regular PSA levels, may benefit from a discussion of both the benefits (eg, possible reduced risk of prostate cancer) and potential risks (eg, adverse effects and the possibility of high-grade tumors) of 5-α-reductase inhibitor therapy.[24] Patients who are prescribed 5-α-reductase inhibitors for benign conditions (eg, lower urinary tract symptoms) may benefit from a similar discussion.

Benefits related to prostate cancer screening remain controversial. PSA measurements can identify small, subclinical prostate cancers, where no intervention may be required. Detecting prostate cancer in those not needing therapy can subject patients to unnecessary health care costs, invasive diagnostic workups, and psychological stress that are related to a potential cancer diagnosis.[19] The AUA does not recommend routine screening for patients with average risk who are between 40 and 54 years old. For men between the ages of 55 and 69 years, the AUA recommends that clinicians discuss the risks and benefits of screening with their patients.[25] In 2018, the US Preventive Task Force recommended that men age 55 to 69 make an individual decision about prostate cancer screening with their clinician (recommendation grade C), and recommended against routine screening for men age 70 and older (recommendation grade D).[26]

CLINICAL PRESENTATION AND DIAGNOSIS (TABLE 92–3)

KEY CONCEPT The prognosis for patients with prostate cancer depends on the histologic grade and stage of the prostate cancer. Details of staging are discussed in Chapter 88. One of the most

Table 92–3

Diagnostic and Staging and Classification Systems Workup for Prostate Cancer

Initial tests	DRE PSA TRUS (if either DRE is positive or PSA is elevated) Biopsy
Staging tests	Gleason score on biopsy specimen Bone scan CBC Liver function tests Serum phosphatases (acid/alkaline) Excretory urography Chest x-ray
Additional staging tests (dependent on tumor classification, PSA, and Gleason score)	Skeletal films Lymph node evaluation Pelvic CT ^{111}In-labeled capromab pendetide scan Bipedal lymphangiogram Transrectal MRI

CBC, complete blood count; CT, computed tomography; DRE, digital rectal examination; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TRUS, transrectal ultrasonography.

important prognostic criteria appears to be the histologic grade, assessed by Gleason score, because poorly-differentiated tumors ultimately impact disease staging. Poorly-differentiated tumors are highly associated with both regional lymph node involvement and distant metastases.[12] Once the tumor has spread into regional lymph nodes, there is a significantly increased risk of disease recurrence after curative intent therapy.[23]

TREATMENT

Desired Outcome

The desired outcome in early-stage prostate cancer is to minimize morbidity and mortality from prostate cancer, with an acceptance that some degree of morbidity may occur as a result of treatment.[27,28] Early-stage disease may be treated with surgery, radiation, or observation/active surveillance. Although surgery and radiation are curative, they are associated with significant morbidity. Because the overall goal is to minimize morbidity and mortality associated with the disease, observation/active surveillance are appropriate in selected individuals who wish to avoid morbidity, or for whom aggressive interventions may not be clinically appropriate (eg, comorbid conditions). Advanced prostate cancer, where there is evidence of metastatic spread, is not curable. Treatment of advanced disease should focus on providing symptom relief and maintaining quality of life. The cornerstone treatment for advanced prostate cancer is ADT, with the goal of reducing testosterone to castration levels through surgical or chemical treatment modalities.

LO 3 LO 4

Clinical Presentation of Prostate Cancer

Localized Disease

Asymptomatic

Locally Invasive Disease

Ureteral dysfunction, frequency, hesitancy, and dribbling

Impotence

Advanced Disease

Back pain

Cord compression

Lower extremity edema

Pathologic fractures

Anemia

Weight loss

General Approach to Treatment

The initial treatment for prostate cancer depends on the disease stage, Gleason score, presence of symptoms, and life expectancy of the patient.[21,28] Asymptomatic patients with a very low risk of recurrence, defined as a T_{1c} tumor, with a Gleason score 2 to 6, and PSA less than 10 ng/mL (mcg/L), may be managed by observation if their life expectancy is less than 10 years, or active surveillance if their life expectancy is between 10 and 20 years. Radiation therapy (external beam or brachytherapy), radical prostatectomy (with or without a pelvic lymph node dissection [PLND]), or active surveillance may be offered to patients with a life expectancy greater than 20 years (Table 92–4).[27,28] Because

LO 3 LO 3

Table 92–4

Management of Prostate Cancer with Very Low, Low, and Intermediate Recurrence Risk

Recurrence Risk	Expected Survival (years)	Initial Therapy
Very Low		
T_{1c} and Gleason ≤ 6 and PSA < 10 ng/mL (mcg/L) and < 3 biopsy cores positive with ≤ 50% cancer in each core and PSA density < 0.15 ng/mL/g	< 10 10–20 20 or more	Observation Active surveillance Active surveillance or RP with or without PLND or radiation therapy
Low		
T_1-T_{2a} and Gleason ≤ 6 and PSA < 10 ng/mL (mcg/L)	< 10 10 or more	Observation Active surveillance or RP with or without PLND or radiation therapy
Intermediate		
T_{2b}-T_{2c} or Gleason 7 or PSA 10–20 ng/mL (mcg/L)	< 10 10 or more	Observation or radiation therapy with or without 4–6 months of ADT RP with or without PLND or radiation therapy with or without 4–6 months of ADT

ADT, androgen deprivation therapy; PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; RP, radical prostatectomy.

Patient Encounter 2: Early Stage Disease

A 62-year-old man was found to have an abnormal DRE. His PSA was found to be elevated at 7 ng/mL. A prostate biopsy was performed by TRUS that reveals adenocarcinoma with a Gleason score of 5 (2+3) and is staged as T_{2a} (tumor involves less than one-half of a lobe of the prostate). He has a past medical history of hypertension but is otherwise healthy. He expresses a wish to pursue aggressive therapy.

How would you stratify this patient's risk of developing progressive or metastatic prostate cancer?

What treatment options are available to this patient?

What patient-specific factors would you consider when choosing a treatment?

patients with asymptomatic, early-stage disease generally have an excellent 10-year survival rate, the immediate morbidities associated with prostatectomy or radiation must be balanced with the lower likelihood of dying from prostate cancer. In general, more aggressive treatments for early-stage prostate cancer are reserved for younger men, although patient preference is a major consideration in all treatment decisions.

Radical prostatectomy and radiation therapy are generally considered therapeutically equivalent for localized prostate cancer.[27] Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve-sparing radical prostatectomy can be performed in many patients; and 50% to 80% regain sexual potency within the first year. Acute complications from radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence (30% incidence).[12,27] Chronic complications include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.[12] Because radiation and prostatectomy have significant and immediate morbidity compared with observation alone, some patients may elect to postpone therapy until they become symptomatic.

Patients with a low risk of recurrence, defined as T_1-T_{2a} tumors, a Gleason score of 2 to 6 and PSA less than 10 ng/mL (mcg/L), may be managed by observation if their life expectancy is less than 10 years. If their life expectancy is 10 years or greater, they may be offered radiation therapy, radical prostatectomy (with or without PLND), or active surveillance (see Table 92–4). LO 3

Patients with an intermediate risk of recurrence, defined as T_{2b}-T_{2c} tumors, or a Gleason score of 7, or PSA ranging from 10 to 20 ng/mL (mcg/L), may be managed by observation (with or without 4–6 months of ADT). Patients with life expectancy of 10 years or greater may be offered either radical prostatectomy (with or without PLND), or radiation therapy (with or without 4–6 months of ADT) (see Table 92–4).[28] LO 3 LO 4

Patients at high risk of recurrence, defined as T_3 tumors, or Gleason score of 8 to 10, or PSA greater than 20 ng/mL (mcg/L), may be managed with 2 to 3 years of ADT with radiation therapy (Table 92–5). Selected individuals with a low tumor volume may receive a radical prostatectomy (with or without PLND).[28] LO 3 LO 4

Patients at very high risk of recurrence, with locally advanced disease, defined as T_{3b}-T_4 tumors, or tumors with a primary Gleason pattern of 5, or greater than 4 biopsy cores with Gleason 8 to 10, may be managed with ADT monotherapy, radiation and 2 to 3 years of ADT, or a radical prostatectomy (with or without PLND). However, these patients are not often candidates for radical prostatectomy because of extensive local spread of the disease (see Table 92–5).[28] KEY CONCEPT Androgen deprivation with an LHRH agonist should be used with radiation therapy for patients with locally advanced prostate cancer to improve outcomes over radiation therapy alone. Patients at very high risk of recurrence due to nodal spread of disease may be managed with 2 to 3 years of ADT (with or without radiation), while patients at very high risk of recurrence due to evidence of distant metastases may be managed with ADT only (see Table 92–5).[28]

Table 92–5

Management of Prostate Cancer with High and Very High Recurrence Risk

Recurrence Risk	Initial Therapy
High	
T_{3a} or Gleason 8–10, PSA > 20 ng/mL (mcg/L)	ADT[a] (2–3 years) and radiation therapy or RP with or without PLND
Very High (Locally Advanced)	
T_{3b}–T_4 or primary Gleason pattern 5 or > 4 cores with Gleason 8–10	ADT[b] (for patients who are not candidates for definitive therapy) or radiation therapy + ADT (2–3 years), RP with PLND
Metastatic	
Any T, $N_{1, M0}$	ADT +/– abiraterone, radiation therapy + ADTA +/– abiraterone
Any T, Any N, M_1	ADT, ADT + abiraterone, ADT + docetaxel

[a]ADT = serum testosterone levels < 50 ng/dL (1.74 nmol/L).

[b]Medical, or surgical ADT are equivalent.

ADT, androgen deprivation therapy; LHRH, luteinizing hormone–releasing hormone; PLND, pelvic lymph node dissection; RP, radical prostatectomy.

KEY CONCEPT Androgen deprivation therapy, with either orchiectomy, an LHRH agonist alone, or an LHRH agonist plus an antiandrogen (combined androgen blockade) can be used to provide palliation for patients with advanced prostate cancer. Secondary hormonal manipulations, therapies that target the AR signaling axis, cytotoxic chemotherapy, immunotherapy, radiopharmaceutical therapy, or best supportive care are used for patients who progress after initial therapy.[26] LO 7

Nonpharmacologic Therapy

▶ *Observation/Active Surveillance*

Observation involves monitoring the course of disease and initiating palliative treatment if the cancer progresses, or the patient becomes symptomatic. PSA and DRE testing are performed every 6 to 12 months, but invasive biopsies are not performed if progression is suspected. The goal of observation is to maintain quality of life in the setting of a prostate cancer diagnosis, and is most appropriate in elderly, frail men with

limited life expectancy. In subtle contrast, patients treated with active surveillance have the intent of initiating curative treatment approaches should the cancer appear to progress. PSA and DRE testing are performed every 6 to 12 months, and prompt biopsies are indicated if progression is expected. Active surveillance is employed in younger patients with long life expectancies who want to delay the morbidity associated with curative treatments, such as surgery, radiation, or ADT.

▶ *Orchiectomy*

Bilateral orchiectomy, or surgical removal of the testes, is a form of ADT that rapidly reduces circulating androgens to castration levels (ie, serum testosterone levels < 50 ng/dL [1.7 nmol/L]).[27,28] However, many patients find this procedure psychologically unacceptable, while others are simply not surgical candidates because of age. Orchiectomy may be the preferred initial treatment for patients with impending spinal cord compression or ureteral obstruction.

▶ *Radiation*

The two commonly used methods for radiation therapy are **external beam radiotherapy (EBRT)** and **brachytherapy**.[27–29] In EBRT, doses of 75 to 79 Gray (Gy) are delivered in 35 to 41 fractions in patients with low-grade prostate cancer and up to 81 Gy for those with intermediate- or high-grade prostate cancer. Brachytherapy involves the permanent implantation of radioactive beads of 145 Gy of ^{125}iodine or 125 Gy of ^{103}palladium, and is generally reserved for individuals with low-risk cancers. Radiation therapy may be used to treat local, or locally advanced prostate cancer with curative intent. In later stages of disease, short courses of EBRT can be used to palliate symptoms.[28,29]

▶ *Radical Prostatectomy*

Radical prostatectomy is performed in patients with resectable disease who are surgical candidates, and who require definitive therapy based on both risk factors and patient preference. Complications from radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence.

Pharmacologic Therapy for Early-Stage Disease

LO 4

▶ *Luteinizing Hormone-Releasing Hormone Agonists*

LHRH agonists are a reversible method of ADT and are as effective as orchiectomy in treating prostate cancer.[27,30] Currently, the list of approved LHRH agonists include leuprolide, leuprolide depot, leuprolide implant, triptorelin depot, triptorelin implant, histrelin LA, and goserelin acetate implant. Leuprolide can be administered every 4, 12, 16, or 24 weeks; gosrelin every 4 or 12 weeks; triptorelin every 4, 12, or 24 weeks; and histrelin every 12 months. The leuprolide depot formulation contains leuprolide acetate in coated pellets. The dose is administered intramuscularly, and the coating dissolves at different rates to allow sustained leuprolide levels throughout the dosing interval. The goserelin implant contains goserelin acetate dispersed in a plastic matrix of D,L-lactic and glycolic acid copolymer, and is administered subcutaneously. Hydrolysis of the copolymer material provides continuous release of goserelin over the dosing period. Triptorelin LA is administered as an intramuscular injection (11.25 mg) every 84 days. Triptorelin depot is a 3.75 mg formulation injected every 28 days. Histrelin LA is surgically implanted every 12 months.

Several randomized trials have demonstrated that leuprolide, goserelin, histrelin, and triptorelin are effective agents when used alone in patients with advanced prostate cancer.[16] Response rates of approximately 80% have been reported. The choice between the four LHRH agonists is usually made on the basis of cost, as well as patient and prescriber administration schedule preferences.

LO 6

The most common adverse effects reported with LHRH agonist therapy include vasomotor symptoms, such as hot flashes, erectile dysfunction, decreased libido, and injection site reactions. Long-term adverse effects include decreased bone mineral density and metabolic syndrome.[29] Disease flare within the first week of therapy can be caused by an initial induction of LH and FSH that is induced by the LHRH agonist, leading to an initial period of increased testosterone production. Tumor flare manifests clinically as an exacerbation of disease-related symptoms, primarily increased bone pain or urinary symptoms.[27] The reaction usually resolves after 2 weeks and has a similar onset and duration pattern for the various depot LHRH agonist formulations. Initiating an antiandrogen (see Table 92–2) prior to LHRH agonist administration, and continuing for 2 to 4 weeks, is a frequently used strategy to minimize initial tumor flare.

LHRH agonist monotherapy can be used as initial therapy of advanced prostate cancer, with response rates similar to orchiectomy.[27] A lower incidence of cardiovascular-related adverse effects associated with LHRH agonist therapy has been observed, when compared to estrogens. Patients should be advised that a tumor flare could occur in the first week, but could be mitigated by the addition of an antiandrogen during that period. Caution should be exercised if initiating LRHH agonists in patients with the potential for ureteral obstruction or spinal cord impingement because irreversible complications may occur.

LO 5

Another potentially serious complication of ADT is a resultant decrease in bone-mineral density, leading to an increased risk for osteoporosis, osteopenia, and an increased risk for skeletal fractures.[31] Men initiated on long-term ADT should generally have a baseline bone mineral density test, and be initiated on calcium and vitamin D supplementation.[28]

LO 5

▶ *Gonadotropin-Releasing Hormone Antagonists*

An alternative to LHRH agonists is the GnRH antagonist, degarelix.[32] Degarelix reversibly binds to GnRH receptors on cells in the pituitary gland, reducing the production of testosterone to castration levels. The major advantage of direct GnRH antagonists is the speed at which they can achieve the drop in testosterone levels; castration levels are achieved in 7 days or less with degarelix (compared against 28 days with leuprolide), which eliminates the risk of tumor flare and the need to initiate a concomitant antiandrogen. Degarelix is equivalent to leuprolide in lowering testosterone levels for up to 1 year, and is approved for the treatment of advanced prostate cancer. Degarelix is available as 40 mg/mL (mcg/L) and 20 mg/mL (mcg/L) vials for subcutaneous injection, and the starting dose is 240 mg followed by 80 mg every 28 days. The starting dose should be split into two 120 mg injections.

LO 6

The most frequently reported adverse effects include injection site reactions, including pain, erythema, swelling, induration, and nodules. Most adverse effects are transient and mild to moderate, leading to discontinuation in less than 1% of patients. Other adverse effects include liver function test (LFT) elevations and

Table 92–6

First-Generation Antiandrogens

Antiandrogen	Usual Dose	Adverse Effects
Flutamide	750 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness Methemoglobinemia
Bicalutamide	50 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (diarrhea) Liver function test abnormalities Breast tenderness
Nilutamide	300 mg/day for first month; then 150 mg/day	Gynecomastia Hot flushes Gastrointestinal disturbances (nausea or constipation) Liver function test abnormalities Breast tenderness Visual disturbances (impaired dark adaptation) Alcohol intolerance Interstitial pneumonitis

LO 5 osteoporosis. Because of the risk for developing osteoporosis, calcium and vitamin D supplementation should be considered. Degarelix is not approved in combination with antiandrogens.

▶ *Antiandrogens*

Antiandrogens bind cytosolic AR, thereby decreasing available binding sites for endogenous androgens to activate the AR. First-generation nonsteroidal antiandrogens are flutamide, bicalutamide, and nilutamide (Table 92–6). Monotherapy with first-generation antiandrogens is less effective than LHRH agonist therapy. Therefore, for advanced prostate cancer, all currently available antiandrogens are indicated only in combination with ADT: flutamide and bicalutamide are indicated in combination with an LHRH agonist, while nilutamide is indicated after orchiectomy.

LO 6 The most common antiandrogen-related adverse effects are listed in Table 92–6. Diarrhea is reported more frequently with flutamide than bicalutamide. Few clinical trials have been conducted to directly compare the first-generation antiandrogens.[28]

▶ *Combined Androgen Blockade*

Although up to 80% of patients with advanced prostate cancer respond to initial hormonal manipulation, almost all patients progress within 2 to 4 years after initiating therapy. Two main mechanisms of androgen reactivation have been proposed: (1) the tumor could be heterogeneously composed of cells that are hormone dependent and hormone independent, or (2) the tumor could be stimulated by extratesticular androgens (including intratumoral synthesis of androgens) that are converted intracellularly to DHT. Combined androgen blockade (CAB), which is the combination of LHRH agonists or orchiectomy with first-generation antiandrogens, aims to interfere with multiple hormonal pathways to more completely ablate androgens.

Many studies have been performed comparing CAB with conventional medical or surgical castration. A meta-analysis of 27 trials revealed a small (3.2%), but statistically significant, improvement in 5-year survival for patients treated with CAB, when compared to ADT alone.[33] However, adverse effects are far more common in patients who receive CAB, and include diarrhea, LFT elevations, and anemia. Because the benefits of CAB are relatively small, and the increased adverse effects are not insignificant, it is appropriate to use either LHRH agonist monotherapy or CAB as initial therapy for metastatic prostate cancer. CAB may be most beneficial for improving survival in patients with minimal disease and for preventing tumor flare.[27,28]

LO 5 All other patients may be started on LHRH agonist monotherapy, and an antiandrogen may be added after several months if androgen ablation is incomplete, or if disease progression occurs despite a castration level of testosterone.[34]

There is considerable debate about when to start ADT in advanced prostate cancer patients.[16] The original recommendation to start therapy when symptoms appeared was based on trials that revealed no overall survival difference between patients who started diethylstilbestrol (DES) initially versus those who crossed over to DES treatment when symptoms arose. More recent data demonstrates that early intervention, before symptoms appear, may be appropriate; however, this continues to be balanced by patient goals and quality of life considerations.[35]

Given the morbidity of ADT, intermittent dosing strategies that allow for a break in therapy to restore quality of life (and some suggest possibly resensitize cancer cells to hormonal blockade) have been investigated. A meta-analysis of 15 separate studies representing over 6000 patients found intermittent ADT noninferior for overall survival and revealed some improvements in quality of life scores, when compared to continuous ADT dosing.[36] Intermittent ADT should be considered in men who experience significant adverse effects from ADT, and who are willing to undergo more frequent PSA and testosterone monitoring during off-treatment periods.

Pharmacologic Therapies in Metastatic and Refractory Disease

Treatment of men who present with highly aggressive or metastatic disease may involve combinations of ADT with

Patient Encounter 3: Presentation of Metastatic Disease

A 58-year-old man presents to the clinic for follow-up of routine DRE and PSA screening tests. Physical examination is positive for a 1-cm nodule in the prostate, and his laboratory results reveal the following: PSA, 22 ng/mL (mcg/L); PSA from 2 years ago was 2.4 ng/mL (mcg/L). A prostate biopsy by TRUS reveals adenocarcinoma of the prostate with a Gleason score of 7 (3+4). A CT scan and bone scan reveal metastatic disease to regional lymph nodes and the lumbar vertebrae, respectively.

Based on his metastatic disease, what are treatment options for this patient?

second generation antiandrogens or cytotoxic chemotherapy. Secondary (or salvage) therapies for patients who progress after their initial treatments depend on the treatment modalities initially employed. For patients diagnosed with localized prostate cancer, radiotherapy may be used for local disease recurrence after radical prostatectomy. Alternatively, ADT can be used in patients who progress after either radiation therapy or radical prostatectomy.[34]

In patients treated initially with ADT only, secondary hormonal manipulations may be considered. This may include adding an antiandrogen for a patient who either incompletely suppresses testosterone secretion with an LHRH agonist or experiences disease progression after castration levels of testosterone have been previously achieved. In patients who progress during CAB, withdrawing antiandrogens, or using agents that inhibit the AR signaling axis may be considered.[34]

KEY CONCEPT Antiandrogen withdrawal can provide additional symptomatic relief for patients who progress while receiving combined hormonal blockade with an LHRH agonist and an antiandrogen. For patients who receive CAB with an LHRH agonist with an antiandrogen, antiandrogen withdrawal can be the first salvage manipulation.[28,34] Somatic genetic mutations in *AR* arise in patients treated with antiandrogens, and cause these agents to exhibit receptor agonist properties. Objective and subjective responses have been reported in patients following antiandrogen discontinuation from their CAB regimen. Patient responses to antiandrogen withdrawal manifest as significant PSA reductions and improved clinical symptoms. Antiandrogen withdrawal responses lasting 3 to 14 months have been reported in up to 35% of patients, and patient responses seem to closely correlate with longer antiandrogen exposure times. Incomplete cross-resistance has been noted in select patients who received bicalutamide after they had progressed on flutamide, which suggests that patients who fail one antiandrogen may still respond to another agent.[34]

KEY CONCEPT When advanced prostate cancer progresses, despite castration levels of testosterone, it is known as CRPC. For patients who initially received an LHRH agonist alone, castration testosterone levels should be documented. Patients with inadequate testosterone suppression (eg, levels > 20 ng/dL [0.7 nmol/L]) can be treated by adding an antiandrogen, or performing an orchiectomy. If castration testosterone levels have been achieved, but symptoms of progression are evident or a PSA rise is observed, the patient's disease is considered to have progressed to CRPC. Because androgens remain a growth signal for the cancer, ADT is continued throughout the treatment course of CRPC, and the cancer may continue to respond to treatments that target the AR signaling axis (eg, enzalutamide or abiraterone).

LO 7 KEY CONCEPT Second-generation therapies that target the AR signaling axis, such as abiraterone and enzalutamide, improve survival in patients with metastatic CRPC (mCRPC). They can both be considered as first-line therapies for mCRPC, or after disease progression following chemotherapy with docetaxel.

Second-Generation Antiandrogen

Despite initial responses to ADT and first-generation antiandrogens, disease progression eventually occurs. Enzalutamide is a second-generation antiandrogen that is effective in mCRPC, even when first-generation antiandrogens have failed. This may be because enzalutamide prevents the AR from translocating into the cell nucleus, further inhibiting androgen signaling. Enzalutamide is an effective first-line treatment option in chemotherapy naive patients, as well as a viable second-line option in patients that have failed prior to docetaxel chemotherapy.[37,38] Enzalutamide improves overall survival in mCRPC, when compared to placebo. Primary adverse effects include fatigue, diarrhea, hot flashes, musculoskeletal pain, and hepatotoxicity (ie, LFT elevations).[37,38] Seizures and posterior reversible encephalopathy syndrome are rare but serious adverse effects. Enzalutamide is a strong inducer and inhibitor of CYP3A4, as well as a moderate inducer and inhibitor of both CYP2C9 and CYP2C19, so drug–drug interactions are a consideration.

LO 7 LO 8 LO 9 LO 8

Patient Encounter 4: Progressive Disease

A 66-year-old man was initially diagnosed with metastatic prostate cancer 5 years ago. He was initiated on ADT (leuprolide), but his treatment summary (discussed next) provides evidence of suspected disease progression. Today, he presents to the clinic with bone pain and a serum PSA of 67 ng/mL (mcg/L). A bone scan reveals evidence of new osseous metastases.

Treatment Summary

Date	PSA	Intervention
1/10/16	25 ng/mL (mcg/L)	Leuprolide initiated (7.5 mg IM monthly)
3/10/16	21 ng/mL (mcg/L)	Leuprolide continued
6/2/16	22 ng/mL (mcg/L)	Bicalutamide added (50 mg PO daily)
9/2/16	5 ng/mL (mcg/L)	Leuprolide and bicalutamide continued
10/2/16	12 ng/mL (mcg/L)	Leuprolide continued; bicalutamide discontinued
11/1/16	7 ng/mL (mcg/L)	Leuprolide continued, but new dose initiated (22.5 mg IM every 3 months)
2/2/17	5 ng/mL (mcg/L)	Leuprolide continued
5/1/17	12 ng/mL (mcg/L)	Leuprolide continued
8/2/17	27 ng/mL (mcg/L)	Leuprolide continued, but patient to be seen 1 month

Why was bicalutamide initiated on 6/2/16, and why was it likely discontinued on 10/2/16?

How would you characterize this patient's disease?

What pharmacotherapeutic options are available to the patient?

Androgen Synthesis Inhibitors

Despite ADT, androgen synthesis can continue to occur in the periphery (eg, adrenal glands) or via intratumoral synthesis. Cytochrome P450 enzymes play a critical role in androgen synthesis. CYP17A1 inhibition prevents the conversion of pregnenolone to DHEA, a requisite precursor for testosterone. Abiraterone acetate is a potent and specific inhibitor of CYP17A1, resulting in further testosterone reductions, when combined with continued ADT. Abiraterone has demonstrated benefit in combination with ADT in hormone-sensitive prostate cancer as initial treatment, as well as in mCRPC.[28,39,40] Inhibition of CYP17A1 can result in mineralocorticoid excess, which underlies

many of the adverse effects associated with abiraterone, and is the reason why it is prescribed concomitantly with twice daily prednisone (prednisone serves to prevent activation of a response to perceived cortisol deficit via negative feedback). Symptoms of mineralocorticoid excess include fluid retention, hypokalemia, and hypertension. Hepatotoxicity (eg, LFT abnormalities) is a less common but sometimes severe adverse effect. Abiraterone should be administered on an empty stomach (1 hour before or 2 hours after a meal), as food significantly increases absorption. As a CYP3A4 substrate, abiraterone should be used cautiously with concomitant CYP3A4 inhibitors and inducers (Table 92–7).

Androgen synthesis inhibitors, such as aminoglutethimide 250 mg orally every 6 hours or ketoconazole 400 mg orally three times daily, can provide symptomatic relief for a short time in approximately 50% of patients with progressive disease despite previous ADT.[41] Adverse effects during aminoglutethimide therapy occur in approximately 50% of patients. Central nervous system effects that include lethargy, ataxia, and dizziness are the major adverse effects. A generalized morbilliform, pruritic rash has been reported in up to 30% of patients. The rash is usually self-limiting and resolves within 5 to 8 days with continued therapy. Adverse effects from ketoconazole include diarrhea, transient rises in liver and renal function tests, and hypoadrenalism. Additionally, ketoconazole is a strong inhibitor of CYP1A2 and CYP3A4. Ketoconazole absorption requires gastric acidity; therefore, ketoconazole should not be administered with H_2-blockers, proton pump inhibitors, or antacids. Ketoconazole should be combined with hydrocortisone to prevent symptomatic hypoadrenalism.[28]

KEY CONCEPT Chemotherapy with docetaxel and prednisone improves survival in patients with mCRPC. Chemotherapy with cabazitaxel and prednisone improves survival in patients with mCRPC who have either progressed on or are intolerant to docetaxel.

▶ *Chemotherapy*

Docetaxel is an antimicrotubule taxane, which has been shown to improve survival in mCRPC patients when administered at 75 mg/m^2 every 3 weeks, and combined with twice daily prednisone.[42] More recently, docetaxel in combination with ADT has demonstrated improved overall survival in hormone-sensitive prostate cancer, and is an option in metastatic patients who are treatment naive.[28] The most common adverse effects include nausea, alopecia, bone marrow suppression, fluid retention, and peripheral neuropathy. Docetaxel undergoes extensive hepatic metabolism; patients with hepatic impairment may not be eligible for treatment with docetaxel due to an increased risk for adverse effects (Table 92–8).

Cabazitaxel is also an antimicrotubule taxane with demonstrated activity in docetaxel-resistant cell lines and animal models of human cancer. Low-affinity for the P-glycoprotein efflux transporter, when compared to docetaxel, could conceivably be

Patient Encounter 5: Metastatic Castration Resistance Prostate Cancer

An 80-year-old man has metastatic prostate cancer, with evidence of bone metastases on bone scan. He has a PMH significant for hypertension (controlled on lisinopril), restless leg syndrome (untreated, but currently controlled), and a mechanical mitral valve replacement in 2009 (currently receiving warfarin).

He has received leuprolide acetate 22.5 mg subcutaneously every 3 months for the last 4 years, but recently his medical oncologist observed a biochemical recurrence (PSA rise with rapid doubling time) despite castration level testosterone. It was determined that his prostate cancer was now castration resistant, and he presents to clinic today with symptomatic bone metastases. Notably, a recent ECHO revealed an ejection fraction of 33%.

Which available pharmacotherapeutic options would be preferable for this patient?

Are there any pertinent drug–drug interactions that should be considered with the pharmacotherapy you have selected for this patient?

Table 92–7

AR Axis Targeted Therapies for Metastatic Castration Resistant Prostate Cancer

Drug	Usual Dose	Adverse Effects	Dose Adjustments
Androgen Synthesis Inhibitor			
Abiraterone	1000 mg/day	Gastrointestinal disturbances (diarrhea), edema, hypokalemia, hypophosphatemia, hypertension, LFT abnormalities, hypertriglyceridemia	*Hepatic* Reduce starting dose to 250 mg/day for moderate hepatic impairment (Child-Pugh class B), and avoid in Child Pugh class C; withhold treatment if AST/ALT > 5 × ULN or bilirubin > 3 × ULN; *DDI* Use cautiously with concomitant CYP3A4 inhibitors and inducers
Second Generation Antiandrogen			
Enzalutamide	160 mg/day	Gastrointestinal disturbances (diarrhea), musculoskeletal issues (eg, arthralgias and myalgias), asthenia, fatigue, peripheral edema, LFT abnormalities, seizures, PRES	*No renal or hepatic dose adjustments* *DDI* Strong CYP3A4 inducer Moderate CYP2C9 and CYP2C19 inducer Avoid CYP3A4, CYP2C9, and CYP2C19 sensitive substrates Avoid strong inducers and inhibitors of CYP2C8

ALT, alanine aminotransferase; AR, androgen receptor; AST, aspartate aminotransferase; CYP, cytochrome P450; DDI, drug–drug interaction; PRES, posterior reversible encephalopathy syndrome; ULN, upper limit of normal.

Table 92–8

Chemotherapy and Immunotherapy for Metastatic Castration Resistant Prostate Cancer

Drug	Usual Dose	Adverse Effects	Dose Adjustments
Antimicrotubule Agents			
Docetaxel	75 mg/m^2 IV every 3 weeks	Fluid retention, alopecia, mucositis, myelosuppression, hypersensitivity	*Hepatic* Do no administer if AST/ALT > 1.5 × ULN and ALP > 2.5 ULN *DDI* Avoid concomitant use of CYP3A4 inhibitors *Hematologic* Ensure CBC recovery prior to administration
Cabazitaxel	20 mg/m^2 IV every 3 weeks	Fluid retention, constipation, mucositis, myelosuppression, hypersensitivity	*Hepatic* Discontinue if patient ALT > 2 × ULN, or if patient develops jaundice *DDI* Avoid concomitant use of CYP3A4 inhibitors and inducers *Hematologic* Ensure CBC recovery prior to administration
Immunotherapy			
Sipuleucel-T	> 50 million autologous CD54+ cells obtained from leukapheresis. CD54+ cells are activated with PAP-GM-CSF. 3 total doses given.	Hypersensitivity, chills, fever, fatigue, headache, and myalgias	*No renal or hepatic dose adjustments* *DDI* The use of immunosuppressants may lessen the therapeutic effects of sipuleucel-T

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; CYP, cytochrome P450; DDI, drug–drug interaction; IV, intravenous; PAP-GM-CSF, prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor; ULN, upper limit of normal.

the reason why cabazitaxel remains effective in the setting of docetaxel resistance. In docetaxel-pretreated patients, cabazitaxel (25 mg/m^2 every 3 weeks with prednisone 10 mg/daily) significantly improved progression-free survival and overall survival compared with mitoxantrone and prednisone.[43] Recently, the cabazitaxel dose was reduced to 20 mg/m^2 every 3 weeks based on evidence of similar efficacy but better tolerability, when compared to 25 mg/m^2.[44] The most significant adverse effects associated with cabazitaxel include neutropenia, neuropathy, and diarrhea. Hypersensitivity reactions can occur with cabazitaxel, so premedication with an antihistamine, corticosteroid, and H_2 antagonist is recommended. Cabazitaxel undergoes extensive hepatic metabolism, and should be avoided in patients with hepatic dysfunction. Cabazitaxel is a CYP3A4 substrate, so concomitant use of CYP3A4 inhibitors and inducers should be avoided (see Table 92–8).

LO 9 LO 8

► *Immunotherapy*

LO 7

Sipuleucel-T is an autologous immunotherapy that was approved for patients with asymptomatic or minimally symptomatic mCRPC.[45] Eligible patients first undergo leukapheresis to collect peripheral blood mononuclear cells (the cellular fraction that contains dendritic cells), which are sent to a central processing laboratory. These are stimulated with a fusion protein of prostatic acid phosphatase (PAP) and granulocyte macrophage colony-stimulating factor (GM-CSF). PAP is a specific tumor antigen, while GM-CSF is an immune cell activator. The cultured cells are then returned and infused into the patient. This procedure is performed every 2 weeks for a total of three treatments. Adverse effects associated with sipuleucel-T are generally mild to moderate, and include transient chills, fever, and headache (see Table 92–8). Sipuleucel-T was shown to improve overall survival, when compared to placebo.[45] Despite a modest improvement in survival, sipuleucel-T did not decrease the time to disease progression, and thus does not offer significant relief from disease-related symptoms. It is not appropriate in symptomatic patients with rapidly progressing disease for whom treatments that delay tumor progression are feasible.

LO 9

► *Bone Protective Therapies*

LO 7

Radium-223 is an alpha particle-emitter and calcium-mimetic radiopharmaceutical that provides significant palliation to mCRPC patients with bone metastases.[46] Radium-223, infused every 4 weeks for six total treatments, has been shown to significantly improve overall survival, as well as skeletal pain and patient quality of life. Common adverse effects are nausea, vomiting, peripheral edema, and moderate myelosuppression. Radium-223 has been associated with lower rates of myelosuppression compared to other alpha-emitting radiopharmaceuticals. Radium-223 is appropriate for first-, second-, or third-line treatment of patients with mCRPC and symptomatic bone pain.

LO 9

Skeletal metastases from hematogenous spread are the most common sites of distant spread of prostate cancer. Typically, the bone lesions are osteoblastic or a combination of osteoblastic and osteolytic. Bisphosphonates may prevent skeletal-related events, and improve bone mineral density. Zoledronic acid, 4 mg infused every 3 weeks, reduces the incidence of skeletal-related events (such as the need for palliative radiation or pathologic fracture) by 25%, when compared to placebo.[47]

Denosumab, a monoclonal antibody targeted against the receptor activator of nuclear factor kappa-B (RANK) ligand, also decreases the incidence of skeletal-related events in mCRPC patients with bone metastases. Denosumab is a 120-mg

Patient Care Process

Collect Information:

- Obtain complete past medical history, family history, and social history.
- Obtain complete list of any concomitant prescription and over-the-counter medications; be sure to include herbal, vitamin, and mineral supplements.
- Verify completion of prostate cancer workup and staging, including PSA level, pathology results, and staging scans if indicated.
- Discuss symptom burden with the patient to identify bothersome symptoms that should be addressed by treatment plan.
- Obtain labs to evaluate organ function in order to appropriately choose therapy plan.

Assess the Information:

- Identify prognostic factors that influence the development of metastatic prostate cancer.
- Risk stratify the patient with regard to stage of disease, Gleason score, PSA level, comorbid conditions, and life expectancy.
- Assess laboratory values and organ function with regard to treatment options.
- Identify treatment-related morbidity that would be a barrier to adherence based on the patient's current symptoms and goals of care.

Develop a Care plan:

- Using cancer stage, risk level, and patient-directed goals of therapy, determine if drug therapy is indicated.
- Identify appropriate pharmacotherapy that maximizes efficacy while minimizing toxicity based on patient-specific comorbidities, organ function, and care goals.
- Assess cost of proposed therapies and ensure that they are affordable and reasonable for the patient.

Implement the Care Plan:

- Discuss the benefits and risks of appropriate treatment options with the health care team and patient.
- If drug therapy is selected, review patient medical history for drug–drug and drug–herbal interactions.
- Discuss clear goals of care with the patient.
- Initiate therapy.

Follow-up: Monitor and Evaluate:

- If patient is asymptomatic, monitor PSA and circulating androgens for castration level of testosterone. If patient is symptomatic, monitor symptoms for improvement or worsening. Obtain imaging studies to evaluate response of distant metastases.
- Monitor for any new signs or symptoms of progression, and adverse effects from therapy. Evaluate adherence to ADT. Consider intermittent ADT if patient reports intolerance or significant decrease in quality of life.
- Consider removal of antiandrogen if CAB approach is chosen and patient demonstrates progression.
- Consider PSA velocity and symptom burden when assessing for the need for treatment changes.

subcutaneous injection administered every 4 weeks. While it may cause a higher incidence of hypocalcemia compared to zoledronic acid, it also provides greater protection against skeletal-related events. Similar to zoledronic acid, patients should be counseled to supplement with calcium and vitamin D.[48] Both denosumab and zoledronic acid are associated with osteonecrosis of the jaw. Dental procedures should be avoided while receiving these agents, and dental screening prior to initiation is recommended.[49]

OUTCOME EVALUATION

LO 5 LO 8

Prostate cancer monitoring depends on the grade and stage of the cancer. When definitive, curative therapy is attempted, check objective parameters (eg, imaging studies, DRE) to assess tumor response, and monitor PSA to assess for recurrence or progression. Following definitive therapy, PSA is checked every 6 months for the first 5 years and then annually thereafter.[27,28] Local recurrence in the absence of a rising PSA may occur, so annual DRE and radiologic studies based on patient-reported symptoms are also performed. In the metastatic setting, treatments that target AR signaling and traditional chemotherapies have been shown to increase survival. Clinical efficacy is measured using imaging studies, symptom scores, weight changes, analgesic requirements, and PSA response. When using PSA as a surrogate for disease progression, it is important to consider not only the degree of elevation, but also the velocity at which the marker changes. A rapid PSA velocity has been associated with an increased risk of all-cause mortality, and should warrant consideration of therapeutic intervention. Monitoring for adverse effects is different for each treatment modality, but is similarly important.[50] For oral agents, medication adherence is also an important monitoring parameter at each clinic visit.

Abbreviations Introduced in This Chapter

ADT	Androgen deprivation therapy
AR	Androgen receptor
AUA	American Urological Association
BPH	Benign prostatic hyperplasia
CAB	Combined androgen blockade
CRPC	Castration-resistant prostate cancer
CT	Computed tomography
CYP	Cytochrome P450
DES	Diethylstilbestrol
DHT	Dihydrotestosterone
DRE	Digital rectal examination
EBRT	External beam radiation therapy
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
Gy	Gray
LFT	Liver function test
LH	Luteinizing hormone

LHRH	Luteinizing hormone–releasing hormone
mCRPC	Metastatic castration resistant prostate cancer
PAP-GM-CSF	Prostatic acid phosphatase granulocyte macrophage colony-stimulating factor
PLND	Pelvic lymph node dissection
PSA	Prostate-specific antigen
RANK	Receptor activator of nuclear factor kappa-B
SNP	Single nucleotide polymorphism
TRUS	Transrectal ultrasound

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. Brawley OW. Prostate cancer epidemiology in the United States. World J Urol. 2012;30:195–200.
3. Perez-Cornago A, Key TJ, Allen NE, et al. Prospective investigation of risk factors for prostate cancer in the UK Biobank cohort study. Br J Cancer. 2017;117(10):1562–1571.
4. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. In Vivo. 1994;8:439–443.
5. Sun JH, Lee SA. Association between CAG repeat polymorphisms and the risk of prostate cancer: a meta-analysis by race, study design and the number of (CAG)n repeat polymorphisms. Int J Mol Med. 2013;32:1195–1203.
6. Hsieh K, Albertsen PC. Populations at high risk for prostate cancer. Urol Clin North Am. 2003;30:669–676.
7. Maia S, Cardoso M, Paulo P, et al. The role of germline mutations in the BRCA1/2 and mismatch repair genes in men ascertained for early-onset and/or familial prostate cancer. Fam Cancer. 2016;15:111–121.
8. Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016;375:443–453.
9. Zheng SL, Sun J, Wiklund F, et al. Cumulative association of five genetic variants with prostate cancer. N Engl J Med. 2008;358:910–919.
10. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies. Int J Cancer. 2014;135:1884–1897.
11. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2009;301:39–51.
12. Iczkowski KA. Current prostate biopsy interpretation: criteria for cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, and use of immunostains. Arch Pathol Lab Med. 2006;130:835–843.
13. De Marzo AM, Meeker AK, Zha S, et al. Human prostate cancer precursors and pathobiology. Urology. 2003;62(5 suppl 1):55–62.
14. Nieto M, Finn S, Loda M, Hahn WC. Prostate cancer: re-focusing on androgen receptor signaling. Int J Biochem Cell Biol. 2007;39:1562–1568.
15. Culig Z. Role of the androgen receptor axis in prostate cancer. Urology. 2003;62(5 suppl 1):21–26.
16. Meani D, Solarić M, Visapää H et al. Practical differences between luteinizing hormone-releasing hormone agonists in prostate cancer: perspectives across the spectrum of care. Ther Adv Urol. 2017;10:51–63.
17. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. JAMA. 2005;294:238–244.
18. Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. JAMA. 2014;311:1143–1149.
19. Brawley OW. Prostate cancer screening: what we know, don't know, and believe. *Ann* Intern Med. 2012;157:135–136.
20. Schmid HP, Prikler L, Semjonow A. Problems with prostate-specific antigen screening: a critical review. Recent Results Cancer Res. 2003;163:226–231.
21. Cuzick J, Thorat MA, Andriole G, et al. Prevention and early detection of prostate cancer. Lancet Oncol. 2014;15: e484–e492.
22. Wilt TJ, Macdonald R, Hagerty K, et al. 5-alpha-Reductase inhibitors for prostate cancer chemoprevention: an updated Cochrane systematic review. BJU Int. 2010;106:1444–1451.
23. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349:215–224.
24. Kramer BS, Hagerty KL, Justman S, et al. Use of 5alpha-reductase inhibitors for prostate cancer chemoprevention: American Society of Clinical Oncology/American Urological Association 2008 Clinical Practice Guideline. J Urol. 2009;181:1642–1657.
25. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. J Urol. 2013;190:419–426.
26. US Preventive Services Task Force, Grossman DC, Curry SJ, et al. Screening for prostate cancer: US Preventive Services Task Force Recommendation statement. JAMA. 2018;319:1901–1913.
27. Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011;59:61–71.
28. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology—Prostate Cancer Version 02.2017. 2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed September 26, 2017.
29. Martin NE, D'Amico AV. Progress and controversies: radiation therapy for prostate cancer. CA Cancer J Clin. 2014;64:389–407.
30. Novara G, Galfano A, Secco S, Ficarra V, Artibani W. Impact of surgical and medical castration on serum testosterone level in prostate cancer patients. Urol Int. 2009;82:249–255.
31. Ahmadi H, Daneshmand S. Androgen deprivation therapy for prostate cancer: long-term safety and patient outcomes. Patient Relat Outcome Meas. 2014;5:63–70.
32. Carter NJ, Keam SJ. Degarelix: a review of its use in patients with prostate cancer. Drugs. 2014;74:699–712.
33. Lukka H, Waldron T, Klotz L, et al. Maximal androgen blockade for the treatment of metastatic prostate cancer—a systematic review. Curr Oncol. 2006;13:81–93.
34. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467–479.
35. Ryan CJ, Small EJ. Early versus delayed androgen deprivation for prostate cancer: new fuel for an old debate. J Clin Oncol. 2005;23:8225–8231.
36. Magnan S, Zarychanski R, Pilote L, et al. Intermittent vs continuous androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. JAMA Oncol. 2015;1:1261–1269.
37. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424–433.
38. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187–1197.
39. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995–2005.
40. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138–148.

41. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline. J Clin Oncol. 2014;32:3436–3448.
42. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502–1512.
43. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147–1154.
44. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III study comparing a reduced dose of cabazitaxel (20 mg/m^2) and the currently approved dose (25 mg/m^2) in postdocetaxel patients with metastatic castration-resistant prostate cancer—PROSELICA. J Clin Oncol. 2017;35:3198–3206.
45. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363:411–422.
46. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213–223.
47. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96:879–882.
48. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011;377:813–822.
49. Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72:1938–1956.
50. Wo JY, Chen MH, Nguyen PL, et al. Evaluating the combined effect of comorbidity and prostate-specific antigen kinetics on the risk of death in men after prostate-specific antigen recurrence. J Clin Oncol. 2009;27:6000–6005.

93 Skin Cancer

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LEARNING OBJECTIVES

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

LO

1. Identify the risk factors associated with skin cancer.
2. Devise a plan of lifestyle modifications for the prevention of skin cancer.
3. Discuss the importance of mutation testing in the therapy selection for metastatic melanoma treatment.
4. Explain the goals of therapy for the treatment of the different nonmelanoma and melanoma stages.
5. Compare and contrast the available pharmacologic treatment options for nonmelanoma and melanoma skin cancer.
6. Suggest management options for patients experiencing adverse effects of pharmacologic therapy.

INTRODUCTION

Skin cancer is the most common malignancy in the United States with over 5 million new diagnoses reported in roughly 3 million individuals as of 2012. Of these, more than 95% are diagnosed with nonmelanoma skin cancer (NMSC), while the rest of skin cancer diagnoses are accounted for by malignant melanoma (MM).[1,2] NMSC incidence increased 300% since 1994 and continues to rise due to increasing high-risk populations, such as organ transplant and photosensitizing medication users. NMSC consists of basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs), which originate in the basal cell layer and the hair follicle stem cells, respectively.[3] MM differs substantially from NMSC with regard to its metastatic potential, prognosis, and treatment options.

MALIGNANT MELANOMA

EPIDEMIOLOGY AND ETIOLOGY

MM is the most diagnosed malignancy in young adults and ranks among top five most incident cancer diseases in the United States, representing approximately 5% of all cancer cases. Although accounting for less than 3% of the skin cancer diagnoses, MM is responsible for the majority of skin cancer deaths (75%).[1,4] With a median age at diagnosis of 64, about half of the MM cases were diagnosed between ages 55 and 74. Approximately 91,270 new cases are predicted to occur in 2018, a forecast impacting males more than females, according to the Surveillance Epidemiology and End Results (SEER) age-adjusted analyses.[5] However, these figures may be underestimated since many superficial and in-situ melanomas are treated in outpatient settings and, thus, not included in the SEER registry.

RISK FACTORS

LO 1

MM risk factors include environmental and host factors. KEY CONCEPT Sun exposure and ultraviolet-based artificial tanning are the main environmental triggers for melanoma occurrence. While MM can occur in any ethnic group and also on less exposed areas of the body, individuals with genetic susceptibility may develop exacerbated skin reactions to sun or ultraviolet radiation (UVR), particularly UVB. Interestingly, although UVB-induced DNA damage was determined to be lifetime cumulative, the most prevalent (over 70%) UV-induced genetic modification—C to T—is, paradoxically, irrelevant for most well-known melanoma mutations, *BRAF V600E*, and *NRAS Q61L/R*.[6] Yet, recent evidence supports a UVR-induced mutation mechanism for melanoma occurrence: the hot-spot mutations in *RAC1*, *STK19*, and *PPP6C*.[7]

Further, well-documented UVR-induced *TP53* tumor suppressor gene mutations are responsible for ineffective DNA-repair, resulting in apoptosis dysregulation, modified keratinocyte expansion, and initiation of skin cancer. Today, it is estimated that over two-thirds of MMs are attributable to UVR. Moreover, childhood severe sunburns were associated with twice the risk of developing melanoma.

According to Narayanan, epidermal melanin acts as sun protection factor in individuals with darker skin tones, providing an SPF of up to 13.4 in blacks.[8] Family history of MM in a first-degree relative is associated with twice the risk for MM. Benign melanocytic nevi (benign moles) are also consistently identified as a risk factor for MM development. The risk of developing MM is also higher in patients with a personal history of MM, NMSC, or dysplastic nevus syndrome.[9] Having five or more dysplastic nevi increases the risk of MM up to six times. A similarly increased risk was noted in cases with congenital melanocytic nevi (bigger than 20 cm diameter).[9] A set of host-related risk factors used in the assessment of MM risk is provided in Table 93–1.

LO 1

PRIMARY PREVENTION OF SKIN CANCER

LO 2

Educating patients to avoid excessive exposure to the sun is strongly supported by the American Academy of Dermatology, American Cancer Society, Environmental Protection Agency, and Centers for Disease Control and Prevention. These programs

Table 93–1

Host-Related Risk Factors for Melanoma Development

Demographics
- Gender: male
- Age: > 60 years

Skin Phenotype
- Fitzpatrick skin type: pale white skin, blue or green eyes, blond or red hair
- Tanning ability: tendency to sunburn
- Moles: increased count and size with atypical features and pattern

Past Medical History
- Sunburns: multiple with or without blistering
- Cancer: benign or malign skin cancer or childhood cancers
- Impaired immune system: hematopoietic or solid organ transplant, HIV/AIDS
- Genodermatoses: *Xeroderma pigmentosum*

Genotype
- First degree family history
- Susceptibility genes (*CDKN2A, CDK4, MC1R, BRCA2*)

Data from Refs. 4 and 7.

aim at increasing public awareness about the mutagenic effect of UVR exposure and at changing social norms related to sun protection and tanning, their ultimate goal being to lower skin cancer incidence and deaths related to MM. The following are expert-approved strategies to minimize UVR exposure:

LO 2
- Seek shade when outdoors, especially between 10 AM and 2 PM
- Wear hats that provide shade for the face, ears, and neck
- Wear protective clothing made of tightly woven fabric that covers the arms, legs, and torso
- Avoid sun-bathing and indoor tanning
- Take extra caution when located near water, sand, and snow
- Use UVA/B sunscreen with a minimum skin protection factor (SPF) of 30; reapply every 2 hours if sweating or swimming
- If wearing makeup, use one with SPF and reapply high SPF makeup setting mist every 2 hours

Protective sunscreen lotion or spray should not be the sole agent used for skin cancer prevention as they have only been proven to reduce the risk of actinic keratosis (AK) and SCC. Limited evidence exists that sunscreen application has protective effects against BCC and MM. It is well documented that sunprotection options can lead to or increase the risk of vitamin D deficiency or insufficiency.[10] Therefore, vitamin D level should be closely monitored and appropriate supplementation is recommended for blood levels lower than 30 ng/dL.

Patient Encounter 1, Part 1

A 65-year-old Caucasian man presents to his dermatologist with complaints of pain surrounding a mole located on his left breast.

History: He has a family history of dysplastic nevus syndrome and has been getting his moles checked regularly for the past 10 years. He has three prominent moles located on his chest, neck, and stomach, but six larger, notable nevi on his back. Over the last month, he noted a new mole appearing on his left shoulder blade and has increasing pain surrounding the mole on his chest.

The man reports that he loves swimming in his outdoor pool and has done so three to five times weekly for the last 5 years. He does use sunscreen but never reapplies after coming out of the water.

What risk factors does this patient have for the development of melanoma?

Are any of his risk factors modifiable?

What concerns exist with the development of a new mole at his age?

SECONDARY PREVENTION OF SKIN CANCER

Secondary prevention of skin cancer involves early detection of premalignant cancers for early intervention to increase the likelihood of cure and lower mortality. Regular screening by skin self-examination or total skin examination performed by health care providers consistently identify smaller and thinner lesions in high-risk patients.[11] To date, the recommendations for melanoma screening are conflicting because there are no randomized, controlled, prospective melanoma trials demonstrating that routine screening reduces mortality. However, evidence exists that clinical whole-body skin examination reduces the incidence of thick melanomas, a pathological feature known to be directly associated with MM mortality.

PATHOPHYSIOLOGY

Although the vast majority of MMs originate from the skin, few may arise from various other epithelial tissues, including the conjunctiva, oral mucosa, penis, urethra, and others. The malignant process originates in abnormal melanocyte proliferation as a consequence of genetic susceptibility and/or exposure to a mutagenic agent, such as UVB. Interestingly, in individuals with high genetic susceptibility, MM may develop on body sites only exposed intermitently, such as the trunk or thighs, while it requires significant chronic UVB exposure of areas such as face and neck, in individuals with low genetic susceptibility.[12] Thus location alone may be an indication regarding the occurrence mechanism.

Genetic Basis of Melanoma Development

LO 3 MM has the highest prevalence among the cancers caused by chronic mutagenic exposure.[6] Approximately half of MM cases carry *BRAF V600* mutations and are expected to derive a clinical benefit from BRAF inhibitors.[7] BRAF is a serine/threonine protein kinase that is a member of the RAF kinase family, which is a part of the RAF/MEK/ERK serine threonine cascade (also known as ERK/MAP kinase pathway or "classical" MAPK pathway).[12] Mutations in *BRAF* activate the ERK/MAP pathway and thus trigger melanocyte proliferation and clonal expansion. *BRAF* mutant melanomas tend to occur in individuals younger than 55 years with Fitzpatrick skin types I or II, lower cumulative UV exposure, and on skin areas intermittently exposed to sun. Out of more than 50 *BRAF* mutations described, the valine to glutamic acid (*BRAF V600E*) substitution accounts for over 75% of all *BRAF* mutations.[13] KEY CONCEPT BRAF kinase inhibitors are the mainstay treatment for *BRAF* mutation positive metastatic melanoma.

Table 93–2

Characteristics of Different Types of Skin Cancer

	Malignant Melanoma				Nonmelanoma Skin Cancer	
	Superficial Spreading	Nodular	Lentigo Maligna	Acral Lentiginous	Basal Cell Carcinoma	Squamous Cell Carcinoma
Frequency	70%	10%–15%	10%	< 10%	75%	20%
Location	Female: Head, neck, legs Male: Trunk	Trunk, head, neck	Face, head, neck	Palms, soles, nailbeds	Head and neck	Face, hands, forearms
Age	Fifth decade	Seventh decade	Eighth decade	Sixth decade	> 40 years	> 40 years
Ethnicity	White	White	White	Ethnic groups of color	Nonspecific	African Americans
Prognosis	Good	Very poor	Good	Very poor	Good	Poor
Clinical features	Long horizontal growth phase (5–7 years)	Very aggressive, deeply invasive, no identifiable horizontal growth phase	Long horizontal growth phase (10 years) In-situ, only 5% are malignant	Aggressive, rapid progression from horizontal to vertical growth	Rarely metastasizes Several subtypes	Metastasizes Premalignant and in-situ variants

Data from Refs. 8 and 10.

Since melanocytes' differentiation, proliferation and survival regulation is controlled by a microphthalmia-associated transcription factor (MITF), its alteration impacts antiapoptotic proteins leading to uncontrolled growth and tumor development. Other relevant MM mutations include *CDKN2A* and *PTEN* deletions, as well as *RAC1*, *NRAS*, *PPP6C*, and *STK19*.

Clinical Presentation and Diagnosis

There are four major subtypes of cutaneous MM: superficial spreading, nodular, lentigo maligna melanoma, and acral lentiginous (Table 93–2). They each vary in clinical and growth characteristics.[14]

SEER data show that 84% of diagnosed MM are locally confined, 9% are diagnosed after the cancer has spread regionally, 4% are diagnosed with distant metastasis, and the remaining 3% cannot be staged.[5] KEY CONCEPT Once skin cancer is diagnosed, the disease is staged to determine confinement to the original location or any spread to other sites, such as the lymph nodes, liver, brain, lungs, or bone. The purpose of staging is to determine prognosis and aid in clinical decision making. As with most solid tumors, the tumor, node, metastasis (TNM) classification is used to stage MM. Staging of solid tumors is described in Chapter 88.

Determination of lymph node involvement is an independent prognostic factor and it provides therapy selection guidance. MM patients whose peripheral and deep margin status after biopsy indicate a risk for disease spread to the lymph nodes also receive a **sentinel lymph node** (SLN) biopsy. An SLN is the nearest lymph node to receive lymph draining directly from the biopsied tumor.

Other prognostic factors considered for assessment include primary tumor thickness (Figure 93–1), the presence of ulceration at the primary site, local mitotic activity, the presence of tumor infiltrating lymphocytes (TIL), and gender.[15,16] Male sex is associated with poor prognosis and adverse outcome in MM.[17]

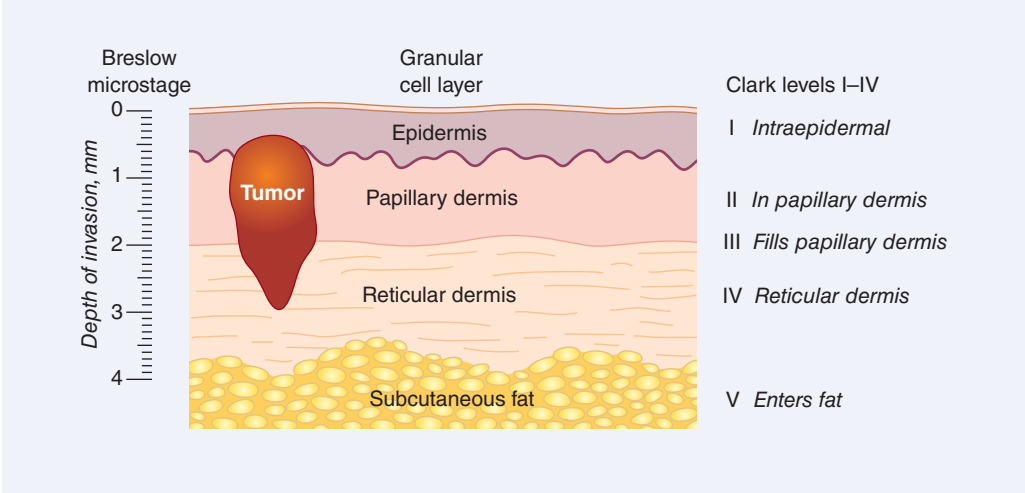

FIGURE 93–1. Skin anatomy: Breslow microstaging and Clark levels. Clark level refers to the level of penetration into the dermis. Breslow classification measures tumor thickness in millimeters from the epidermis to the deepest depth of penetration into the dermis. (From Langley RGB, Barnhill RL, Mihm Jr MC, et al. Neoplasms: Cutaneous melanoma. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatologyin General Medicine, 6th ed. New York: McGraw-Hill; 2003:938.)

Clinical Presentation of MM

MM lesions may occur anywhere on the body. The most common sites are the head, neck, trunk, and extremities. MM appearance such as thickness, presence, or absence of ulceration, as well as any lesion characteristic changes are important risk indicators. Abnormal presentations of a mole or lesion indicate the need for further assessment.

- **Asymmetry:** Half the lesion does not mirror the other half
- **Border:** Sharp, ragged, uneven, and irregular borders
- **Color:** Multiple shades of brown, black, red, blue, or gray
- **Diameter:** Larger than 6 mm or the size of a pencil head eraser
- **Evolving:** Significant change in shape, size, symptoms, surface, or shades of color

Other signs and symptoms to monitor for in a lesion, in addition to ABCDE, include:

- Sudden or continuous lesion enlargement or elevation
- Changes in the skin surrounding the nevus
- Presence of redness, swelling, itching, tenderness, or pain
- Friability of the lesion with bleeding or oozing (ie, ulceration) is an indicator of poor outcomes

Less Common Sites and Manifestations of MM

It is important to examine these sites for "hidden" MM:

- Nailbed
- Mucosal tissue
- Scalp
- Eye

In the nailbed, a black streak or wide variegated brown streak, elevation of nailbed, darker skin surrounding the nail, deformed or destroyed nail, or an increasing nail streak size over time are all possible manifestations of MM.

Diagnostic Tests

- Dermoscopy
- Biopsy

Staging Tests (Depending on Patient's Presentation)

- Baseline chest radiography
- Tumor cell mitotic rate
- LDH level
- CT of chest, abdomen, pelvis
- SLN biopsy: KEY CONCEPT The status of the SLN involvement is one of the most powerful independent prognostic factors predicting survival. It also provides the clinician with guidance for therapy decisions and accurate staging.
- PET
- MRI

Skin Examination

The *ABCDE* acronym is a helpful mnemonic for recognizing the signs and symptoms of early MM (Figure 93–2).[9] Not all MMs, including nodular melanoma, have all ABCDE characteristics, thus *ABCDE* is not meant to provide a comprehensive evaluation of all MM features. The characteristics for each of the letters are described in Figure 93–2. It should be noted that evolution of a lesion is one of the most important warning signs of danger in the assessment of moles for MM.

TREATMENT

LO 4

Early diagnosis of MM is key to improved prognosis. New onset melanoma cases usually present with a recent history of unusual melanocyte growth or an area of irritation around a patch of melanocyte cells. Alternately, the melanoma may have gone undetected for years. In either of the two possibilities, a definitive diagnosis of any suspected cutaneous malignancy should be confirmed by a biopsy before treatment could be initiated. MM treatment options depend on the tumor size, location,

Patient Encounter 1, Part 2

PMH: HTN since 5 years ago, NSTEMI with stent placement 2 years ago, dysplastic nevus syndrome. Patient has developed an intolerance for fluoroquinolones and his current UTI is treated with doxycycline.

FH: Father had dysplastic nevus syndrome but no melanoma. Mother had diabetes and hypertension.

SH: Patient is a recently retired office worker. Married with one adult child.

Examination: Reveals an asymmetrical new nevus of ~5 mm with irregular reddish borders and a lighter center on the left breast with no lesions noted.

Biopsy: Excisional biopsy of the chest nevus reveals melanoma

CT Scan: No distant metastases

Laboratory Data: Normal

He underwent wide surgical excision of the lesion with a 3-mm margin resection after lymphatic mapping with sentinel lymph node biopsy. Pathology revealed negative margins and one of three nodes positive for melanoma. His melanoma is diagnosed as a stage IIB. Lymphadenectomy of the left axilla has been performed as well.

Would surgical excision of the lesion be curative in this patient?

Could medications typically used to treat his current disease states increase his risk of developing melanoma?

Considering the patient has stage IIB melanoma, what pharmacologic treatment would you recommend?

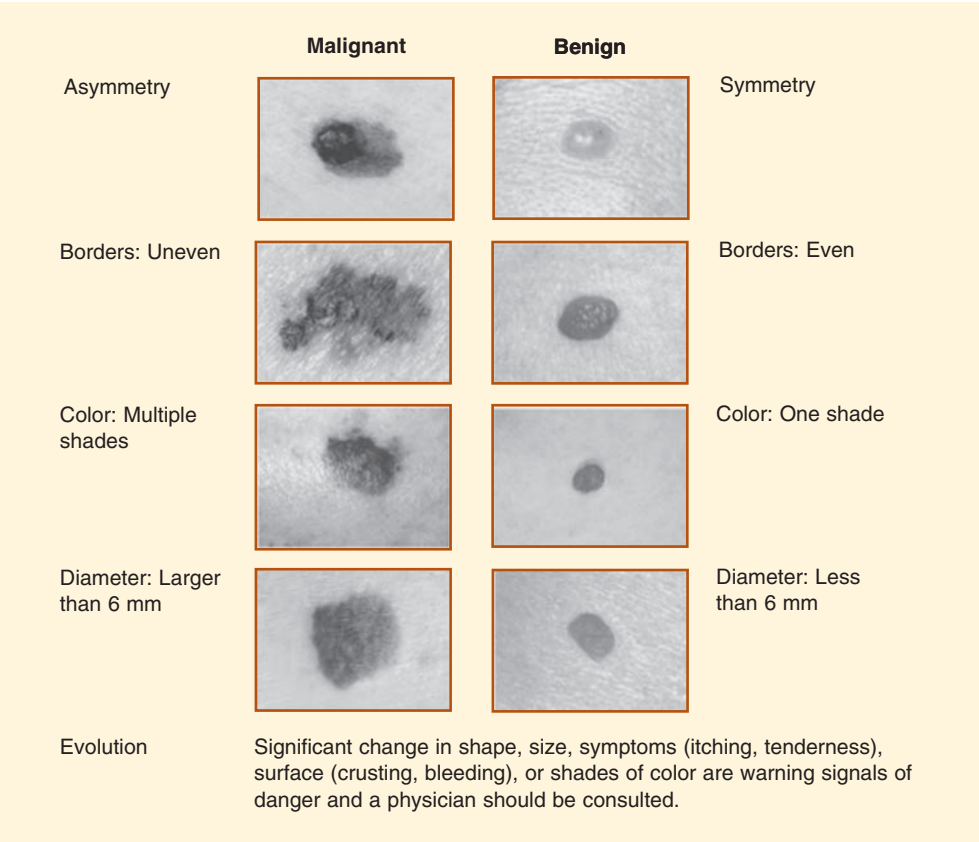

FIGURE 93–2. ABCDE features of early melanoma. (Images courtesy of the Skin Cancer Foundation, New York, www.skincancer.org.)

pathological features and stage. The age of the patient and past medical history, including the results of genotyping studies, all play a role in the clinical decision making. The considered options include surgery, radiation, **immunotherapy**, **targeted therapy**, and biochemotherapy, a combination of immunotherapy and chemotherapy.

Desired Outcomes

LO 4

The primary goal in MM treatment is the eradication of the tumor, lowering the risk of recurrence and metastasis. Secondary goals of MM therapy include preserving skin tissue integrity, appearance, and function while providing optimal cosmetic outcomes. For localized MM (stages I and IIA), surgical resection of the tumor is curative. Thus, probability of cure may be considerably improved with early diagnosis. Patients with regional disease, however—stages IIB, IIC, and III—have a poorer prognosis, characterized by a higher chance for recurrence. In cases with regional disease the goal of therapy is relapse prevention and maintenance of the quality of life. Lastly, in melanoma patients with disseminated disease, neither cure nor prevention of relapse is achievable outcomes; the goal of therapy becomes rather the local control of the disease and the palliation of symptoms.

MM treatment outcomes largely depend on the clinical disease stage at the time of diagnosis. Based on the data published in the SEER Cancer Statistics Review, the 5-year survival rate for patients with localized MM is 98%, the rate decreases to 62% in cases with regional disease, and drops below 20% in individuals diagnosed with distant disease.[5]

Nonpharmacologic Therapy

▶ *Surgery*

KEY CONCEPT The primary treatment modality for local/regional disease (stages I to III) is surgical excision of the tumor with lymphadenectomy in patients with positive SLN. The goals of surgical excision are to gain local control and achieve potential cure, while minimizing morbidity. Achieving adequate surgical margins for the primary tumor is important in preventing local recurrence and improving overall survival. The extent of the surgical margin is, generally, dictated by the tumor thickness, but also by the result of the SLN.[18] The most common first site of recurrence in primary melanoma after tumor excision is the lymph nodes. In patients with regional or distant melanoma, surgical excision provides temporary symptomatic relief. Individuals with regional disease presenting with a good performance status and less aggressive tumor biology may observe longer disease-free intervals after surgery; however, this is only possible if disease can be successfully contained within the anatomical region. By contrast, in patients with stage IV melanoma median survival ranges from 5 to 8 months and the 5-year survival rate is under 5%. Surgical resection of symptomatic or life-threatening brain lesions may be an option to reduce neurologic deficits, seizures, and intracranial hypertension in patients with MM disseminated to the brain.[18]

▶ *Radiation*

Radiation is rarely indicated for the treatment of primary melanoma except for when surgery cannot be performed or is unreasoable. Radiation treatment may be administered as

adjuvant therapy in areas where complete excision of the tumor is difficult, such as the face; or may be employed in lymphatic areas when complete lymphadenectomy is not feasible. In cases with bone metastasis, radiation may be indicated as palliative therapy to decrease fracture risk, control spinal cord compression, and improve pain management.[19]

Brain metastasis is common in melanoma, between 10% and 40% of patients presenting with central nervous system (CNS) disease.[18] In such cases life expectancy ranges from 3 to 5 months and the chance of survival after 1-year is roughly 1 in 10. Headaches and seizures are common presenting symptoms; radiation therapy is indicated for CNS symptoms' palliation and as adjuvant treatment after resection of the CNS metastasis.[19]

Whole-brain radiation therapy (WBRT) WBRT is indicated if more than three CNS metastases are present, for surgically inaccessible lesions, and extensive systemic disease. WBRT does not improve survival in melanoma with CNS metastasis, nor provide a cure; however, it is effective in relieving neurologic symptoms,[18] preventing further disease dissemination, reducing symptomatic recurrence, and decreasing the need for salvage therapy.[19] WBRT also improves neurologic deficits in 50% to 75% of cases and relieves headaches in 80% of patients.[20]

Pharmacologic Therapy

▶ *Immunotherapy*

Infrequent reports of spontaneous remissions and the documentation of improved outcomes in cases with brisk lymphocytic infiltrates indicate that melanoma responds to immunotherapy.[21] Spontaneous serologic and cellular immunities were reported in a high proportion of patients with advanced melanoma.[22] Thus, enhancing patients' immune response with the goal of erradicating melanoma led to the development of several immune-modulating therapies and vaccines. Melanoma is an immunogenic tumor and strategies to enhance tumor-kill by modulating a patient's immune response are an area of active research and drug development.

LO 5

Interferon-α-2b Interferon is naturally-produced signaling protein with diverse mechanisms of action, including antiviral activity, impact on cellular metabolism and differentiation, and antitumor activity. The latter is attributable to both direct antiproliferative effects on the tumor and indirect immune-mediated effects.[23] It is believed that the indirect immune-mediated effects result from the interferon-driven TH_1 lymphocyte traffic to the primary tumor.[24] KEY CONCEPT Interferon-α-2b and peginterferon-α-2b are approved adjuvant therapies for patients who are free of disease after surgical resection but are at high risk for recurrence. This includes patients with bulky disease or regional lymph node involvement, such as stages IIB, IIC, or III (Table 93–3). High-dose (HD) interferon demonstrated a significant risk reduction in relationship with both recurrence and death when compared to observation and vaccine treatment.[24,25] However, close evaluation of the patient's medical history is essential as immunotherapy may not be tolerated by individuals with an autoimmune disorder history.

LO 5

LO 6

Substantial toxicities associated with interferon treatment should also be accounted for in the decision making for treatment selection. Both acute and chronic side effects have been reported with interferon utilization and they can be categorized in four major groups: constitutional, neuropsychiatric, hematologic, and hepatic. Patient counseling with regard to the expected and potential side effects as well as the interventions available to minimize the toxicities is mandatory. HD-interferon duration is

LO 5

LO 6

Table 93–3

Systemic and Regional Therapy for Primary Melanoma and Metastatic Disease

	Stage II_B/II_C	Stage III (SLN+)	Stage III (Clinical Node +)	Stage III with Local Disease	Metastatic or Recurrent Disease
IFN	X	X	X	X	
HD-Ipilimumab		X	X		
Biochemotherapy[a] IFN + IL-2 + Dacarbazine or Cisplatin or Vinblastine			X		
Biochemotherapy[b] Dacarbazine or Temozolomide + Cisplatin or Carboplatin +/– Vinblastine or Nitrosourea + IFN + IL-2					X
Intralesional therapy T-VEC, BCG, or IL-2				X	X[c]
Isolated limb infusion/perfusion Melphalan				X	
Topical therapy Imiquimod				X	

[a]Indicated in regionally disseminated disease.

[b]Indicated in recurrent or metastatic disease.

[c]T-VEC.

BCG, Bacile Calmette-Guerin; HD, high-dose; IFN, interferon; IL-2, Interleukin-2; SLN+, sentinel lymph node positive; T-VEC, talimogene laherparepvec.

Data from NCCN Melanoma Treatment Guidelines 2017; www.nccn.org. Last accessed December 15, 2017.

1 year for stages IIB to III, or up to 5 years if stage III at first dose. Low or intermediate dose are not recommended (Table 93–4). Doses prescribed and the duration of action differ between interferon and pegylated-interferon, the latter having a longer effect that is compatible with weekly administration. The side effects are similar, although the incidence seems to be less in the pegylated form. The monitoring recommendations are identical for both drugs.

Table 93–4

Melanoma Treatment Dosing Recommendations[a]

Immunotherapy

High-dose interferon: 20 million units/m^2 IV daily ×5 days/week × 4 weeks, then 10 million units/m^2 SC 3 days/week ×48 weeks

Peginterferon: 6 mcg/kg/week SC ×8 weeks, then 3 mcg/kg/week up to 5 years

Interleukin-2: 600,000 international units/kg IV every 8 hours (over 15 min) × 14 doses; may repeat after 9 days drug-holiday for up to 28 doses

Intralesional Therapy

Talimogene laherparepvec: 4 × 10^6 PFUs in ≤ 4 mL injected by intralesional fanning; inject 4 × 10^8 PFUs in ≤ 4 mL injected by intralesional fanning after 3 weeks, and biweekly thereafter for up to 24 doses

Immune Checkpoint Inhibitors

Ipilimumab: 3 mg/kg IV (over 90 min) every 3 weeks ×4 doses; permanently discontinue if not completed within 16 weeks;[e]

Nivolumab: 3 mg/kg IV (over 1 hour) every 2 weeks until;[c,d,e]

Pembrolizumab: 2 mg/kg IV (over 30 min) every 3 weeks;[d,e]

RAF-MEK-ERK Pathway Inhibitors

Vemurafenib: 960 mg orally twice daily every 12 hours;[b,d]

Dabrafenib: 150 mg orally every 12 hours;[d,f]

Trametinib: 2 mg orally once daily;[d,e,f]

Cobimetinib: 60 mg orally once daily days 1–21 of each 28 day cycle

Chemotherapy

Dacarbazine: 250 mg/m^2/day IV, days 1–5, every 21 days[g]

Temozolomide: 150–200 mg/m^2 orally ×5 days, every 4 weeks

Vinblastine: 2 mg/m^2 days 1–4 and 22–25 of 6 week cycle

Cisplatin: 75 mg/m^2 IV day 1 with temozolomide 200 mg/m^2 orally ×5 days, cycled every 4 weeks

Carboplatin: target AUC 6 day 1 of a 21 days cycle

Carmustine: 150 mg/m^2 IV day 1 with cisplatin 25 mg/m^2 IV days 1–3; repeat cycle with dacarbazine and cisplatin every 21 days; repeat cycle of carmustine every 42 days

[a]Refer to clinical trials to determine the specific dose based on the regimen the patient is receiving.

[b]Caution in severe renal or hepatic impairment; no dose adjustment needed for mild to moderate impairment.

[c]Baseline renal, liver, and thyroid function required; monitor periodically during treatment.

[d]Continue regimen until disease progression or unacceptable toxicity occurs.

[e]No formal studies have been done to assess cytochrome p450 interactions interactions[32].

[f]Take on empty stomach.

[g]Inactive until metabolized by the liver; it requires reasonably good liver function.

IV, intravenous; SC, subcutaneous.

Data from U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Last accessed December 15, 2017.

Patient Encounter 1, Part 3

This patient presents 1 month later after the initiation of interferon-α-2b with unbearable flu-like symptoms and new-onset depression.

What, if any, changes would be appropriate to this patient's stage IIB melanoma treatment?

What additional laboratory tests are appropriate to request at this time?

LO 5 **Interleukin-2** Interleukin-2 (IL-2) is a biologically-occuring cytokine capable of inducing tumor lysis by stimulating the proliferation and activation of the cytotoxic T lymphocytes (CTLs). The overall response rate in patients with metastatic melanoma receiving HD IL-2 is 16%, result that provides proof of the immunotherapy concept.[26] Its approval relies on the benefit noted in 270 patients enrolled in eight clinical trials performed between 1985 and 1993. High-dose IL-2 therapy is associated with significant severe toxicities and morbidity and is not an option for the majority of patients. Treatment must be performed inpatient and requires experienced personnel for administration. Nevertheless, among the few eligible responding patients, benefit is seen for extended periods (see Table 93–4 for dosing). While IL-2 is no longer the primary option for metastatic melanoma patients, this immunotherapy is part of biochemotherapy options for patients with regional recurrent and metastatic melanoma. Table 93–5 lists the most common IL-2 side effects and current recommendations for management.

LO 5 LO 6

▶ *Biochemotherapy*

LO 5 Given the responsiveness of melanoma to immunotherapy, cytoxic chemotherapy is not a first-line treatment. However, a treatment option combining both cytotoxic and immunotherapies or "*biochemotherapy*" regimen is an option for some patients. KEY CONCEPT Patients eligible to receive biochemotherapy are cases with metastatic or inoperable MM who are not candidates for targeted therapy. The goal of biochemotherapy is to reduce tumor size, and it is an accepted palliative therapy for stage IV melanoma. Among the cytotoxic agents used in melanoma treatment are dacarbazine, temozolomide, cisplatin, carboplatin, vinblastine, carmustine, and paclitaxel (see Table 93–3).[27]

▶ *Intralesional Therapy*

Intralesional therapies show promising results in patients with intralymphatic metastases and are options for advanced melanoma treatment. Advantages include good local response rates and tolerable side effects.

Talimogene Laherparepvec

LO 5 One of the newest additions to the arsenal against MM, Talimogene laherparepvec is the first FDA-approved intralesional therapy for the treatment of unresectable or metastatic melanoma. It is a genetically modified herpes simplex oncolytic virus therapy administered directly into the cutaneous or subcutaneous melanoma lesions or into the visible or palpable nodal lesions.[23]

LO 5 The virus is designed to selectively multiply in the tumor cells. Its mechanism of action is still investigated; however, the therapeutic benefit likely occurs via the involvement of the tumor antigens which are thought to serve as an autologous vaccine.

Table 93–5

IL-2 Toxicities

Cardiovascular
SE: Hypotension (64%), supraventricular tachycardia (17%)
Management: fluid management for SBP > 80–90 mm Hg; discontinue BP meds; PRN α-agonist vasopressor

Gastrointestinal
SE: Vomiting and diarrhea (55%), nausea (24%), stomatitis (14%)
Management: 5-HT_3 antagonist, prochlorperazine; H_2-blocker; loperamide/diphenoxylate/atropine PRN diarrhea

Neurologic
SE: Confusion (30%), somnolence agitation, anxiety, insomnia
Management: haldol PRN agitation, lorazepam PRN anxiety, zolpidem PRN insomnia

Pulmonary
SE: Dyspnea (31%), pulmonary edema, ARDS
Management: quit smoking 2 weeks before therapy; discontinue if > 4 L O_2 or 40% O_2 mask required for 95% Sat

Hepatic
SE: Elevated bilirubin (51%), transaminase (39%)
Management: if severe, consider discontinuation

Renal
SE Oliguria (49%), elevated serum creatinine (35%), anuria (8%)
Management: normal saline or 2 mcg/kg/min dopamine for oliguria; monitor electrolytes

Hematologic
SE: Thrombocytopenia (43%), anemia (29%), leukopenia (21%)
Management: PRN packed red blood cells and/or platelets

Skin
SE: Rash (27%), exfoliative dermatitis (15%), pruritus
Management: hydroxyzine, diphenhydramine, oatmeal powder baths, lubriderm lotion

General
SE: Fever and or chills (47%), malaise (34%), infection (15%)
Management: acetaminophen/NSAIDs around the clock for fever; meperidine if chills are severe; prophylactic clindamycin or cefazolin

Hypothyroidism
SE: May occur in one-third of patients
Management: monitor thyroid function tests

ARDS, adult respiratory distress syndrome; 5-HT_3, serotonin; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PRN, as needed; SBP, systolic blood pressure.

Data from Robert, C., Long, G.V., Brady, B., et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320–330.

The drug is delivered by injection using a "fanning" technique (one needle entry with multiple direction of administration). Grade 3 or 4 treatment-related adverse events were reported in 7.3% of the treated patients and included nausea and vomiting, abdominal pain, fever and chills, and wound infection.[23] Of the treated patients, 12.2% achieved a complete response. Talimogene laherparepvec is currently approved in the United States, European Union, and Australia.

Bacille-Calmette-Guerin

LO 5

An attenuated strain of *Mycobacterium bovis* originally developed as a vaccine against tuberculosis, the Bacille-Calmette-Guerin is sometimes used for intralesional administration to stimulate an immune respone toward the injected site. Its utilization as a therapy for advanced melanoma aims at stimulating patient's own immune system to fight against the injected lesion.[28]

Other intralesion-injected agents for advanced melanoma are the rose bengal dye, the granulocyte macrophage colony-stimulating factor, velimogene aliplasmid, IL-2, and interferon. However, the intralesional administration of many of these therapies remains experimental.

▶ *Immune Checkpoint Inhibitors*

T-cell activation involves two different signals that enhance the host immune response:[29]

- T-cell receptor binding to the major histocompatibility complex presented peptide located on the antigen-presenting cell (APC)
- T-cell costimulatory receptor (CD28) interaction with a costimulatory ligand (B7) on the APC surface

The Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) is expressed in CD4+ and CD8+ T-cells and regulatory T-cells. CTLA-4 is a member of the immunoglobulin (Ig) super family that migrates to the T-cell surface upon its activation allowing binding with a higher affinity to the B7 ligand than CD28. This results in a downregulation on the immune response; in other words, CTLA-4 acts as a "brake" on the activation of the immune system.[29]

Ipilimumab As a monoclonal CTLA-4-specific antibody, ipilimumab has a high affinity for CTLA-4 and prevents CTLA-4 from binding to B7, an action that inhibits the downregulation of the immune response.[29] Ipilimumab increases proliferation of activated T-cells and increases the interactions between T-cells and cancer cells. Ipilimumab is FDA approved for unresectable metastatic melanoma, either as a single agent or incombination with nivolumab, as well as the adjuvant treatment of stage III melanoma.[30] The median overall survival among ipilimumab users with metastatic melanoma was 13.5 months as compared to 10.7 months in the ipilimumab-naive group.[31] T-cell activation can lead to severe adverse events, such as enterocolitis, hepatitis, dermatitis including toxic epidermal necrolysis, neuropathy, and endocrinopathy, both providers and patients have to be enrolled in the FDA Risk Evaluation and Mitigation Strategy (REMS).[32] Corticosteroids are the treatment of choice for ipilimumab-induced adverse events. The administration of steroids to treat the side effects does not affect ipilimumab's effectiveness. Interestingly, there may be a correlation between immune-related adverse events and treatment success[33] (Table 93–6 for adverse effects and their management).

LO 5
LO 6

Nivolumab Many tumor cells express programmed death-ligand 1 (PD-L1), a surface marker that can interact with programmed death-1 (PD-1) receptor on T-cells and B-cells thus diminishing the body's immune response. Nivolumab is an IgG4 fully humanized antibody that targets PD-1 hence preventing the PD-L1 binding to PD-1. As a result, T-cells remain active to mount an immune response against the tumor. Nivolumab is indicated for both unresectable and metastatic MM following ipilimumab and, if *BRAF V600* mutation positive, a BRAF inhibitor. It is also used frequently in the adjuvant setting for stage III, resected melanoma. Patients with confirmed unresectable, previously treated, stage III or IV melanoma without *BRAF* mutation receiving nivolumab had 72.9% overall survival rate at 1 year, as compared to 42.1% in the dacarbazine group.[34] Common side effects may include rash, puritus, peripheral edema, and cough. Rare but serious adverse events may include ventricular arrhythmia, infection, hepatotoxicity, and neuropathy.

LO 5
LO 3

Table 93–6

Ipilimumab Toxicities[a]

Dermatologic (47%–68%)
SE: Maculopapular rash, pruritus, vitiligo
Management: do not stop or reduce dose; topical corticosteroid and urea-containing cream; antipruritic agent (hydroxyzine); for grade 3–4, give oral corticosteroid with prednisone 1 mg/kg or dexamethasone 4 mg every 4 hours with a 4-week taper

GI (31%–46%)
SE: Mild diarrhea, severe diarrhea, or colitis
Management: loperamide, hydration, electrolyte replacement; budesonide 9 mg/day or prednisone 1 mg/kg or high-dose IV steroids (methylprednisolone 2 mg/kg once or 2× daily or dexamethasone 4 mg every 4 hours), upon symptom resolution taper over 4 weeks (up to 8 weeks may be needed); ensure slow taper. If no response to steroids in 48–72 hours, give biweekly infliximab 5 mg/kg. Discontinue antibody if severe colitis occurs

Inflammatory Hepatoxicity (3%–9%)
Management: methylprednisolone 2 mg/kg/day up to 2× daily for LFT > 8× ULN or total bilirubin > 5× ULN; give mycophenolate 1 g IV or 1.5 g orally 2× daily if symptoms persist

Endocrine (4%–6%)
SE: Hypophysitis
Management: monitor thyroid function tests, serum cortisol levels, ACTH, testosterone, FSH, LH, and prolactin; if confirmed, dexamethasone 4 mg every 4 hours ×7 days; taper over > 4 weeks; hormone substitution PRN; consult endocrinologist

Neurologic (1%)
SE: Guillain–Barré syndrome, sensory or motor neuropathy, myasthenia gravis
Management: give corticosteroids; if severe, discontinue antibody therapy

[a]In general, for severe grade 3 or 4 ipilimumab toxicities, therapy should be discontinued permanently. Women of childbearing age should receive contraceptive treatment throughout the duration of ipilimumab treatment.

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LFT, liver function tests; LH, luteinizing hormone; ULN, upper limit of normal.

Data from Kähler, C., Hauschild, A. Treatment and side effect management of CTLA-4 antibody therapy in metastatic melanoma. J Dtsch Dermatol Ges. 2011;9:277–285.

Pembrolizumab Previously known as lambrolizumab, this checkpoint inhibitor is an anti-PD-1 humanized antibody. The FDA-approved indication includes unresectable and metastatic MM following ipilimumab and, if *BRAF* V600 mutation positive, a BRAF inhibitor. In patients with measurable locally advanced unresectable metastatic melanoma having adequate organ function and performance score, the Response Evaluation Criteria in Solid Tumors (RECIST) confirmed response rate to pembrolizumab was 38%.[35] Common side effects may include arthralgia and constipation/diarrhea while rare but serious adverse events may include colitis, hepatitis, pancreatitis, pneumonitis, and hypophystitis. According to a recent study comparing the incidence of immune-related adverse events associated with ipilimumab versus pembrolizumab, significantly fewer gastrointestinal and dermatological adverse events were reported with pembrolizumab use; however, a higher incidence of thyroiditis and pneumonitis was noted.[36]

▶ *RAF-MEK-ERK Pathway Targeted Therapy for BRAF Mutant MM*

KEY CONCEPT BRAF/MEK combined regimens provide a considerable therapeutic advantage against occurrence of melanoma resistance in patients with metastatic melanoma.

Vemurafenib/Cobimetinib The serine/threonine kinase B-Raf (BRAF) is an intermediary in the signal transduction through the RAF-MEK-ERK mitogen-activated protein kinase (MAPK) pathway. BRAF activation is followed downstream by the activation of ERK with increase in the cyclin D1 levels, and enhanced cellular proliferation.[37] The proto-oncogene B-Raf *(BRAF)* is mutated in approximately 50% of melanomas, and over 75% of these mutations are *BRAF V600E*.[13] Vemurafenib is an oral serine/threonine kinase inhibitor that binds to the adenosine triphosphate binding domain of *BRAF* mutant, hence presence of the mutation is required for treatment effect.[38]

KEY CONCEPT Vemurafenib selectively targets the BRAF V600E isoform and has an indication for the treatment of unresectable stage III_C or metastatic melanoma that is *BRAF V600* mutation positive. Although vemurafenib was initially approved as a single agent, resistance develops rapidly via activation of MEK and the combination of vemurafenib and the MEK inhibitor cobimetinib demonstrates improved progression-free survival compared to vemurafenib alone in patients with BRAF mutant metastatic melanoma[39] (see Figure 93–3 and Table 93–4 for dosing recommendations).

Common side effects associated with vemurafenib may include photosensitivity, rash, arthralgia, and alopecia. Rare but serious side effects may include QT interval prolongation, hand–foot syndrome, vision changes, and SCC, although the latter can be excised without discontinuation of the agent.[37] Vemurafenib is metabolized by CYP3A4 and thus may interact with its inducers or inhibitors. It may increase the serum concentration of substrates of CYP1A2 and 2D6. It may decrease the serum concentration of substrates of CYP3A4.

Cobimetinib commonly causes photosensitivity, diarrhea, elevations in liver function tests (LFTs), as well as electrolyte abnormalities. Decreases in ejection fraction and hypertension can occur in up to 20% of the patients. Rare but serious adverse effects include bleeding and secondary neoplasms, including squamous and basal cell skin cancer and melanoma. Cobimetinib is metabolized by CYP3A4 and thus may interact with its inducers or inhibitors.

Dabrafenib/Trametinib Similar to vemurafenib, dabrafenib is a selective inhibitor of BRAF V600E kinase. While it is approved as both monotherapy for unresectable and metastatic MM with *BRAF V600E* mutation and as combination therapy with trametinib for unresectable and metastatic MM with BRAF *V600E* or *V600K* mutation, the drugs are used almost exclusively in combination, as the combination has demonstrated superior efficacy than either drug administered as a single agent. The combination also significantly reduces the risk of recurrence of melanoma in completely resected patients with stage III melanoma when compared to placebo.[40] Common side effects with dabrafenib include hypoglycemia, arthralgia, and neutropenia while rare but serious adverse events may include QT prolongation, serious febrile reactions, uveitis, iritis, and SCC. Similar to vemurafenib, SCC can be excised without discontinuing dabrafenib. Dabrafenib is metabolized by CYP3A4 and 2C8 and thus may interact with its inducers or inhibitors. It may decrease the serum concentration of substrates of CYP3A4 and 2C9.

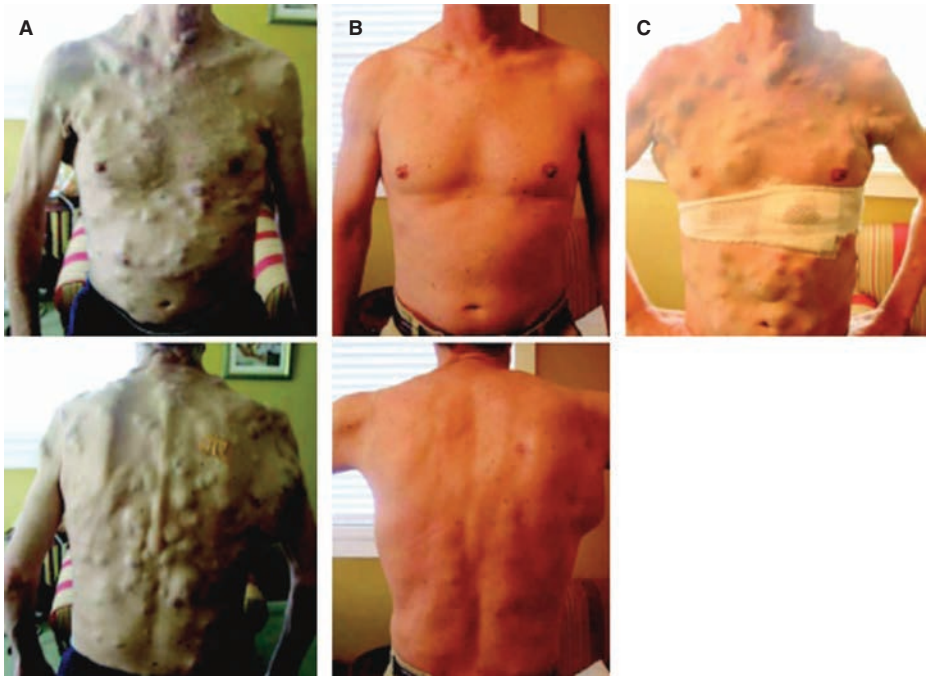

FIGURE 93–3. RAF inhibition resistance in melanoma. A 38-year-old man with BRAF-mutant melanoma. **(A)** Before initiation of RAF inhibitor. **(B)** After 15 weeks of therapy with a RAF inhibitor. **(C)** After relapse, after 23 weeks of therapy. (Reproduced with permission from the Journal of Clinical Oncology. Wagle, N., Emery, E., Berger, M.F., et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol. 2011;29(22):3085–3096.)

LO 3

Trametinib is a MEK-1 and MEK-2 kinase inhibitor targeting MAPK pathway downstream of BRAF. The drug is approved as monotherapy or in combination with dabrafenib for *BRAF V600E* or V600K mutation positive unresectable and metastatic melanoma, although currently only used in combination. Common side effects with trametinib include dry skin and nail changes while rare but serious adverse events may include vision changes and rhabdomyolysis.

OUTCOMES EVALUATION

When evaluating MM therapy outcomes, refer to the primary and secondary goals for the respective MM stage, treatment selection, and case-related particularities, such as cosmetic considerations. Always evaluate the awareness and approach to avoid sun or UVR exposure, including compliance with regular total-body skin self-examination, regardless of disease stage and implemented treatment. Advise for appropriate changes if needed.

Patient Encounter 1, Part 4

Several weeks later, while awaiting enrollment in a clinical trial, the patient presents with general malaise, weakness, and acute shortness of breath. His labs are insignificant except for an LDH of 1500 units/L. He has no new lesions.

New imaging studies confirm metastases to the lung, the workup resulting in a new diagnosis of stage IV metastatic melanoma.

What laboratory workup is necessary to direct the next clinical decision?

Depending on the results of the laboratory workup, what therapy changes can be made?

For localized disease:

- Evaluate skin integrity after tumor resection, appearance, and function.
- Assess the quality of life after surgery and whether any skin graft-related complications have been reported.
- Verify patient and family understanding regarding recurrence prevention.

For regional disease:

- Assess skin appearance and recovery after radiation therapy, as well as the quality of life and motor function recovery after lymphadenectomy.
- Evaluate effectiveness of any antibiotic treatment.
- Review the relevant labs and make necessary treatment changes.
- Review treatment adverse events and the appropriateness of their management.
- Discuss treatment alternatives and options for recurrence prevention.

For disseminated disease:

- Identify patient's and family goals and their compatibility with the observed treatment outcomes.
- Review the relevant labs and evaluate the effectiveness of palliative treatment.
- Assess chronic therapy side effects and evaluate to the appropriateness of adverse event reporting and management.
- Assess patients' psychological, physical, and social functioning.
- Evaluate the use of current resources, such as the hospital's social service department or the American Cancer Society for assistance in dealing with the disease emotionally. Recommend attending support group meetings or talking to a counselor if or before they become overwhelmed with the diagnosis.

PATIENT CARE PROCESS

Refer to the section at the end of the chapter for the patient care process recommended for both MM and NMSC care.

KERATINOCYTE CARCINOMA

EPIDEMIOLOGY AND ETIOLOGY

Also known as nonmelanoma skin cancer (NMSC), keratinocyte carcinoma[41] accounts for the vast majority of all newly diagnosed cancers each year. BCC is the most common form of keratinocyte carcinoma followed by the SCC as the second most common in the United States (see Table 93–2).

The true prevalence of keratinocyte carcinoma may be underestimated due to its treatment in outpatient settings, without formal reporting to cancer registries. Yet, understanding its incidence is critical to designing treatment strategies and providing proper resource allocation for its prevention.[42] The number of individuals with at least one NMSC procedure in the Medicare fee-for-service database increased by over 14% between 2006 and 2012. Although, BCC was previously reported as the most common form of NMSC, comprising of 75% of the NMSC, the most recent study indicates a 50-50 ratio of BCC to SCC diagnosed in a Medicare population.[42] The majority of NMSCs are curable, and the mortality rate is low, however not negligible; cure rates approach 98%, and the overall 5-year survival rate is considerably greater than 95%. Metastasis occurs in fewer than 0.1% of BCCs compared to 3.6% of SCCs. Roughly 75% of all keratinocyte carcinoma deaths are attributed to SCC.[43] Keratinocyte carcinoma is associated with considerable morbidity related to functional and cosmetic deformity. In addition, it is an economic burden; the associated costs for NMSC treatment reaching $4.7 billion between 2007 and 2011, nearly double as compared to NMSC expenditure between 2002 and 2006. Importantly, both these figures exceed the costs of MM expenditure for the corresponding time-frame.[44]

RISK FACTORS

LO 1

The risk of developing keratinocyte carcinoma is multifactorial. Skin phenotype plays a similar role as in the MM development; individuals with pale skin, blue or green eyes, and blond or red hair are at risk for developing NMSC as well. A tendency to sunburn or an increased cumulative lifetime UVR exposure, particularly UVB due to its penetrability and higher energy, leads to biologically damaging effects including direct DNA damage, signaling receptor-mediated pathways activation, and reactive oxygen species (ROS) formation.[3] Greater cumulative lifetime sun exposure is associated with a higher risk of developing SCC, but intermittent and childhood sun exposure correlates more with BCC. Individuals with a keratinocyte carcinoma have a 10-fold increased risk of developing subsequent skin cancer as compared to the general population.[45]

The vast majority of BCC cases are sporadic, although a small number occur in patients with Gorlin syndrome, an autosomal dominant disorder caused by mutations in the *PTCH1* gene. Additionally, up to 70% of patients with sporadic BCC have a mutation in the *PTCH1* gene.[45] By contrast, individuals with previous SCC are more likely to acquire additional SCC and, potentially melanoma.[3] SCC has been reported to occur 100-fold more often in organ transplant recipients as compared to the general public, possibly due to the immunosuppressive therapy requirements in transplant patients.

Table 93–7

Photosensitizing Drugs

Antidepressants: citalopram, bupropion, fluoxetine
Glucose lowering meds: glimepiride, glyburide, glipizide
Immunosuppressants: methotrexate, cyclosporine
Antibiotics: azithromycin, doxycycline, sulfonamides, ketoconazole, voriconazole, griseofulvin, trimethoprim
Insomnia/seizure/anxiety meds: alprazolam, quetiapine, zolpidem, valproic acid, gabapentin
Antiarrhytmics: amiodarone
Other: estrogens, cholesterol-lowering meds, NSAIDs, isotretinoin, vitamin A, St. John's wort
Blood pressure meds: lisinopril, labetalol, hydralazine, diuretics

LO 1

Although responsible for a smaller number of keratinocyte carcinomas, arsenic has been shown to promote the expression of SCC-related keratins possibly by epigenetic modifications. Other reported offenders linked to the occurrence of NMSCs include photosensitizing drugs (Table 93–7), human papilloma virus and smoking, with the latter being reported rather in association with SCC than BCC.[46]

PATHOPHYSIOLOGY

NMSCs arise from epidermal keratinocytes and involve primarily squamous cells and basal cells of the epidermis and dermis skin layers. BCCs arise from interfollicular basal cells or keratinocytes in hair follicles or sebaceous glands.[46] Among them, AKs are the most common premalignant lesions. Incidence of AKs is primarily driven by increased cumulative UVR exposure. It is estimated that up to 16% of the AKs will progress to SCC, while approximately a quarter will undergo regression within a year.[46]

CLINICAL PRESENTATION AND DIAGNOSIS

BCC is characterized as *circumscribed* or *diffuse*, and within these two groups, it is further classified according to the type, degree of differentiation, and depth of invasion. The circumscribed types include nodular BCC, adenoid BCC, fibroepithelioma, and basosquamous or metatypical carcinoma. The diffuse BCC types are plaque-like with horizontal spread and poorly differentiated margins and include the superficial BCC, the morpheaform BCC, and the micronodular BCC.

Patient Encounter 2, Part 1

A 33-year-old woman presents to her dermatologist with a raised lesion located in front of her left ear. She states that it got enlarged over the past few months.

History: The lesion began as a "reddish spot" nearly a year ago, then has raised, becoming gradually enlarged and more noticeable over the last 3 months.

The woman reports being an occasional tanning bed user due to her pale complexion but uses sunscreen regularly while outside, especially when vacationing on the beach. However, she does not typically reapply sunscreen on her face due to her makeup.

What are some characteristics that differentiate BCC from SCC?

What counseling points can be provided concerning the use of sunscreen or UV protective sprays on the head and face?

Nodular BCC is the most common type of BCC followed by superficial BCC. The morpheaform BCC is the most aggressive subtype while superficial BCC is the least.[13] BCC has indolent growth characteristics with a very low metastatic and mortality rate.[47] Paradoxically, BCCs can cause extensive local destruction and significant disfigurement. Approximately 80% of BCCs occur on the head and neck. Superficial BCC occurs predominantly on the trunk. Early-stage BCC is usually small, translucent or pearly with raised telangiectatic edges.[47] BCC may also appear as raised, yellowish-reddish lesions with a border resembling a string of pearls and telangiectasia. Dermatoscopy may distinguish between a benign and malignant lesion; however, clinical examination is usually sufficient for diagnosis of BCC. Depending on the size of the tumor, subtype, and treatment planned, a biopsy may be needed.

SCC usually presents on sun-exposed sites because of UVR damage to the skin. Unlike BCC, SCCs are preceded by premalignant lesions such as dysplastic leukoplakia (DL), AK, or SCC in situ (Bowen disease).[47] DL appears as a thickened skin formed in response to trauma or benign human papilloma virus infections. Its occurrence in other locations, such as the oral mucosa, may be due to chronic exposure to chewing tobacco. AK presents as a small papule on areas of sun damage to the skin. The rate of AK progression to SCC is 1% to 10% in 10 years and may be higher if a patient has more than five AKs.[47] Patients with a Bowen lesion present with slowly enlarging erythematous scaly or crusted plaques and have a 3% to 5% risk of progressing to SCC. A typical SCC lesion has an adherent crust and ill-defined edges; the first sign of malignant SCC is the induration of the lesion. The rate of metastasis for SCC is 2% to 6% and may be as high as 10% to 14% in high-risk sites such as the ear and lip and 30% in the genital area.[48] If progressing to metastasis, this may occur 1 to 2 years after the diagnosis of the primary SCC with 80% of metastasis involving the regional lymph nodes.

Keratinocyte carcinoma staging follows the TNM staging system recommended by the American Joint Committee on Cancer, based on tumor size, lymph node involvement, and dissemination. It is seldom done for patients with BCC because nodal and visceral metastasis are rare for this type of keratinocyte carcinoma.[47] Dermatoscopy may be employed for such instances, a technique involving the use of epiluminescence microscopy or surface microscopy. This test is usually performed by the dermatologist and may improve early detection.

TREATMENT

LO 4

KEY CONCEPT In patients diagnosed with BCC and SCC, the primary goal of therapy is cure and prevention of recurrence. Despite the low mortality rate, the tissue destruction, functional impairment, and disfigurement associated with keratinocyte carcinoma diagnosis and treatment are very significant issues. Therefore, secondary goals of therapy for NMSC are preservation of function and restoration of cosmesis. The treatment options for NMSC involve surgery, pharmacologic therapy, or a combination thereof. Treatment selection depends on factors such as tumor size, the site of the lesion, patient comorbidities, histologic particularities, and clinical nature of the cancer.

Nonpharmacologic Therapy

▶ *Surgery*

Surgery is the primary treatment modality for all patients diagnosed with keratinocyte carcinomas. Full-thickness ablative procedure in the form of surgical excision of the tumor along with a margin of normal tissue surrounding the tumor is the preferred method for high-risk tumors. Obtaining negative surgical margins is critical for cure and decreasing the risk of tumor recurrence. A margin of 4 to 5 mm in the case of well-defined keratinocyte carcinomas ensures peripheral clearance in 95% of cases. Depending on the tumor size, degree of differentiation, and invasion of surrounding structures, larger margins of resection may be necessary.[47] The two most common surgical techniques used are electrodessication and curettage (ED&C) and Mohs micrographic surgery (MMS). The indications of each of these procedures are described below.

Low-risk tumors defined as small, well-differentiated, and slow growing can be treated with superficial ablative techniques, including ED&C and cryotherapy.[47] ED&C is a simple, cost-effective technique that uses repeated cycles of using a curette to cut through malignant tissue followed by the application of high voltage low current to the skin causing drying or desiccation of the tissue. ED&C is indicated for well-defined superficial lesions that are not located in areas with increased risk for metastasis. The disadvantage of this technique is that histologic confirmation of complete tumor removal is not possible.[43] This procedure is not recommended for treatment of recurrent disease, tumors of the face, and high-risk tumors.[43]

For high-risk NMSC or for tumors located in cosmetically or anatomically sensitive areas, MMS is the procedure of choice. The goal of this therapy is complete removal of the cancer with preservation of as much surrounding normal tissue as possible. MMS involves careful dissection, staining of frozen sections, and anatomic mapping of the tumor specimen. Sections are assessed immediately under the microscope by the surgeon, and the process is repeated until a tumor-free margin is attained. MMS cures 93% of primary NMSC and 90% to 94% of recurrent disease compared with 92% and 77% cure rate with standard excision for primary and recurrent disease, respectively.[49] Cure rates for all modalities decrease with the presence of high-risk features but are still superior with MMS.[49]

Cryotherapy is a procedure used primarily for smaller, low-risk keratinocyte carcinomas with clearly defined margins. It involves delivering liquid nitrogen at subzero temperatures as a spray or with a supercooled metal probe to destroy the malignant tissue in a single cycle or multiple cycles.[43] This technique can achieve comparable results to conventional surgery for well-differentiated, not too large, superficial tumors in older patients with BCC.[43] The procedure is contraindicated in the hair-bearing scalp, upper lip, and distal portion of lower leg because of delayed healing and high rates of recurrence.[43]

Patient Encounter 2, Part 2

PMH: The patient is 2 years status postrenal transplantation.

FH: Father has HTN and atherosclerosis. Mother has osteoporosis.

Examination: Reveals a round, flesh-colored, waxy papule 0.5 cm in diameter positioned 1 cm from the tragus of the left ear with a pearly appearance and slight pigmentation in the center. Two irregular blood vessels are visible.

Which type of NMSC is most likely present on this patient?

What risk factors, if any, does this patient have for recurrence of the disease or progression to metastases?

What is the most appropriate initial treatment option in this patient?

▶ *Radiation*

Radiation is not standard therapy for the treatment of keratinocyte carcinomas; however, there are circumstances in which radiation may be preferred. It may be offered to patients in whom surgery is not possible because the tumor is inoperable or surgery would lead to unacceptable cosmetic or functional impairment.[49] Radiation to the lip, ear, and nasal entrance for SCC may provide the best cosmetic and functional result. On the other hand, some patients may develop dyspigmentation, radiodystrophy, or telangiectasia at the irradiated site, resulting in poorer cosmetic outcomes. It should be used with caution in patients younger than 65 years because latent NMSC can develop after 15 to 20 years of radiation exposure.[47]

▶ *Photodynamic Therapy*

Photodynamic therapy (PDT) involves the topical application of a photosensitizing light-activated agent that causes tumor cell damage and death. The photosensitizer is converted to protoporphyrin IX after it is preferentially taken up by active tumor cells. Damage to cell membranes, organelles, and surrounding vasculature occurs when protoporphyrin IX is activated after exposure to a light source. Protoporphyrin IX has absorption bands at 408, 510, 543, 583, and 633 nm; therefore, blue light (corresponding to 408-nm band) and red light (corresponding to 633-nm band) are the most commonly used light wavelengths.[46] Blue light is used for superficial lesions because of its shorter wavelength and because it does not penetrate the skin as well as red light.[43]

δ-Aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) are two photosensitizing agents that have FDA approval for the treatment of AK (Table 93–8 for dosing).[27] PDT has also been shown to be effective in the treatment of SCC in situ, but it is not indicated for SCC because of its extensive invasiveness and metastatic potential.[27] In patients with superficial BCC, MAL-PDT may be considered when surgery may result in suboptimal cosmetic outcomes or complications.[27] For patients with nodular BCC, MAL-PDT may be considered but not ALA-PDT.[27,43]

Table 93–8

Topical Therapy for Actinic Keratosis

Methyl Aminolevulinate Hydrochloride
Apply maximum 1 g topically on lesion(s) for one PDT session, followed by occlusive dressing for 2.5–4 hours, then red light illumination for 7–10 minutes. Two PDT sessions 1 week apart are required.

Aminolevulinic Acid
Apply topically to lesion(s) and let dry, then repeat once; rinse and pat dry after 14–18 hours, then expose to blue light photodynamic therapy illuminator; may repeat after 8 weeks. Cover and protect lesions with light-opaque material for 40 hours; sunscreen is ineffective.

Topical Fluorouracil
Apply 2% or 5% solution or cream topically twice daily over lesions for 2–6 weeks or apply 0.5% microsphere formulation once daily for up to 4 weeks.

Imiquimod
Apply topical formulation at bedtime daily 5 × per week for 6 weeks; leave on skin for 8 hours

The doses presented here are general. Clinicians should refer to reference materials to determine the specific dose based on the regimen the patient is receiving.

PDT, photodynamic therapy.

Pharmacologic Therapy

▶ *Fluorouracil*

LO 5

Nonsurgical treatment is used frequently for superficial keratinocyte carcinomas. Topical 5-fluorouracil has been used for the treatment of dermatologic disorders for approximately 45 years, and it has FDA approval for the treatment of AK and superficial BCC. Fluorouracil is available as both solution and cream with strengths ranging from 1% to 5%. There is also a microsphere-encapsulated 0.5% cream that has reduced systemic absorption with enhanced skin retention to reduce systemic side effects. The microsphere formulation is applied only once a day, providing patient preference and convenience over the twice-daily application with the other formulations. The FDA has approved 2% to 5% cream or solution and 0.5% microsphere formulation for AK. For superficial BCC, only the 5% strength is FDA approved for this indication. The most common side effects with topical fluorouracil are expected to occur within the initial 5 to 10 days of treatment, and include possible erythema, irritation, burning sensation, pruritus, and pain along with hypo- or hyperpigmentation. Patients may also experience inflammatory reactions that include crusting, edema, and oozing. The fluorouracil strength or frequency of application may be reduced if severe reactions occur. Topical steroids may be used concurrently with fluorouracil cream and for 1 to 2 weeks after treatment.[27] Caution should be used in administering fluorouracil to patients with dihydropyrimidine dehydrogenase deficiency, an enzyme critical in the metabolism of fluorouracil, because increased toxicity may occur.

LO 5

▶ *Imiquimod*

This therapy option works by stimulating innate and cell-mediated immune responses. It is FDA approved for the treatment of AK and for superficial BCC of the trunk, neck, or extremities when surgery may not be employed and follow-up is assured. Imiquimod has been shown to have complete clearing of AK in 50% of patients and partial clearing in 75% of patients with AK compared with 5% for those treated with placebo. Cure rates for imiquimod 5% in patients with superficial BCC are greater than 90%. The response rate is much lower for nodular BCC at 75%; therefore, it should be used in these patients only if they are not able to undergo surgery, radiation, or cryotherapy and the tumor is small and in a low-risk area. Imiquimod is not recommended for the treatment of invasive SCC, but data for SCC in situ showed a 93% cure rate; thus, it may be considered for this patient population.

Imiquimod is available in 3.75% strength, which may be applied daily on larger areas of skin, the balding scalp, or the full face, and 5% strength, which may be used on areas of skin that are 25 cm^2 or smaller (see Table 93–4). Imiquimod should be applied before bedtime and left on the skin for 6 to 10 hours. The most common side effects with imiquimod involve the area of application and present as erythema, pruritus, a burning or stinging sensation, and tenderness. Less commonly, hypopigmentation, fever, diarrhea, and fatigue may also occur. Temporary discontinuation of imiquimod and application of topical steroids may be necessary to alleviate the irritation symptoms. Imiquimod may be resumed at a decreased frequency after the symptoms have resolved.[27]

LO 6

▶ *Vismodegib*

Genetic alterations in the Hedgehog signaling pathway cause loss of function of *PTCH1*, which normally inhibits the signaling

Patient Care Process

Collect Information:

- Review current diagnosis with emphasis on skin cancer clinical signs (ABCDE)
- Obtain demographic information, family history, geographical location, and any specific lifestyle habits that may constitute risk factors
- Document medical and treatment history with emphasis on immune conditions, immunodeficiencies and immunosuppressive therapies, and medications associated with increased sun-related sensitivity (see Table 93–8)
- Any allergy or history of intolerance to biologics
- Understand cosmetic expectations and identify socioeconomic factors that may interfere with access to treatment and regular follow-ups

Assess the Information:

- Assess the possible causes of tumor occurrence (medical history, lifestyle, treatment, etc)
- Evaluate current performance status and assess other medications compliance
- Evaluate any treatment history that may (have) cause(d) photosensitivity
- Determine eligibility for immunotherapy and other current pharmacotherapy options
- Assess BRAF genotype status
- Review relevant laboratory tests (eg, electrolytes, liver panel, renal panel)
- Identify any predisposition to expected adverse events

Develop a Care Plan:

- Identify any contraindications for specific treatment options and select the best therapy
- Identify counseling points relevant to the patient and family
- Design a medication administration plan
- Design an adverse event monitoring and management plan

Implement the Care Plan:

- Educate the patient about the current options, explain the therapy selection, medication administration, common adverse events, reporting and management
- Review the patient's practices for skin cancer prevention
- Discuss importance of medication adherence and lifestyle modifications to reduce skin cancer risk
- Address any patient concerns about treatment outcomes
- Determine access to health care insurance and ensure smooth delivery of the treatment
- Assess patient expectations and verify their understanding regarding the course of treatment

Follow-up: Monitor and Evaluate:

- Evaluate how tumor resection affected the skin integrity, appearance, and function, the quality of life postoperative
- Assess skin recovery after radiation
- Verify patient and family understanding regarding subsequent prevention and systematic skin self-examination
- Review reported adverse events and appropriateness of their management
- Discuss treatment alternatives and options for recurrence prevention
- Review the appropriateness of lab monitoring for the ongoing treatment plan
- Address any palliative care symptoms and assess patients' psychological, physical, and social functioning

LO 3

activity of Smoothened (SMO), a transmembrane protein involved in Hedgehog signal transduction. This first-in-class, oral inhibitor of the Hedgehog signaling pathway is a small molecule that binds to and inhibits SMO. Vismodegib is approved by the FDA for the treatment of adult locally advanced or metastatic BCC that has recurred following surgery or has not been a candidate for surgery or radiation.

OUTCOMES EVALUATION

- Evaluate awareness and approach to avoid sun exposure and perform total-body skin self-examination.
- Assess treatment tolerance at every visit and ensure proper administration technique with topical treatments, such as fluorouracil or imiquimod: cleaning of treatment area before application, lesion area coverage with a 1-cm margin, and use of gloves, as well as hands washing after application.
- Assess side effects' management such as pain, itching, and inflammation and reinforce the need for dermatologist consult if worsening.
- Verify the presence of the *PTCH1* mutation before initiation of oral SMO inhibitor treatment and assess compliance.

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Abbreviations Introduced in This Chapter

AK	Actinic keratosis
ALA	δ-Aminolevulinic acid
APC	Antigen-presenting cell
BCC	Basal cell carcinoma
BRAF	Proto-oncogene B-raf
CDKN2A	Cyclin-dependent kinase inhibitor-2A
CNS	Central nervous system
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
CYP	Cytochrome P-450
DL	Dysplastic leukoplakia
ED&C	Electrodessication and curettage
ERK	Extracellular-signal-regulated kinase
HD	High dose

IFN	Interferon-α-2b
Ig	Immunoglobulin
IL-2	Interleukin-2
LFT	Liver function test
MAL	Methyl aminolevulinate
MAL-PDT	Methyl aminolevulinate–photodynamic therapy
MAP	Microtubule-associated protein
MAPK	Mitogen-activated protein kinase
MEK	MAPK/ERK kinases
MITF	Microphtalmia-associated transcription factor
MM	Malignant melanoma
MMS	Mohs micrographic surgery
NMSC	Nonmelanoma skin cancer
NRAS	Neuroblastoma RAS viral oncogene
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PDT	Photodynamic therapy
PPP6C	Protein phosphatase 6 catalytic subunit
PTCH1	Patch homolog-1
PTEN	Phosphatase and tensin homolog
RAC-1	Ras-related protein C3 botulinum toxin substrate 1 precursor
RAF	Protooncogene raf-1
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SLN	Sentinel lymph node
SMO	Smoothened
SPF	Skin protection factor
SRS	Stereotactic radiosurgery
STK19	Serine/threonine-protein kinase 19
TIL	Tumor infiltrating lymphocytes
TNM	Tumor, node, metastasis
UVA/B	Ultraviolet (radiation) A/B
UVR	Ultraviolet radiation
WBRT	Whole-brain radiation therapy
XP	Xeroderma pigmentosum

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2016. CA Cancer J Clin. 2016;66:7–30.
2. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the US population, 2012. JAMA Dermatol 2015; 151(10):1081–1086.
3. Feehan RP, Shantz LM. Molecular signaling cascades involved in nonmelanoma skin carcinogenesis. Biochem J. 2016;473(19): 2973–2994.
4. Chen ST, Geller AC, Tsao H. Update on the epidemiology of melanoma. Curr Dermatol Rep. 2013;2:24–34.
5. Cancer Stat Facts: Melanoma of the Skin. National Cancer Institute. Surveillance Epidemiology and End Results (SEER) Program. Available from: https://seer.cancer.gov/statfacts/html/melan.html. Accessed July 23, 2018.
6. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463): 415–421.
7. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. Cell. 2012;150:251–263.
8. Narayanan D, Saladi R, Fox J. Ultraviolet radiation and skin cancer. Int J Dermatol. 2010;49(9):978–986.
9. Cho Y, Chiang M. Epidemiology, staging (new system), and prognosis of cutaneous melanoma. Clin Plastic Surg. 2010;37: 47–53.
10. Reichrath J, Nurnberg B. Cutaneous vitamin D synthesis versus skin cancer development. The Janus faces of solar UV-radiation. Dermatoendocrinol. 2009;1(5):253–261.
11. Rigel D, Russak J, Friedman R. The evolution of melanoma diagnosis: 25 years and beyond the ABCDs. CA Cancer J Clin. 2010;60(5):301–316.
12. Ko J, Velez N, Tsao H. Pathways to melanoma. Semin Cutan Med Surg. 2010;29:210–217.
13. Menzies AM, Long GV, Murali R. Dabrafenib and its potential for the treatment of metastatic melanoma. Drug Des Devel Ther. 2012;6:391–405.
14. Netscher D, Leong M, Orengo I, et al. Cutaneous malignancies: melanoma and nonmelanoma types. Plast Reconstr Surg. 2011;127:37e.
15. Langley RGB, Barnhill RL, Mihm Jr, MC, et al. Neoplasms: cutaneous melanoma. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. Fitzpatrick's Dermatologyin General Medicine, 6th ed. New York: McGraw-Hill; 2003:938.
16. Spatz A, Batista G, Eggermont AM. The biology behind prognostic factors of cutaneous melanoma. Curr Opin Oncol. 2010;22:163–168.
17. Ross M, Gershenwald J. Evidence-based treatment of early-stage melanoma. J Surg Oncol. 2011;104:341–353.
18. Tarhini A, Agarwala S. Management of brain metastases in patients with melanoma. Curr Opin Oncol. 2004;16:161–166.
19. Rao N, Yu H, Trotti III A, Sondak V. The role of radiation therapy in the management of cutaneous melanoma. Surg Oncol Clin North Am. 2011;20:115–131.
20. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. Eur J Cancer. 2010;46:270–283.
21. Haanen JB. Immunotherapy of melanoma. EJC Suppl. 2013;11(2):97–105.
22. Weber J. Immunotherapy for melanoma. Curr Opin Oncol. 2011;23:163–169.
23. Chesney J, Awashti S, Curti B, et al. Phase IIIb safety results from an expanded-access protocol of talimogene laherparepvec for patients with unresected, stage IIIb-IVM1c melanoma. Melanoma Res. 2018;28(1):44–51.
24. Tarhini AA, Gogas H, Kirkwood JM IFN-α in the treatment of melanoma. J Immunol. 2012;189:3789–3793.
25. Mocellin S, Pasquali S, Rossi C, Nitti D. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2010;102:493–501.
26. Atkins M, Lotze M, Dutcher J, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17:2105–2116.
27. NCCN Guidelines. National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed December 15, 2017.
28. Sloot S, Rashid OM, Sarnaik AA, et al. Developments in intralesional therapy for metastatic melanoma. Cancer Control. 2016;23(1):12–20.
29. Boasberg P, Hamid O, O'Day S. Ipilimumab: unleashing the power of the immune system through CTLA-4 blockade. Semin Oncol. 2010;37:440–449.
30. Hodi F, O'Day S, McDermott D, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711–723.
31. Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015;33(17):1889–1894.
32. Approved Risk Evaluation and Mitigation Strategies (REMES). U.S. Food and Drug Administration. Available from: https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm249435.pdf. Accessed December 17, 2017.

33. Kähler C, Hauschild A. Treatment and side effect management of CTLA-4 antibody therapy in metastatic melanoma. J Dtsch Dermatol Ges. 2011;9:277–285.
34. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372(4):320–330.
35. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013;369(2):134–144.
36. Teply BA, Lipson EJ. Identification and management of toxicities from immune checkpoint-blocking drugs. Oncology (Williston Park). 2014;28(3):30–38.
37. Chapman P, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2010;364:2507–2516.
38. Luke J, Hodi F. Vemurafenib and BRAF inhibition: a new class of treatment for metastatic melanoma. Clin Can Res. 2012; 18(1):9–14.
39. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016; 17(9):1248–1260.
40. Long GV, Hauschild A, Santinami M. Adjuvant dabrafenib plus trametinib in stage III braf-mutated melanoma. N Engl J Med. 2017;377(19):1813–1823.
41. Karimkhani C, Boyers LN, Dellavalle RP, Weinstock MA. It's time for "keratinocyte carcinoma" to replace the term "nonmelanoma skin cancer". J Am Acad Dermatol. 2015;72(1):186–187.
42. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer in the U.S. population, 2012. JAMA Dermatol. 2015;151(10):1081–1086.
43. LeBoeuf N, Schmults C. Update on the management of high-risk squamous cell carcinoma. Semin Cutan Med Surg. 2011;30:26–34.
44. Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002–2006 and 2007–2011. Am J Prev Med. 2015;48(2):183–187.
45. Athar M, Walsh SB, Kopelovich L, Elmets CA. Pathogenesis of nonmelanoma skin cancers in organ transplant recipients. Arch Biochem Biophys. 2011;508(2):159–163.
46. Ratushny V, Gober MD, Kick R, et al. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. J Clin Invest. 2012;122(2):464–472.
47. Madan V, Lear J, Szeimies R. Non-melanoma skin cancer. Lancet. 2010;375:673–685.
48. Kwasniak L, Garcia-Zuazaga J. Basal cell carcinoma: evidence-based medicine and review of treatment modalities. Int J Dermatol. 2011;50:645–658.
49. Galiczynski E, Vidimos A. Nonsurgical treatment of non melanoma skin cancer. Dermatol Clin. 2011;29:297–309.
50. Wagle N, Emery E, Berger MF, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol. 2011;29(22):3085–3096.

94 Ovarian Cancer

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LEARNING OBJECTIVES

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

1. Demonstrate understanding of the etiology and risk factors associated with the development of ovarian cancer.
2. Justify the risk and benefits of the surgical and chemoprevention options available for decreasing the potential risk of developing ovarian cancer.
3. Interpret and understand the utility of the screening tests and serologic markers for diagnosing ovarian cancer.
4. Distinguish the nonspecific physical signs and symptoms of ovarian cancer.
5. Recommend the appropriate surgical and chemotherapy treatment options for newly diagnosed, persistent, and recurrent ovarian cancer patients.
6. Discuss the role of maintenance treatment for improving overall survival for ovarian cancer patients.
7. Compare and contrast chemotherapy options for women with recurrent platinum-resistant ovarian cancer.

INTRODUCTION

Ovarian cancer is relatively uncommon but is the most incurable of the gynecologic cancers. Ovarian cancer is often denoted as the "silent killer." KEY CONCEPT The primary reason for the high mortality rate associated with ovarian cancer is the nonspecific symptoms and difficulty for early detection or screening that result in patients presenting with advanced disease. The majority of ovarian cancers are of epithelial origin. Each time ovulation occurs, the epithelium of the ovary is broken followed by occurrence of cell repair. The incessant ovulation hypothesis proposes that the increasing number of times the ovary epithelium undergoes cell repair is associated with the increasing risk of mutations and ultimately ovarian cancer. Although the majority of patients will achieve a complete response (CR) to primary surgery and chemotherapy, disease recurs in more than 50% of patients in the first 2 years after completion of primary treatment. KEY CONCEPT Ovarian cancers often cause metastasis via the lymphatic and blood systems to the liver, and/or lungs. Common complications of advanced and progressive ovarian cancer include **ascites** and small bowel obstruction (SBO), which often are associated with the end of life.

EPIDEMIOLOGY AND ETIOLOGY

In 2018, there were an estimated 22,240 new cases of ovarian cancer diagnosed with an associated 14,070 deaths.[1] Ovarian cancer remains the number one gynecologic killer and the fifth leading cause of cancer-related death in women. Despite great efforts and extensive research, addition of new agents and routes of administration, there has been little change in the mortality rate associated with ovarian cancer over the past six decades. Again, this high mortality rate associated with ovarian cancer can be attributed to its insidious onset of nonspecific symptoms, resulting in the majority of patients not presenting until the cancer has progressed to stages III to IV disease.

LO 1

As with many other disease states, a significant risk factor associated with ovarian cancer is aging. Risk of ovarian cancer increases from age 40 to 79 years, with the mean age at diagnosis being 63 years and the majority of women being diagnosed between 55 and 64 years.[2]

LO 1

Ovarian cancer is a sporadic disease; fewer than 10% of ovarian cancers can be attributed to heredity. KEY CONCEPT The majority of cases of ovarian cancer occur sporadically, making it difficult to screen and prevent. Although hereditary accounts for fewer than 10% of all ovarian cancer cases, when there is a family history, it appears to be an important risk factor in the development of ovarian cancer in some patients.[3] If one family member has a diagnosis of ovarian cancer, the associated risk is about 9%, but this risk increases to greater than 50% if there are two or more first-degree relatives (ie, mother and sister) with a diagnosis of ovarian cancer or multiple cases of ovarian and breast cancer.[3] Both breast cancer activator gene 1 (*BRCA1*) and breast cancer activator gene 2 (*BRCA2*) mutations have been associated with ovarian cancer. However, *BRCA1* is more prevalent, being associated with 90% of hereditary and 10% of sporadic cases of ovarian cancer.[3] Hereditary breast and ovarian cancer (HBOC) syndrome is one of the two different forms of hereditary ovarian cancer and is associated with germline mutations in *BRCA1* and *BRCA2*.[3,4] The hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is a familial syndrome with germline mutations causing defects in enzymes involved in DNA mismatch repair, which has been associated with up to 12% of hereditary ovarian cancer cases.[4]

Patient Encounter 1

The patient is a 71-year-old active, nonobese woman, who has been in good health up until recently (about 8 weeks or so) when she started to feel fatigued often and have difficulties with bowel movements. On New Year's Day she mentioned to her daughter that she felt so bloated because she has had not been able to have a bowel movement in over a week despite use of OTC laxative medications. The following Monday she saw her general physician that recommended dietary modifications and new aggressive bowel regimen including an enema that evening. One month later, her symptoms persisted, so her physician ordered an abdominal CT scan which came back positive for fluid in abdominal cavity and 20 cm noncystic mass on right ovary extending to outside of colon wall. Of note, she has been married for 35 years with only two sexual partners in her lifetime. They have two daughters who are all grown adults. Her first menses was when she was 13 years old and menopause was at age 57 years. She has had infrequent alcohol on social occasions only and denies any tobacco use.

Based on the results from the abdominal CT scan, what laboratory tests are needed and what type of specialist should she be referred to complete her workup?

In the context of this patient, discuss why ovarian cancer is often denoted the "silent killer" and what needs to be done for earlier diagnosis of ovarian cancer.

Discuss the type of surgery recommended and outcome goal for this surgery.

Patient Encounter 2

A 37-year-old woman diagnosed with stage IIIC adenocarcinoma of the ovary with positive *BRCA1* mutation status post optimal debulking surgery completed six cycles of paclitaxel 175 mg/m^2 IV plus carboplatin AUC 5 IV. Her CT scan findings suggest no detectable disease and CA-125 within the normal range (28 U/mL [28 kU/L]) upon completion of her chemotherapy. She feels great and has no obvious symptoms of ovarian cancer at this time.

Discuss the advantages and disadvantages of treatment options for maintenance treatment with PARP-inhibitor versus bevacizumab for this patient.

Describe the role of second-look surgery for this patient.

LO 1

Although it is not clearly defined, hormones and reproductive history are associated with the risk of developing ovarian cancer. **Nulliparity**, infertility, early menarche, or late menopause is associated with an increased risk of ovarian cancer.[5]

Ovarian cancer is associated with certain dietary and environmental factors as well. A diet that is high in galactose and animal fat and meat increases the risk of ovarian cancer, whereas a vegetable-rich diet is suggested to decrease the risk.[6,7]

Screening and Prevention

▶ *Screening*

Currently, there is no standard effective screening tool that is adequately specific or sensitive for early detection.

Pelvic examinations are effective for detecting obvious tumors present with a sensitivity of 67% for detecting all tumors; however, minimal or microscopic disease cannot be detected on physical examination.[8] Pelvic examinations are noninvasive and well accepted, but they do not usually detect ovarian cancer until it is in advanced stage. Transvaginal ultrasound (TVUS) is a component of current screening practices. Typically, it is used in combination with cancer antigen-125 (CA-125) or could be used as a single modality. TVUS releases sonic sound waves that create an image of the ovary to evaluate the size and shape and detect the presence of cystic or solid masses. Limitations of this technique are lack of specificity and an inability to detect peritoneal cancer or cancer in normal size ovaries.[2,9] Most prevention clinics use this multimodality approach to screen high-risk women and recommend yearly ultrasound in combination with CA-125 blood test every 6 months.

LO 3

Serum CA-125 is the most extensively evaluated tumor marker for ovarian cancer. KEY CONCEPT Because CA-125 is a nonspecific marker, it is not a standard recommendation for routine screening for prevention of ovarian cancer. Unfortunately, since CA-125 is nonspecific, elevated levels can be associated with a number of other gynecologic and GI-related diseases. CA-125 levels in a woman without ovarian cancer are static or tend to decrease over time, but levels associated with malignancy continue to rise.[9,10]

▶ *Prevention*

Ovulation is considered a hostile event to the ovarian epithelium, making it more susceptible to damage and cancer. Interventions or conditions that limit the number of ovulations in a woman's reproductive history, including **multiparity**, have a protective effect.

LO 2

Chemoprevention Investigational chemoprevention strategies used for ovarian cancer include oral contraceptives (OCs), aspirin, nonsteroidal anti-inflammatory agents, and retinoids, although none of these is currently accepted as standard treatment for the prevention of ovarian cancer. The theory that OCs reduce the number of ovulatory events is a basic explanation of its protective effect. Recent studies have suggested that progestin-induced apoptosis of the ovarian epithelium is responsible for the chemopreventive effect of OCs. The theory is that cells that have genetic damage but are not yet neoplastic have an increased chance of undergoing apoptosis.[11] OCs decrease the relative risk to less than 0.4% in women that use OCs for longer than 10 years.[12] However, the maximum protective effect of OC use in women with *BRCA* mutations has been reported to be between 3 and 5 years.[12] At the same time, OC use has been associated with an increased risk of breast cancer.[11,13] Thus, women with a family history of breast cancer would not be ideal candidates for this preventive measure.

LO 2

Nonsteroidal anti-inflammatory agents, aspirin, and acetaminophen have been suggested for use in the prevention of different cancers, especially hereditary nonpolyposis colon cancer.[13] Although observational studies have linked these to a reduction of ovarian carcinoma risk, evidence is still lacking. Potential mechanisms include effects on normal ovulation shed and inhibition of ovulation.[13] Other pharmacologic interventions that have been suggested but are still being evaluated include vitamin A, lutein, and other carotenoids.[14,15] The protective effect of these agents is associated with inhibition of cell growth as well as promotion of cellular differentiation.[14]

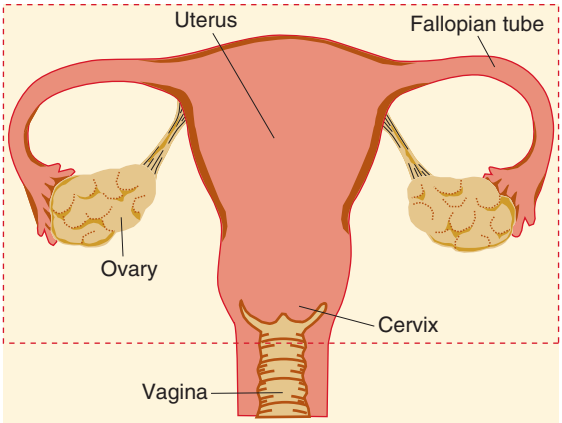

FIGURE 94–1. Diagram of female reproductive tract (uterus, fallopian tubes, ovaries, vagina). The *dashed line box* outlines what is removed during the total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO).

Prophylactic Surgery Surgical strategies are also used in the prevention of ovarian cancer. The goal is to remove healthy, at-risk organs and ultimately reduce the risk of developing cancer. These surgeries include prophylactic **bilateral salpingo-oophorectomy** (BSO) or tubal ligation (**Figure 94–1**).

LO 2 Prophylactic oophorectomy should be considered in any woman with a high risk of developing ovarian cancer.[16] The criteria for defining high risk includes any woman with two or more first-degree relatives with epithelial ovarian carcinoma; a family history of multiple occurrences of **nonpolyposis** colon cancer, endometrial cancer, and ovarian cancer; and a family history of multiple cases of breast and ovarian cancer.[17] Patients undergoing prophylactic oophorectomy need to be made aware that complete protection is not guaranteed.[17–19] Although a 67% reduction in risk has been shown, a potential 2% to 5% risk of peritoneal **carcinomatosis** remains.[18–20]

LO 2 **Tubal Ligation** Tubal ligation is another procedure that has shown potential for risk reduction. However, it is not recommended as a sole procedure in prophylaxis. The protective effect may be attributable to limiting exposure of the ovary to environmental carcinogens. A case-control study conducted by Narod and colleagues[19] found that a history of tubal ligation in *BRCA*-positive women was associated with a statistically significant 63% reduction in risk.

Genetic Screening Genetic screening is recommended for high-risk patients. Patients should be screened for genes such as *BRCA1* and *BRCA2* or other genes such as those associated with HNPCC or the HBOC syndrome.[3,21] Patient and family counseling and genetic counseling should be available for the patient and family to prepare and deal with the health and psychosocial implications of the genetic test results. Before this decision, the potential preventive options should be discussed, such as prophylactic BSO and/or total **hysterectomy**. Cancer risk and patient's health need to be balanced, but typically surgery can be held off until after the childbearing years.[20,21]

PATHOPHYSIOLOGY

The three current theories are the incessant ovulation hypothesis, the pituitary gonadotropin hypothesis, and the chronic inflammatory processes hypothesis.[2] The incessant ovulation hypothesis proposes that the pathogenesis of ovarian cancer is connected to continual ovulation. Ovulation is considered a "hostile" event to the ovaries, perhaps with not enough time for adequate repair. Each time ovulation occurs, the ovary epithelium is disrupted, and cell damage occurs. Thus, repeated ovulations may lead to a greater number of repairs of the ovarian epithelium and increase the possibility of aberrant repairs, mutation, and **carcinogenesis**.[22] The pituitary gonadotropin hypothesis associates the disease with elevations in gonadotropin and estrogen levels.[2] This leads to an increase in the number of follicles and therefore an increased risk of malignant changes. Finally, the chronic inflammatory processes may be involved with various environmental carcinogens to cause cancer.[2,13]

The three major pathologic categories of ovarian tumors include sex-cord stromal, germ cell, and epithelial. About 85% to 90% of ovarian cancers are of epithelial origin. Epithelial ovarian tumors are composed of cells that cover the surface of the ovary such as serous, mucinous, endometrioid, clear cell, and poorly differentiated adenocarcinomas. Germ cell tumors involve the precursors of ova with the most common type being dysgerminoma, which are most commonly diagnosed in women younger than the age of 40 years and generally have a better prognosis.[2] Sex-cord stromal tumors are not only indolent tumors that produce excess estrogen and androgens but also have a better overall prognosis.[2] Although the histologic type of the tumor is not a significant prognostic factor, it is important to know the histopathologic grade with high-grade being more aggressive and low-grade slower growing. Similar to other solid tumors, clear cell histology tends to be high grade and often chemotherapy-resistant. Undifferentiated tumors are associated with a poorer prognosis than lesions that are considered to be well or moderately differentiated.

TREATMENT

Desired Outcomes

Health care providers use a multimodality approach, including surgery and chemotherapy, in initial treatment of patients with ovarian cancer with a curative intent, or restoring a normal life span. KEY CONCEPT Although the majority of patients initially achieve a CR, disease will recur within the first 2 years in more than 50% of patients.[2,23] CR to treatment is defined as no evidence of disease can be detected by physical examination or diagnostic tests and patient has a normalized CA-125.

The stage of disease at the time of diagnosis is the most important prognostic factor affecting overall survival in ovarian cancer patients.[24] The estimated 5-year survival rates of patients with localized, regional, distant, and unstaged ovarian cancer are 92.1%, 73.2%, 28.3%, and 22.8%, respectively.[24] The histology of the disease is another predominant prognostic factor influencing treatment outcomes. Clear cell and undifferentiated tumors do not respond as well to chemotherapy.[2] The extent of residual disease and tumor grade are also predictive of response to chemotherapy and overall survival.[2] There are other prognostic factors that may predict how well a patient will respond to adjuvant chemotherapy.

The treatment goals shift when a patient presents with recurrent ovarian cancer. The desired outcomes focus on relief of symptoms such as pain or discomfort from ascites, slowing disease progression, and prevention of serious complications such as SBO. When a patient relapses, the prognostic factors are similar as after initial surgery except that the amount of time that has lapsed since the completion of chemotherapy should

Clinical Presentation and Diagnosis of Ovarian Cancer

General

Ovarian cancer typically has delay in diagnosis due to the common nonspecific signs and symptoms often initially suggesting GI-related complications. By the time symptoms become unrelenting and bothersome, patients most likely have advanced stage disease.

Symptoms

LO 4

Patients may experience episodes or persistent symptoms such as abdominal pain, constipation or diarrhea, flatulence, urinary frequency, or incontinence.

Signs

The degree of abdominal swelling secondary to fluid accumulation may present like "pregnant abdomen" and irregular vaginal bleeding.

Laboratory Test

- CA-125. The normal level is less than 35 U/mL (35 kU/L). Note: This test is associated with a lack of specificity. CA-125 can be elevated in a number of other states such as different phases of the menstrual cycle, endometriosis, and nongynecologic cancers. Therefore, it is important to rule out other cancers associated with the abdominal cavity.
- Carcinoembryonic antigen (CEA). CEA is a marker for colon cancer. A normal value is less than 3 ng/mL (3 mcg/L). However, this can also be elevated in serous papillary carcinomas of ovary.
- CA-19–9 is a marker for many GI tumors such as cholangiocarcinomas.

Chemistries with Liver Function Tests (LFTs)

- LFTs and serum creatinine might be suggestive of extent of disease. The majority of this information is needed to determine if the patient is a surgical candidate. Laboratory study results should be within normal limits.

Complete Blood Count (CBC)

- Abnormalities in CBC are not associated with ovarian cancer; however, this information is needed to determine if the patient is a surgical candidate. Laboratories should be within normal limits.

Other Diagnostic Tests

To characterize local disease, one or both of the following are completed:

- TVUS
- Abdominal ultrasound

To evaluate the extent of disease, only one of the following is completed:

- CT scan
- MRI
- PET scan

Chest x-ray is also often done as part of clearance for surgery.

Ovarian cancer is usually confined to the abdominal cavity, but spread can occur to the lung and liver and less commonly to the bone or brain. Disease is spread by direct extension, peritoneal seeding, lymphatic dissemination, or bloodborne metastasis. Lymphatic seeding is the most common pathway and frequently causes ascites.

be considered to determine if drug resistance is emerging in the tumor. Recurrent platinum-sensitive ovarian cancer patients generally have a better prognosis than platinum-resistant patients.

Nonpharmacologic Therapy

KEY CONCEPT Surgery is the primary treatment intervention for ovarian cancer.[25–27] A total hysterectomy with BSO (TH-BSO) (see Figure 94–1), **omentumectomy**, and lymphonectomy (or lymph node dissection) is the standard initial surgical treatment of ovarian cancer.[25] The objective of the surgery is to debulk the patient to less than 1 cm of residual disease remains. Residual disease less than 1 cm correlates with better CR rates to chemotherapy and better overall survival compared with patients with bulky residual disease (> 1 cm).[26,27] The size of residual tumor masses after primary surgery is found to be another important prognostic factor in patients with advanced ovarian cancer.[27]

LO 5

A thorough exploratory **laparotomy** is essential for the accurate staging of the patient.[25–27] KEY CONCEPT Ovarian cancer is staged surgically using the International Federation of Gynecology and Obstetrics (FIGO) staging algorithm. For certain patients with limited stage disease, surgery may be curative.

Other surgical procedures have been evaluated to improve overall survival. Debulking surgery is intended to relieve symptoms associated with complications such as SBO and help improve the patient's quality of life but does not have a curative intent. Interval debulking that is completed after two to three cycles of chemotherapy has not translated to an improved survival benefit. Often debated, the benefit of the "second-look laparotomy" to evaluate residual disease after the patient has completed chemotherapy remains controversial because it has been difficult to establish any impact on patients' overall survival. It has questionable benefit because although approximately 40% of patients with advanced disease have a negative second look, 50% still relapse.[2] The role of **laparoscopic** surgery is somewhat controversial for initial surgery but is more often considered in debulking of recurrent or advanced disease when the intent is palliative rather than curative.[25]

Pharmacologic Therapy

▶ *First-Line Chemotherapy*

KEY CONCEPT After initial surgery, the gold standard of care is six cycles of taxane/platinum-containing regimen for patients with advanced ovarian cancer.[28–30] Patients with limited disease, that is, stage IA, will have observation alone after surgery (**Figure 94–2**).

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Majority of patients though will receive adjuvant chemotherapy within 3 to 4 weeks after surgery. Most often, paclitaxel is the taxane agent used in combination with carboplatin as the preferred platinum agent.[28–30] Depending on patients' preexisting comorbidities and how well they tolerate chemotherapy regimens, substitution with docetaxel or cisplatin might be considered.

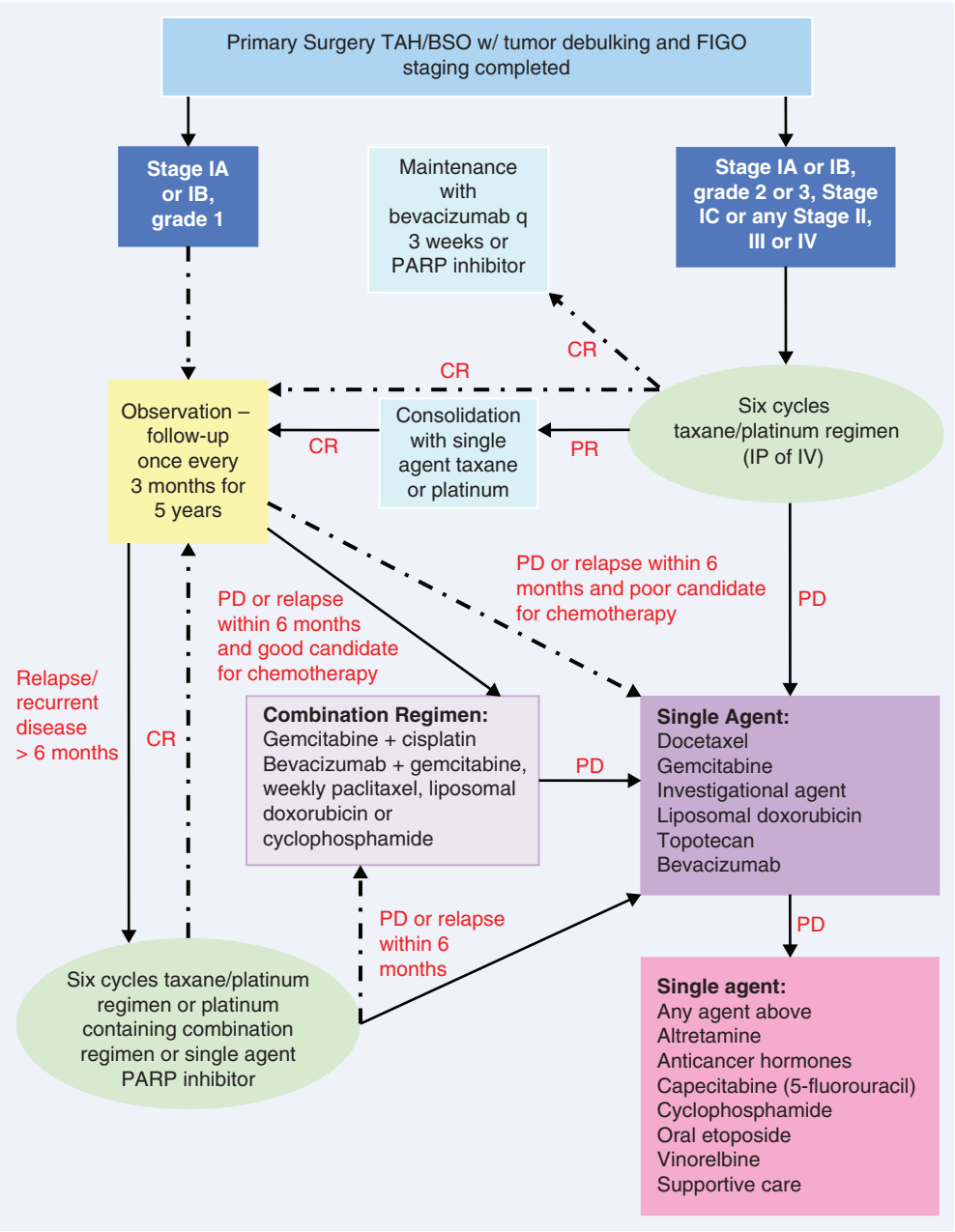

FIGURE 94–2. Summary of a chemotherapy treatment algorithm for epithelial ovarian cancer. (CR, complete response; FIGO, Federation of Gynecology and Obstetrics; PD, progressive disease; PR, partial response; TAH-BSO, total abdominal hysterectomy with bilateral salpingo-oophorectomy.)

The route of administration should also be discussed. Although intravenous (IV) administration is often used, intraperitoneal (IP) administration has been shown to improve overall survival and should be considered as an option for first-line treatment; however, patient selection for IP therapy is critical[31] (Table 94–1). Close monitoring of organ function, nausea/vomiting, myelosuppression, and neuropathies is necessary for all taxane/platinum regimens (Table 94–2).

▶ *Intraperitoneal Chemotherapy*

For more than four decades, numerous investigators have evaluated the IP route for administration of chemotherapy; however, it was not until the third report of an improvement in overall survival that brought its use to the forefront in the first-line setting.[32] The principal theory supporting IP administration is to increase drug concentration in the site of disease, specifically the abdominal cavity. Patient characteristics greatly influence response and tolerability of IP chemotherapy. To be selected to receive IP chemotherapy for first-line treatment of ovarian cancer, the patient should have tumor optimally debulked and no bowel resection with primary surgery, normal renal and liver function, younger age, and no significant comorbidities.

When IP therapy is administered, the placement of an IP catheter should occur at the time of surgery unless otherwise contraindicated. During IP administration, chemotherapy is delivered to the peritoneal space in 1 L of normal saline (NS) that has been warmed followed by another liter of NS to enhance

Table 94–1

Summary of First-Line Chemotherapy Regimens for Advanced Ovarian Cancer

Gold standard first-line chemotherapy after initial surgery for treatment of ovarian cancer:

Paclitaxel 175 mg/m^2 IV infused over 3 hours + carboplatin AUC = 5 IV infused over 1 hour. Regimen is given once every 21 days × 6 cycles (+/– bevacizumab 7.5 mg/kg once every 3 weeks × 6 cycles followed by additional 12 cycles after completion of primary chemotherapy)

Alternative first-line regimen: Paclitaxel IV with substitution of carboplatin IV with cisplatin IP and addition of paclitaxel IP therapy:

Patient selection is critical: must have optimally debulked disease (< 1 cm) and no significant comorbidities; younger patients tolerate better

Day 1: paclitaxel 135 mg/m^2 IV infused over 24 hours + day 2: cisplatin 100 mg/m^2 IP infused over 1 hour + day 8: paclitaxel 60 mg/m^2 IP infused over 1 hour. Regimen is given once every 21 days × 6 cycles

Alternative first-line regimen: Dose density. Consider for patients with optimal debulking, no comorbidities, good performance status:

Paclitaxel 80 mg/m^2 IV infused over 1 to 3 hours once a week with carboplatin AUC = 6 IV infused over 1 hour on day 1 only of 21-day cycle

Alternative first-line regimen: Substitution of cisplatin in place of carboplatin. Consider for patients experiencing difficulty with maintaining platelet counts:

Paclitaxel 135 mg/m^2 IV infused over 24 hours + day 2: cisplatin 75 mg/m^2 IV infused over 4 hours. Regimen is given once every 21 days × 6 cycles

Alternative first-line regimen: Substitution of docetaxel in place of paclitaxel. Consider for patients with preexisting or increased risk of neuropathies:

Docetaxel 75 mg/m^2 IV infused over 1 hour + carboplatin AUC = 5 IV infused over 1 hour. Regimen is given once every 21 days × 6 cycles

AUC, area under the curve; IV, intravenous.

drug distribution as tolerated.[33,34] The current standard IP regimen includes the administration of paclitaxel IV on day 1 followed by cisplatin IP on day 2 and then paclitaxel IP on day 8 given on a 21-day cycle for a total of six cycles (see Table 94–2). The most common toxicities associated with IP administration include abdominal pain, myelosuppression, neurotoxicity, and catheter-related infections. The substitution of carboplatin IP in place of cisplatin remains investigational and should not be recommended outside a clinical trial protocol.

► *Neoadjuvant Chemotherapy*

Neoadjuvant chemotherapy is first-line treatment for patients who are poor surgical candidates or patients with bulky or significant tumor burden.[23] For patients who are poor surgical candidates because of significant comorbidities, a combination of taxane with platinum agent is administered every 21 to 28 days as tolerated with the intent to relieve symptoms and slow progression of disease. In some cases, especially in elderly patients, single-agent carboplatin is used as palliative treatment instead. Chemotherapy alone has not been curative for patients with advanced ovarian cancer.[23]

In patients with bulky disease or significant tumor burden, neoadjuvant chemotherapy can be used to decrease tumor burden to increase the likelihood of optimal tumor debulking during surgery.[31] Typically, three cycles of the standard combination taxane/platinum regimen is administered once every 21 days. After surgery, patient will receive another three to six cycles depending on their response to chemotherapy.

► *Consolidation and Maintenance Chemotherapy*

Consolidation chemotherapy is the addition of cycles of the taxane/platinum regimen or the addition of single-agent platinum or single taxane after completion of first-line chemotherapy.[35,36] If the tumor has a partial response (PR) to first-line chemotherapy evident by a significant decline in CA-125 by greater than 50% presurgery level and/or tumor regression or decrease in size, then cancer is still considered taxane/platinum sensitive. Additional cycles of chemotherapy are given until CR is achieved (see Figure 94–2). In 2014, bevacizumab was approved as the first targeted therapy for maintenance treatment for ovarian cancer based on the improved overall survival observed in the ICON-7 study.[37] Maintenance chemotherapy is similar to consolidation chemotherapy except maintenance chemotherapy is given to patients who have achieved a clinically CR.[38] The rationale for maintenance chemotherapy is used to extend progression-free and overall survival by eliminating any microscopic disease present after completion of primary chemotherapy. Two agents from the class of poly(ADP-ribose) polymerase (PARP) inhibitors, niraparib and olaparib, have also demonstrated benefit in improving progression-free survival as maintenance therapy following achieving clinical CR to primary treatment.[39–41] PARP inhibitors were the second class of targeted therapy agents approved for maintenance treatment of ovarian cancer. While greater benefit has been observed in the presence of BRCA1 mutations, clinical benefit has been observed even in the absence of BRCA1 mutations as well.[40,41]

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For an extensive description of the common agents used in first-line, consolidation, and maintenance chemotherapy of ovarian cancer, please see Chapter 88. A brief overview of the regimens is provided in Table 94–1 and adverse effects are provided in Table 94–2.

Chemotherapy After Recurrence

In the recurrent setting, platinum sensitivity of the tumor is assessed first. If recurrence occurs in less than 6 months or disease progresses while the patient is receiving a platinum-based regimen, the cancer is considered platinum resistant (see Figure 94–2). These parameters are also used to determine if tumors are taxane sensitive or resistant. However, patients resistant to paclitaxel may still respond to docetaxel.[42] If the treatment goal is palliative care, then often single therapy will be used, but curative care typically is an aggressive combination regimen (see Figure 94–2 and Table 94–3). Sometimes an investigational agent may achieve responses equivalent or surpassing standard therapy, and should be considered for most patients.

► *Platinum Sensitive*

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In patients who experienced a CR to first-line chemotherapy and have had greater than a 6-month platinum-free interval, retreatment with a platinum-containing regimen is appropriate. The combination of carboplatin with gemcitabine, liposomal doxorubicin, or paclitaxel for the treatment of platinum-sensitive recurrent ovarian cancer with a curative intent is recommended[31,43,44] (see Table 94–3). However, in patients who

Table 94–2

Summary of Chemotherapy Agents Used for First-Line and Maintenance Treatment of Advanced Ovarian Cancer

Mechanism of Action of First-Line Agents
Platinum analogues: Produce intra- and interstrand cross-links and DNA adducts to disrupt DNA replication
Taxanes agents: Stabilize microtubules and prevent depolymerization of tubulin

Mechanism of Action of Maintenance Agents
PARP Inhibitors: Result in double stranded DNA breaks that cannot be repaired in cancer cells with BRCA mutations
Anti-angiogenic Agents: Inhibit VEGF-R, decrease microvasculator growth

Agent	Common Adverse Effects	Monitoring/Comments
First-Line		
Paclitaxel	Peripheral neuropathy (DLT), nausea/vomiting, alopecia, hypersensitivity reactions	1. Use caution with any elevation in AST (SGOT) 2. Give proper dosing for liver dysfunction. At least a 50% dose reduction generally recommended 3. Do not give if total bilirubin is > 5 mg/dL (86 µmol/L) 4. Premedicate for hypersensitivity reactions: dexamethasone, diphenhydramine, and cimetidine
Docetaxel	Neutropenia (DLT) hyperlacrimation, fluid retention, nail disorders, myelosuppression	1. Use with caution in liver dysfunction. Patients with bilirubin greater than the ULN and/or liver transaminases > 1.5 times, the ULN should not receive docetaxel 2. Do not give if biliary tract is obstructed 3. Premedicate for hypersensitivity reactions: dexamethasone
Carboplatin	Myelosuppression (DLT), nephrotoxicity, nausea/vomiting, electrolyte wasting, diarrhea, stomatitis, hypersensitivity reactions	1. Prehydration not required 2. If using BSA dosing, then give proper dosing for renal dysfunction CrCl ≥ 60 mL/min (1.00 mL/s): no dosage adjustment needed CrCl 41–59 mL/min (0.68–0.99 mL/s): give 250 mg/m^2 CrCl 16–40 mL/min (0.26–0.67 mL/s): give 200 mg/m^2 CrCl ≤ 15 mL/min (0.25 mL/s): do not give NOTE: Calvert formula (AUC dosing) is based on renal function, so no additional dose adjustment is needed 3. Premedicate for hypersensitivity reactions: dexamethasone, diphenhydramine, and cimetidine 4. Appropriate antiemetic regimen for prevention of acute and delayed nausea
Cisplatin	Neurotoxicity (DLT), nausea/vomiting, ototoxicity, nephrotoxicity, myelosuppression, electrolyte wasting, diarrhea	1. Prehydration and posthydration with electrolyte replacement (ie, potassium chloride 10 mEq [10 mmol] and magnesium sulfate 16 mEq [8 mmol]) required 2. Do not use if SrCr > 1.5 mg/dL (133 µmol/L) or BUN > 25 mg/dL (8.9 mmol/L) 3. Give proper dosing for renal dysfunction CrCl 46–60 mL/min (0.77–1.00 mL/s): decrease dose by 50%. CrCl 31–50 mL/min (0.51–0.83 mL/s): decrease dose by 75%. CrCl ≤ 30 mL/min (0.50 mL/s): do not use 4. Appropriate antiemetic regimen for prevention of acute and delayed nausea
Maintenance		
Niraparib	Fatigue, nausea, thrombocytopenia, neutropenia, elevated liver function tests	1. Monitor CBC closely for first 4–6 weeks of treatment then monthly thereafter; 2. Consider antiemetic PRN
Olaparib	Edema, fatigue, hypomagensemia, nausea, thrombocytopenia, neutropenia	1. Monitor CBC monthly 2. Recommend antiemetics PRN
Rucaparib	Nausea, fatigue, elevations in liver function tests, rash, thrombocytopenia	1. Monitor CBC monthy 2. Recommend antiemetics PRN
Bevacizumab	Hypertension, proteinuria, infusion-related reactions, fluid retention, increase risk of thrombosis, myelosuppression	1. Monitor urine-to-creatinine baseline and every two cycles; hold therapy if ratio > 2 or measure urine protein every cycle and addition testing if positive for proteinuria 2. Use caution in patients with a history of thrombosis

AST, aspartate aminotransferase; AUC, area under the curve; BSA, body surface area; BUN, blood urea nitrogen; CrCl, creatinine clearance; DLT, dose-limiting toxicity; SrCr, serum creatinine; ULN, upper limit of normal.

are unable to tolerate additional combination chemotherapy regimens, carboplatin alone or any one of the second-line agents would be appropriate.[45] The PARP inhibitors (niraparib, olaparib, and rucaparib) are also approved for the treatment of platinum sensitive recurrent ovarian cancer[39–41] (see Table 94–2).

▶ *Platinum Resistant*

Recurrent or persistent ovarian cancer after platinum-based regimens has a discouraging prognosis. KEY CONCEPT Single-agent chemotherapy is standard practice for recurrent platinum-resistant ovarian cancer and any active agent that has not been used during initial treatment can be used. However, two combination regimens have demonstrated promising activity in the recurrent setting: (a) gemcitabine plus cisplatin because gemcitabine may modulate platinum resistance allowing it to regain its cytotoxic activity, and (b) bevacizumab with metronomic oral cyclophosphamide.[46–49] Other active agents include altretamine (formerly hexamethylmelamine), anastrozole, capecitabine (5-fluorouracil), cyclophosphamide, docetaxel, gemcitabine, liposomal doxorubicin, oral etoposide, vinorelbine, topotecan, bevacizumab, or investigational agents. In 2016, the FDA approved the addition of bevacizumab with paclitaxel, gemcitabine, or liposomal doxorubicin to improve

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Table 94–3

Summary of Combination Chemotherapy Regimens Used for Treatment of Recurrent Ovarian Cancer

Drug(s)	Regimen Dosing	Drug Monitoring Comments[b]
Combination Regimens		
Platinum Sensitive		
Paclitaxel and carboplatin	175 mg/m^2 IV (3-hour infusion) AUC 5–7.5 IV every 21 days	• Monitor closely for hypersensitivity reactions
Paclitaxel and cisplatin	135 mg/m^2 IV (24-hour infusion) 75 mg/m^2 IV	• Monitor closely for hypersensitivity reactions
Docetaxel and carboplatin	75 mg/m^2 IV AUC 5 IV every 21 days	• Monitor closely for hypersensitivity reactions
Gemcitabine and carboplatin	800 mg/m^2 IV days 1 and 8 AUC 5 IV day 1 every 21 days	• Monitor platelet counts closely • Monitor closely for hypersensitivity reactions
Liposomal doxorubicin and carboplatin	30 mg/m^2 IV over 1–3 hour AUC 5 IV every 28 days	• Monitor closely for hypersensitivity reactions • Liposomal doxorubicin infusion starts over 3 hour and decreases to 1 hour as tolerated • Counsel patient for PPE prevention
Niraparib	300 mg cap PO once daily	• Monitor CBC closely for first 4–6 weeks of treatment then monthly thereafter • Consider antiemetics PRN
Olaparib	300 mg tab PO BID	• Monitor CBC monthly • Recommend antiemetics PRN
Rucaparib	600 mg tab BID	• Monitor CBC monthly • Recommend antiemetics PRN
Platinum-Resistant[a]		
Gemcitabine and cisplatin	1000 mg/m^2 IV days 1 and 15 40 mg/m^2 IV days 1 and 15 every 28 days	• Monitor renal function closely • Monitor ANC closely, consider primary use of growth factor • Monitor closely for hypersensitivity reactions
Liposomal doxorubicin and bevacizumab	40 mg/m^2 IV day 1 only and 10 mg/kg day 1 and day 15 every 28 days	• Liposomal doxorubicin infusion starts over 3 hour and decreases to 1 hour as tolerated • Counsel patient for PPE prevention • Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis
Gemcitabine and bevacizumab	800 mg/m^2 IV day 1 and day 15 & 10 mg/kg IV day 1 and day 15 every 28 days	• Use with caution in renal or liver dysfunction. No specific guidelines available • Counsel patient for PPE prevention • Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis
Paclitaxel and bevacizumab	80 mg/m^2 IV weekly days 1, 8, 15, & 21 and 10 mg/kg IV day 1 and 15 every 28 days	• Monitor closely for hypersensitivity reactions • Counsel patient for PPE prevention • Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis
Cyclophosphamide and bevacizumab	50 mg PO once daily 10 mg/kg IV once every 2 weeks every 28 days (continuous)	• Monitor for hypertension; hold therapy blood pressure > 140/90 mm Hg • Monitor urine-to-creatinine baseline and every two cycles; hold therapy if the ratio is > 2 or measure urine protein every cycle and addition testing if positive for proteinuria • Use caution in patients with history of thrombosis

[a]*Platinum resistance* = disease progression while on platinum agent or recurrence within 6 months of completion of platinum-based therapy.

[b]See Table 94–2 for specific monitoring parameters.

ANC, absolute neutrophil count; AUC, area under the curve; IV, intravenous; PO, oral; PPE, palmar-plantar erythrodysesthesia.

outcomes in the recurrent ovarian cancer setting[50] (see Figure 94–2). KEY CONCEPT Because the efficacy of the agents is similar, the selection of agent for treatment of recurrent platinum-resistant ovarian cancer is dependent on residual toxicities, clinician preference, and patient convenience. Table 94–4 gives a short summary of the adverse effects and monitoring parameters for chemotherapy agents commonly used for the treatment of recurrent ovarian cancer.

OUTCOME EVALUATION

Overall survival is impacted by success of initial surgery to debulk tumor to less than 1 cm of disease and response to first-line chemotherapy. The CA-125 level should be monitored with each cycle, and at least a 50% reduction in CA-125 after four cycles of taxane/platinum chemotherapy is related to an improved prognosis. Patients who achieve CR should have

Table 94–4

Summary of Chemotherapy Single-Agent Regimens Used for Treatment of Progressive and Recurrent Platinum-Resistant Ovarian Cancer

Agent	Dose	Response Rate (%)	Common Adverse Effects	Monitoring/Comments
Docetaxel	75 mg/m^2 IV over 1 hour repeat every 21–28 days vs 30–40 mg/m^2 IV over 1 hour once every week	22 NR	Neutropenia (DLT) hyperlacrimation, fluid retention, nail disorders, myelosuppression	1. Premedicate for hypersensitivity reactions with dexamethasone 2. Use with caution in liver dysfunction. Patients with bilirubin greater than the ULN and/or liver transaminases > 1.5 times the ULN should not receive docetaxel 3. Do not give if the biliary tract is obstructed
Gemcitabine	800 mg/m^2 IV infused over 30 minutes once a week on days 1, 8, and 15 followed by 1 week of rest	13.9–27	Myelosuppression (DLT), flulike symptoms, headache, somnolence, nausea/vomiting, stomatitis, diarrhea, constipation, rash	1. Use with caution in renal or liver dysfunction. No specific guidelines available
Liposomal doxorubicin	40 mg/m^2 IV infused over 3 hours cycle 1 and 2; then infused over 1 hour; thereafter repeat every 28 days	12.3–18	Myelosuppression, stomatitis, mucositis, alopecia, flushing, shortness of breath, hypotension, headaches, cardiotoxicity, hand–foot syndrome	1. Give proper dosing for liver dysfunction; total bilirubin 1.2–3 mg/dL (21–51 µmol/L): reduce dose by 50%; total bilirubin ≥ 3 mg/dL (51 µmol/L): reduce dose by 75% 2. Do not give if total bilirubin is > 5 mg/dL (86 µmol/L)
Topotecan	1.5 mg/m^2 IV infused over 30 minutes on days 1, 2, 3, 4, and 5; repeat every 21 days *OR* 4 mg/m^2 IV infused over 30 minutes once a week for 3 consecutive weeks followed by 1-week rest	6.5–17 31	Myelosuppression (DLT), nausea/vomiting, diarrhea, stomatitis, abdominal pain, alopecia, AST/ALT elevation	1. Give proper dosing for renal dysfunction; CrCl 40–60 mL/min (0.67–1.00 mL/s): no dosage adjustment needed; CrCl 20–39 mL/min (0.33–0.66 mL/s): reduce dose by 50% 2. Do not give if CrCl < 20 mL/min (0.33 mL/s)
Altretamine (Hexalen)	260 mg/m^2 PO daily for 14–21 days; repeat every 28 days	9.7	Nausea/vomiting, diarrhea, abdominal cramping, myelosuppression	1. Monitor for potential CYP450 drug interactions
Capecitabine	1800–2500 mg/m^2 PO as divided dose twice daily for 14 consecutive days followed by 1 week of rest	29	Myelosuppression, hand–foot syndrome, nausea/vomiting, edema, stomatitis, diarrhea, cardiotoxicity, rash	1. Monitor for PPE and recommend regular use of lotions on hands and feet 2. Use with caution in renal dysfunction; CrCl ≥ 51 mL/min (0.84 mL/s): no dose adjustment; CrCl 30–50 mL/min (0.50–0.83 mL/s): reduce dose by 25%; CrCl < 30 mL/min (0.50 mL/s): do not give 3. Use with caution in liver dysfunction; no specific guidelines available
Etoposide	50 mg/m^2/day PO in divided doses given daily for 3 weeks followed by 1 week of rest	18	Myelosuppression, nausea/vomiting, anorexia, alopecia, headache, fever, hypotension	1. Give proper dosing for liver dysfunction; total bilirubin 1.5–3 mg/dL (26–51 µmol/L): decrease dose by 50%; total bilirubin 3–5 mg/dL (51–86 µmol/L): decrease dose by 75% 2. Do not give if total bilirubin is > 5 mg/dL (86 µmol/L) 3. Give proper dosing for renal dysfunction; CrCl 60–45 mL/min (1.00–0.75 mL/s): reduce dose by 15%; CrCl 44–30 mL/min (0.74–0.50 mL/s): reduce dose by 20%; CrCl < 30 mL/min (0.50 mL/s): reduce dose by 25%

(*Continued*)

Table 94–4

Summary of Chemotherapy Single-Agent Regimens Used for Treatment of Progressive and Recurrent Platinum-Resistant Ovarian Cancer (*Continued*)

Agent	Dose	Response Rate (%)	Common Adverse Effects	Monitoring/Comments
Letrozole	2.5 mg once daily	15	Headache, nausea, dyspepsia, skin rash	1. No protective effect on bone; recommend calcium supplementation
Tamoxifen	20 mg PO twice a day continuously until PD	10	Thrombocytopenia, anemia, thromboembolism, hot flashes, decreased libido, nausea/vomiting	1. Protective effect on bone and lipids 2. Increased risk for endometrial cancer
Vinorelbine	30 mg/m^2 IV infused over 15 minutes on days 1 and 8; repeat every 21 days	29	Constipation, neutropenia, anemia, thrombocytopenia, neurotoxicity	1. Consider bowel regimen to prevent constipation
Bevacizumab	15 mg/kg IV infused over 30–90 minutes every 21 days	NR	Hypertension, proteinuria, infusion-related reactions, fluid retention, increase risk of thrombosis, myelosuppression	1. Monitor urine-to-creatinine baseline and every two cycles; hold therapy if ratio > 2 or measure urine protein every cycle and addition testing if positive for proteinuria 2. Use caution in patients with a history of thrombosis

CrCl, creatinine clearance; DLT, dose-limiting toxicity; IV, intravenous; NR, not reported; PD, progressive disease; PO, oral; PPE, palmar-plantar erythrodysesthesia; ULN, upper limit of normal.

follow-up examinations once every 3 months, including CA-125, physical examination, and pelvic examination, and appropriate diagnostic scans (ie, computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET] scan) should be evaluated for the detection of disease. While evaluating the patient, specifically assess resolution of any residual chemotherapy-related adverse effects including neuropathies, nephrotoxicity, ototoxicity, myelosuppression, or nausea/vomiting. Younger patients with an active menstrual cycle before surgery will encounter "surgical menopause" and often experience intense hot flushes. Because there are concerns about potential of hormones in the pathogenesis of ovarian cancer, the use of hormone replacement therapy is controversial. The use of phytoestrogen supplements, such as black cohosh or soy, is also controversial. Alternative nutritional supplements with less controversy may include omega3 (fish oil), fiber supplement, or maca root. An effective alternative has been the use of the class of serotonin reuptake inhibitors such as venlafaxine or sertraline.

In the PD or recurrent setting, CA-125 levels should still be monitored with each cycle, but no change in therapy is recommended until after minimum of three cycles of chemotherapy. In addition, appropriate diagnostic scans (ie, CT scan, MRI, or PET scan) should be evaluated once every three cycles. Patients should also have routine physical examinations with each cycle of chemotherapy to evaluate for any physical toxicity associated with chemotherapy such as neuropathies, fluid retention, palmar-plantar erythrodysesthesia, myelosuppression, or nausea/vomiting.

Unfortunately, most patients will eventually progress through all chemotherapy options, and supportive care measures should be provided to maintain patient comfort and quality of life. Common complications while developing a plan for treatment of advanced or progressive ovarian cancer include ascites, uncontrollable pain, and SBO. Precaution should be used in removal of ascites because of the potential complications associated with rapid fluid shifts. Liberal use of opioids to control pain is appropriate as ovarian cancer patients cope with PD and approaching end

Patient Encounter 3

A 53-year-old woman with history of stage IIIC high-grade, clear cell carcinoma of the ovary had optimal tumor debulking and achieved clinical complete response to adjuvant chemotherapy with paclitaxel/carboplatin returns for her 6-month surveillance visit. Previous genetic testing revealed she and her tumor were negative for presence of any mutations. CT scan reveals peritoneal implants and two enlarged lymph nodes and slight fluid accumulation in abdominal cavity. Her CA-125 is 234 U/mL (234 kU/L) today. Her peripheral neuropathy has significantly improved.

Explain how to decide patient's tumor is platinum sensitive or resistant.

What tumor characteristics can you identify that would have suggested this patient was at higher risk for early recurrence?

Today is patient's first recurrence, compare and contrast treatment options to offer to this patient.

of life. Appropriate bowel regimens with laxatives and stool softeners should be used to prevent constipation. However, when a patient with a well-controlled bowel regimen presents with new onset of constipation, additional workup is required before altering the bowel regimen. KEY CONCEPT In ovarian cancer patients, SBO is a common complication of progressive disease. In general, laxatives should not be used in patients with SBOs. Before treating constipation, patients should have a physical examination and abdominal x-ray to rule out SBO. Often, palliative surgery is required to correct SBO and alleviate patient pain. Patients should not eat any solid or liquids until resolution of SBO. If inoperable SBO exists, then parenteral nutrition can be considered but weighed against ultimate treatment objectives. Overall, providing any measures needed to maintain patient comfort is the priority for patients with progressive ovarian cancer.

Patient Care Process

Collect Information:

- Perform medication history for use of prescription and nonprescription medications and nutritional/herbal supplements. Confirm drug allergies/intolerances.
- Review the medical history, family cancer history, and current physical and laboratory assessment findings.
- Speak with patient and review records to identify socioeconomic factors that may affect medication access or compliance with care plan.

Assess the Information:

- Evaluate current symptoms and signs that are disease-related that would be associated with new diagnosis or drug-related side effects from prior treatment.
- Evaluate medication list to determine if there are any potential interactions, therapy duplication, or unnecessary medications. Determine if there is any need for acute or chronic pain medications.
- Review laboratory tests, diagnostic testing, and BRCA1/2 testing.
- Based on family cancer history, determine if additional genetic testing is recommended.
- Review chemotherapy history to determine potential for platinum sensitivity/resistance and consider genetic mutation status in selection of treatment options.

Develop a Care Plan:

If patient is a surgery candidate:

- Evaluate patient comorbidities to determine if additional workup is necessary before tumor debulking surgery.
- Decide if any medications or supplements need to be stopped or changed before surgery (ie, aspirin, warfarin, nonsteroidal anti-inflammatory agents, omega3s, etc).

If patient is a chemotherapy candidate:

- Evaluate patient medications, residual toxicities, renal function, and liver function to determine if any potential dose adjustments ought to be recommended for the selected chemotherapy regimen (see Figure 94–2).
- Determine whether patient has insurance coverage for planned chemotherapy regimen and supportive care medications as indicated. Discuss if potential co-pays are financially feasible as well.

Implement the Care Plan:

Surgery:

- Review plan to use low molecular weight heparin for postoperation thrombosis prevention and submit request for insurance approval. Teach nonpharmacologic recommendations for thrombosis prevention postsurgery.
- Discuss when any medications/supplements should be stopped and when to resume in relation to timing of surgery.
- Review the plan for acute pain management postoperation as well as bowel regimen to prevent constipation/reduce straining after abdominal surgery.

Chemotherapy:

- Provide appropriate patient education on chemotherapy agents. Explain treatment intent—curative verses palliative (relief of symptoms) and the plan for monitoring response to treatment.
- Explain prevention and management of expected side effects such as infection, nausea and vomiting, neuropathy, electrolyte wasting, and bowel habits.

Follow-up: Monitor and Evaluate:

- After surgery, patient should have follow-up 2 to 3 weeks to evaluate wound healing, pain control/resolution, and determine if adjuvant chemotherapy is required.
- While on chemotherapy patient should have a follow-up every cycle to assess symptom control and chemotherapy tolerability.
- A CBC with differential should be checked prior to each chemotherapy dose with complete laboratory values evaluated each cycle.
- Chemotherapy doses should be decreased or discontinued for unacceptable toxicity or organ dysfunction when indicated.
- Tumor markers are also monitored with each cycle but not acted upon unless greater than 50% increase or consistent trend upward each cycle.
- Assess tumor response to chemotherapy once every 3 months with CT scan/MRI/PET scan as indicated. Follow current RECIST criteria to determine stable disease, response, or progression of disease.

Abbreviations Introduced in This Chapter

AUC	Area under the curve
BRCA1	Breast cancer activator gene 1
BRCA2	Breast cancer activator gene 2
BSO	Bilateral salpingo-oophorectomy
CA-125	Cancer antigen-125
CA-19	Cancer antigen 19
CEA	Carcinoembryonic antigen
CR	Complete response
CrCl	Creatinine clearance
DLT	Dose-limiting toxicity
FIGO	International Federation of Gynecology and Obstetrics
HBOC	Hereditary breast and ovarian cancer
HNPCC	Hereditary nonpolyposis colorectal cancer
IP	Intraperitoneal
LFT	Liver function test
NS	Normal saline
OC	Oral contraceptive
PARP	Poly(ADP-ribose) polymerase
PD	Progressive disease
PET	Positron emission tomography
PR	Partial response
SBO	Small bowel obstruction
TAH	Total abdominal hysterectomy
TVUS	Transvaginal ultrasound

REFERENCES

1. American Cancer Society, Cancer Fact & Figures 2018; Atlanta: American Cancer Society; 2018.
2. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. Methods Mol Biol. 2009;472:413–437.
3. Bai H, Cao D, Yang J, Li M, Zhang Z, Shen K. Genetic and epigenetic heterogeneity of epithelial ovarian cancer and the clinical implications for molecular targeted therapy. J Cell Mol Med. 2016;20(4):581–593.
4. Lu KH, Dinh M, Kohlmann W, et al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol. 2005;105:569–574.
5. Sundar S, Neal RD, Kehoe S. Diagnosis of ovarian cancer. BMJ. 2015;351:h4443.
6. Berek JS, Crum C, Friedlander M. Cancer of the ovary. FIOG 2015 Report. Int J Gynecol Oncol. 2015;131:S111–S122.
7. Prentice RK, Thomson CA, Caan B, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification randomized controlled trial. J Natl Cancer Inst. 2007;99:1534–1543.
8. Moyer VA. U.S. Preventive Services Task Force. Screening for ovarian cancer: recommendation statement. Ann Intern Med. 2012;157:900–904.
9. Annual report to the nation 2017: Incidence summary. Available from: https://seer.cancer.gov/report_to_nation/incidence.html. Accessed January 8, 2018.
10. Bast RC Jr, Brewer M, Zou C, et al. Prevention and early detection of ovarian cancer: mission impossible? Recent Results Cancer Res. 2007;174:91–100.
11. Whittemore AS, Balise RR, Pharoah PD, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. Br J Cancer. 2004;91(11):1911–1915.
12. Wu AH, Pearce CL, Lee AW. Timing of birth and oral contraceptives use influences ovarian cancer risk. Int J Cancer. 2017;141:2392–2399.
13. McLaughlin JR, Risch HA, Lubinski J, et al. Reproductive risk factors for ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case control study. Lancet Oncol. 2007;8:26–34.
14. Harris RE, Beebe-Donk J, Doss H, et al. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade. Oncol Rep. 2005;13(4):559–583.
15. Bertone ER, Hankinson SE, Newcomb PA, et al. A population-based case-control study of carotenoid and vitamin A intake and ovarian cancer. Cancer Causes Control. 2001;12:83–90.
16. Meeuwissen PAM, Seynaeve C, Brekelmans CTM, et al. Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer. Gynecol Oncol. 2005;97(2):476–482.
17. Dann RB, Kelley JL, Zorn KK. Strategies for ovarian cancer prevention. Obstet Gynecol Clin North Am. 2007;34(4):667–686.
18. Finch A, Beiner M, Lubinski J, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA. 2006;296(2): 185–192.
19. Narod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 and BRCA2 mutations: a case control study. Lancet. 2001;357(9267):1467–1470.
20. Hartmann LC, Lindo NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Engl J Med. 2016;374(5): 454–468.
21. Pavelka JC, Li AJ, Karlan BY. Hereditary ovarian cancer-assessing risk and prevention strategies. Obstet Gynecol Clin North Am. 2007;34(4):651–665.
22. Klip H, Burger CW, Kenemans P, van Leeuwen FE. Cancer risk associated with subfertility and ovulation induction: a review. Cancer Causes Control. 2000;11(4):319–344.
23. Salzberg M, Thurlimann B, Bonnefois H, et al. Current concepts of treatment strategies in advanced or recurrent ovarian cancer. Oncology. 2005;68:293–298.
24. Wei W, Li N, Sun Y, Li B, Xu L, Wu LY. Clinical outcome and prognostic factors of patients with early-stage epithelial ovarian cancer. Oncotarget. 2017;8(14):23862–23870.
25. Ibeanu OA, Bristow RW. Predicting the outcome of cytoreductive surgery for advanced ovarian cancer: a review. Int J Gynecol Cancer. 2010;20(suppl 1):S1–S11.
26. Lorusso D, Mancini M, Di Rocco R, Fontanelli R, Raspagliesi F. The role of secondary surgery in recurrent ovarian cancer. Int J Surg Oncol. 2012;2012:613980.
27. Hoffman MS, Griffin D, Tebes S, et al. Sites of bowel resected to achieve optimal ovarian cancer cytoreduction: implications regarding surgical management. Am J Obstet Gynecol. 2005; 193(2):582–588.
28. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a gynecologic oncology group study. J Clin Oncol. 2003;21:3194–3200.
29. Neijt JP, Engelholm SA, Tuxen MK, et al. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. J Clin Oncol. 2000;18: 3084–3092.
30. Practice Guidelines in Oncology—Ovarian Cancer, V2. 2015. National Comprehensive Cancer Network (NCCN). Available from: http://www.nccn.org. Accessed October 20, 2017.
31. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006; 354:34–43.
32. Wright AA, Cronin A, Milne DE, et al. Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. J Clin Oncol. 2015;33(26):2841–2847.

33. NCI Clinical Announcement: Intraperitoneal Chemotherapy for Ovarian Cancer. National Cancer Institute. Available from: http://ctep.cancer.gov/highlights/clin_annc_010506.pdf. Accessed December 2, 2017.
34. Alberts DS, Bookman MA, Chen T, et al. Proceedings of a GOG workshop on intraperitoneal therapy for ovarian cancer. Gynecol Oncol. 2006;103:783–792.
35. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet. 2009;374:1331–1338.
36. Bohra U. Recent advances in management of epithelial ovarian cancer. Apollo Med. 2012;9:212–218.
37. Perrin TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011;365(26): 2484–2496.
38. Abaid LN, Goldstein BH, Micha JP, Rettenmaier MA, Brown JV 3rd, Markman M. Improved overall survival with 12 cycles of single-agent paclitaxel maintenance therapy following a complete response to induction chemotherapy in advanced ovarian carcinoma. Oncology. 2010;78:389–393.
39. Lin KY, Kraus WL. PARP inhibitors for cancer therapy. Cell. 2017;169(2):183.
40. Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol. 2016;17(11):1579–1589.
41. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Eng J Med. 2016;375(22):2154–2164.
42. Rose PG, Blessing JA, Ball HG, et al. A phase II study of docetaxel in paclitaxel-resistant ovarian and peritoneal carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2003;88: 130–135.
43. Alberts DS, Liu PY, Wilczynski SP, et al. Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). Gynecol Oncol. 2008;108(1):90–94.
44. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol. 2006;24: 4699–4707.
45. Herzog TJ, Pothuri B. Ovarian cancer: a focus on management of recurrent disease. Nat Clin Pract Oncol. 2006;3:604–611.
46. Boza G, Bamias A, Koutsoukou V, et al. Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pre-treated, ovarian and peritoneal carcinoma. Gynecol Oncol. 2007; 104(3): 580–585.
47. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol. 2008;26(1):76–82.
48. Smith JA, Gaikwad A, Ramondetta LM, Wolf JK, Brown J. Determination of the mechanism of gemcitabine modulation of cisplatin drug resistance in panel of human endometrial cancer cell lines. Gynecol Oncol. 2006;103(2):518–22.
49. Le TN, Harvey RE, Kim CK, Brown J, Coleman RL, Smith JA. A retrospective evaluation of activity of gemcitabine/platinum regimens in the treatment of recurrent ovarian cancer. Gynecol Oncol Res Prac. 2017;4:16.
50. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012;30(17):2039–2045.

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95 Acute Leukemias

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LEARNING OBJECTIVES

LO

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

1. Describe the pathogenesis of acute leukemia.
2. Identify new agents for the treatment of leukemia.
3. Identify the risk factors associated with a poor outcome for the acute leukemias.
4. Explain the importance of minimal residual disease (MRD) and its implication on early bone marrow relapse.
5. Explain the role of induction, consolidation, and maintenance phases for acute leukemia.
6. Define the role of central nervous system preventive therapy for acute leukemia.
7. Recognize the treatment complications associated with therapy for acute leukemias.
8. Describe the late effects associated with the treatment of long-term survivors of acute leukemias.

INTRODUCTION

KEY CONCEPT The acute leukemias are hematologic malignancies of bone marrow precursors characterized by excessive production of immature hematopoietic cells. This proliferation of "blast" cells eventually replaces normal bone marrow and leads to the failure of normal hematopoiesis and the appearance in peripheral blood as well as infiltration of other organs. These blast cells proliferate in the marrow and inhibit normal cellular elements, resulting in anemia, neutropenia, and thrombocytopenia. Leukemia also may infiltrate other organs, including the liver, spleen, bone, skin, lymph nodes, testis, and central nervous system (CNS). Virtually anywhere there is blood flow, the potential for extramedullary (outside the bone marrow) leukemia exists.

KEY CONCEPT Acute leukemias are classified according to their cell of origin. Acute lymphocytic leukemia (ALL) arises from the lymphoid precursors. Acute nonlymphocytic leukemia (ANLL) or acute myelogenous leukemia (AML) arises from the myeloid or megakaryocytic precursors. As a result of clinical trials defining various prognostic (risk) factors that helped guide treatment modifications, the outcomes of acute leukemias, especially ALL, has improved dramatically over the past 50 years.[1] Risk-based treatment strategies that consider multiple phenotypic and biological risk factors and attempt to match the aggressiveness of therapy with the presumed risk of relapse and death are now the standard of care. Despite the overall success in treating patients with acute leukemias, minimal advances have been made in the treatment of relapsed ALL.[1]

EPIDEMIOLOGY AND ETIOLOGY

Epidemiology

Leukemia is a relatively uncommon disease. The current overall age-adjusted annual incidence of acute leukemia in the United States has remained relatively stable at 10 per 100,000 in children and 1 to 2 per 100,000 in adults.[2] In 2018, it is estimated there will be 60,300 new cases of leukemia, or 3.5% of all new cancer cases.[3]

In the pediatric population, leukemia is a common cancer, accounting for almost one-third of all childhood malignancies. ALL accounts for 75% to 80% of all cases of childhood leukemia, whereas AML accounts for no more than 20%. Males generally are affected more often than females in all but the infant age group, and its incidence is higher in whites than among other racial groups.

The incidence of AML in children is bimodal: It peaks at 2 years of age, decreases steadily thereafter to age 9 years, and then increases again at around age 16.[4] The average age of diagnosis for AML is about 65 years and is a result of an increasing incidence of AML with age.

Etiology

The cause of acute leukemias is unknown; multiple influences related to genetics, socioeconomics, infection, environment, hematopoietic development, and chance may play a role.[4] Table 95–1 lists the major conditions associated with acute leukemias. In most cases, however, there is no identifiable cause of the leukemia.

Although leukemia is rarely a hereditary disease, some genetic associations are evident. For example, among identical twins, the concordance for ALL in the initially unaffected twin is 20% to 25% within 1 year. Although the incidence in fraternal twins is much less, there is still a fourfold increase in the risk of leukemia in the initially unaffected twin compared with the healthy population. One explanation for this association may be a shared placental circulation, which allows for transmission of disease from one twin to the other. Additionally, leukemia has an increased incidence in several chromosomally abnormal populations. For example, patients with Down syndrome have a 20 times increased risk of developing leukemia compared with the rest of the population.

Table 95–1

Clinical Conditions Associated with an Increased Frequency of Acute Leukemias

Drugs
Alkylating agents
Epipodophyllotoxins

Genetic Conditions
Down syndrome
Bloom syndrome
Fanconi anemia
Klinefelter syndrome
Ataxia telangiectasia
Langerhans cell histiocytosis
Shwachman syndrome
Severe combined immunodeficiency syndrome
Kostmann syndrome
Neurofibromatosis type 1
Familial monosomy 7
Diamond-Blackfan anemia

Chemicals
Benzene

Pesticides

Radiation
Ionizing radiation

Viruses
Epstein-Barr virus
Human T-lymphocyte virus (HTLV-1 and HTLV-2)

Social Habits
Cigarette smoking
Maternal marijuana use
Maternal ethanol use

Adapted from Bickert-Poon B, Hatfield-Seung A. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill; 2014.

Exposure to environmental agents, such as agricultural chemicals, pesticides, and radiation, is associated with leukemia, but none is conclusively related to the development of leukemia. An increased frequency of ALL is associated with higher socioeconomic status. It is postulated that less social contact in early infancy and thus a late exposure to some common infectious agents may have some impact.[4]

Risk factors for the development of AML include exposure to environmental toxins, Hispanic ethnicity, and genetics.[5] Also of concern is the increased prevalence of AML as a secondary malignancy, resulting from chemotherapy and radiation treatment for other cancers. Alkylating agents, such as ifosfamide and cyclophosphamide, and topoisomerase inhibitors, such as etoposide, are linked to an increased risk of AML and **myelodysplastic syndrome** (MDS).[5]

PATHOPHYSIOLOGY

Hematopoiesis is defined as the development and maturation of blood cells and their precursors. In utero, hematopoiesis may occur in the liver, spleen, and bone marrow; after birth, this process occurs exclusively in the bone marrow. All blood cells are generated from a common hematopoietic precursor, or stem cell. These stem cells are self-renewing and pluripotent and thus are able to commit to any one of the different lines of maturation that give rise to platelet-producing megakaryocytes, lymphoid, erythroid, and myeloid cells. The myeloid cell line produces monocytes, basophils, neutrophils, and eosinophils, whereas the lymphoid stem cell differentiates to form circulating B and T lymphocytes, natural killer (NK) cells, and dendritic cells. In contrast to the ordered development of normal cells, the development of leukemia seems to represent an arrest in differentiation at an early phase in the continuum of stem cell to mature cell.[1]

LO 1

Both AML and ALL are thought to arise from clonal expansion of these "arrested" cells. As these cells expand, they acquire one and often more chromosomal aberrations, including translocations, inversions, deletions, point mutations, and amplifications.[4] The translocation t(12;21) or *TEL–AML1* is found in approximately 25% of cases of pediatric ALL and is associated with a favorable prognosis.[6] This translocation is uncommon in adults. Another example is the t(9;22) translocation (Philadelphia chromosome, Ph^+), which results in the *BCR–ABL* fusion protein. This translocation produces a novel kinase that leads to uncontrolled proliferation, survival, and self-renewal of cells. It is uncommon in childhood ALL and commonly found in adult ALL, especially in older patients.

Patients with MDS or AML as a secondary neoplasm are often characterized by having had prior alkylator-based or etoposide-based chemotherapy. Patients who have received treatment for Hodgkin disease or solid tumors are most at risk for this problem because they often treated with these agents. Patients with MDS have an abnormal bone marrow and a variety of cytopenias involving one or more of their marrow cell lines. They are at high risk of converting to overt leukemia over time. A variety of complex cytogentic findings and monosomies of chromosome 5 or 7, and 11q23 translocations are often present in this population.[5]

Leukemia Classification

Classification methods for leukemia have evolved from simple schemes that were largely phenotypic and considered only age, gender, white blood cell (WBC) count, and blast morphology to now-complex methods that include biological features such as cell-surface receptors, DNA content (ploidy; more or less than normal chromosomal DNA content), and a variety of cytogenetic abnormalities.

For all newly diagnosed patients with leukemia, an aspirate of the liquid marrow and a bone marrow core biopsy are obtained. Analysis of the leukemic cell surface markers (immunophenotyping) establishes three types of ALL, pre-B, mature B, and T-cell precursor ALL. There are eight subtypes of AML (M0 to M7) as classified by the French-American-British (FAB) scheme. The World Health Organization identifies specific entities within the diagnosis of AML based on a combination of karyotypic and molecular mutations (**Tables 95–2** and **95–3**).

Immunophenotyping by **flow cytometry** has taken on an increasingly important role in the diagnosis of leukemia. Owing to the ease of application, sensitivity, and quantifiable results, flow cytometry is the preferred method for leukemic lineage as well as prognostic assignment.[7] This approach takes advantage of the development of diagnostic monoclonal antibodies (MABs) to many cell-surface antigens that are differentially expressed during hematopoietic differentiation. The antigens are referred to as antibody cluster determinants (CDs) that define cells at various stages of development and can easily separate ALL from AML and T-cell from pre–B-cell ALL.[4,7] The combined approach of flow cytometric identification and cytogenetic DNA content, much of which is also revealed by flow cytometry and fluorescent in situ hybridization (**FISH**; microscopic, fluorescence identification of chromosomal features) has facilitated diagnosis and delineation of specific subtypes of the acute leukemias. Common immunophenotypic markers seen in AML and ALL are provided in **Table 95–4**.

Prognostic Factors

KEY CONCEPT The goal of treatment is to match treatment to risk and minimize overtreatment or undertreatment. Patients with leukemia are categorized based on clinical and biological features that mirror their risk of relapse. Risk assessment is an important

Table 95–2

Morphologic (FAB) Classification of AML

Subtype		Frequency of FAB Subtype		
		Adults (%)	Children Older Than 2 Years (%)	Children Younger Than 2 Years (%)
M0	Acute myeloblastic leukemia without maturation	5	Low	Low
M1	Acute myeloblastic leukemia with minimal maturation	15	17	7
M2	Acute myeloblastic leukemia with maturation	25		27
M3	Acute promyelocytic leukemia	10		5
M4	Acute myelomonocytic leukemia	20	30	26
M5a	Acute monoblastic leukemia, poorly differentiated	10	52	26
M5b	Acute monoblastic leukemia, well differentiated	5		
M6	Acute erythroleukemia	5		2
M7	Acute megakaryoblastic leukemia	5		7

FAB, French-American-British.

factor in the selection of treatment. Age, WBC, leukemic cell-surface markers, DNA content, and specific cytogenetic abnormalities predict response to therapy and are used to assign risk and associated treatment.[4] On the basis of these prognostic variables, patients are assigned to standard-, high-, or very-high-risk groups that determine the aggressiveness of treatment.

Table 95–3

WHO Classification of AML and Related Neoplasms

AML with recurrent genetic abnormalities:
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBEB-MYH11*
Acute promyelocytic leukemia (APL) with t(15;17)(q22;q12); *PML-RARA*
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA

AML with myelodysplasia-related change

Therapy-related myeloid neoplasms

AML, not otherwise specified:
Undifferentiated AML (M0)
AML with minimal differentiation (M1)
AML without maturation (M2)
AML with maturation (M2)
Acute myelomonocytic leukemia (M3)
Acute monoblastic/monocytic leukemia (M4)
Acute erythroid leukemia (M5)
Pure erythroid leukemia (M6)
Erythroleukemia, erythroid/myeloid (M6)
Acute megakaryoblastic leukemia (M7)

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome:
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

AML, acute myeloid leukemia.

▶ *Prognostic Factors in ALL*

In both children and adults with ALL, clinical trials have identified several risk factors that correlate with outcome (Table 95–5). Prognostic features include age, WBC count, cytogenetic abnormalities, ploidy (DNA content), leukemic cell immunophenotype, and degree of initial response to therapy, and minimal residual disease (MRD; the degree of subclinical disease remaining at various times after starting treatment).[4,7,8] When these factors are combined, they predict groups of patients with varying degrees of risk for treatment failure. LO 3

The importance of age is evident in both children and adults. Children younger than 1 year or older than 10 years of age have a poorer outcome than others. Likewise, in adults, there is a steady decline in the rate of survival with increasing age. LO 3

Similar to age, the WBC count at presentation is a reliable indicator of complete response (CR) rate and outcome. The WBC count is indicative of tumor burden, although the underlying biological mechanisms that account for the unfavorable outcomes associated with an elevated WBC count are unclear. Patients with WBC counts of less than $50 \times 10^3/mm^3$ ($50 \times 10^9/L$) are considered being at standard risk and have a better outcome than those with higher WBC counts at presentation, which is associated with higher risk of treatment failure (see Table 95–5).

Specific chromosomal abnormalities in leukemic cells also possess prognostic significance. Blast cells with a translocation of parts of chromosome 12 and 21 (the *TEL–AML1* fusion) or trisomies of 4, 10, and 17 are considered to have favorable genetic

Table 95–4

Common Immunophenotypes in Acute Leukemia

Leukemia	Common Immunophenotypes
AML	CD13, CD15, CD33, CD14, CD64, CD65, and C-KIT
B-cell ALL	CD19, CD20, CD10, CD22, CD79a, HLA-DR, Tdt
T-cell ALL	CD2, CD3, CD4, CD5, CD7, Tdt

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CD, cluster determinant.

Adapted from Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatr Clin North Am. 2008;55(1):1–20.

Table 95–5

Prognostic Factors in ALL

	Risk for Leukemic Relapse	
Factor	**Standard/Low**	**High**
Immunologic phenotype	pre–B cell	Null cell, T cell, pre–B cell, mature B cell
WBC count at diagnosis	$< 50 \times 10^3/mm^3$ ($50 \times 10^9/L$)	$> 50 \times 10^3/mm^3$ ($50 \times 10^9/L$)
Patient age	1–10 years	< 1 year or > 10 years
Cytogenetics	Normal karyotype, t(12;21), trisomy 4,10,17	t(9;22); t(4;11); t(17;19), iAmp21, ph-like
Ploidy	Hyperdiploidy	Hypodiploidy, near haploid
CNS leukemia	Absent	Present
MRD at end of induction	< 0.01%	> 0.01%

WBC, white blood cell.

Adapted from Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatr Clin North Am. 2008;55(1):1–20.

LO 3

features.[4] The presence of the Philadelphia chromosome (Ph^+), the result of a specific translocation between chromosome 9 and 22, t(9;22)(q34;q11.2), is a high-risk feature, which is present in about 3% of children but is much more common in adults with ALL. This translocation results in a novel tyrosine kinase that drives cell proliferation.[7,8]

Among children younger than 1 year of age, as many as 70% possess a poor prognostic genotype represented by the presence of the *MLL* (11q22) gene rearrangement. This finding is rare among older patients. Leukemias with the *MLL* gene rearrangement are highly resistant to the key antileukemic drugs such as glucocorticoids and L-asparaginase.[9]

The DNA content of blast cells, hyper-, hypo-, or diploid, corresponding to increased, decreased, or normal chromosome numbers, is also a prognostic factor. Lower risk patients with hyperdiploidy (> 50 chromosomes per leukemic cell) generally include approximately 25% of children who have B-cell lineage ALL.[6] These children are between the ages of 1 and 9 years, but the higher risk patients with normal diploidy (50 chromosomes) generally are older. Hypodiploid ALL with less than 44 chromosomes occurs in 1% to 5% of pediatric patients with ALL and is an independent risk factor for poor prognosis with declining prognosis with decreased chromosome number.[10]

Patients with cell-surface markers indicating that the blasts are early in the B-cell lineage (CD markers) are considered favorable and standard risk, whereas those with mature B-cell and T-cell blasts are considered high risk. T-cell ALL is found in approximately 15% of childhood ALL. Compared with B-lineage ALL, T-cell ALL is relatively resistant to different classes of drugs, including methotrexate and cytarabine.

Patients completing induction treatment and in apparent remission still harbor malignant cells in their bone marrow even though they appear disease free by peripheral blood and bone marrow morphology. Assuming that most patients present with about a 10^{11} leukemic cell burden at diagnosis, at least 10^9 cells remain after initial treatment. These residual leukemic cells are below the limits of detection using standard morphologic examination. Measurement of this population of cells has become an increasingly significant prognostic factor and a determinant of the aggressiveness of postinduction therapy. Through flow cytometric analysis and **polymerase chain reaction**, it is possible to detect one leukemic cell among 10^6 normal cells, representing 1000-fold greater sensitivity than morphologic examination.[11,12]

LO 4

KEY CONCEPT Minimal residual disease (MRD) is a quantitative assessment of subclinical remnant of leukemic burden remaining at the end of the initial phase of treatment (induction) when a patient may appear to be in a complete morphologic remission. This measure has become one of the strongest predictors of outcome for patients with acute leukemia. The elimination of MRD is a principal objective of postinduction leukemia therapy. Several studies in children, in whom ALL is common, have evaluated disease levels at the end of induction and correlated

Patient Encounter 1, Part 1

A 22-year-old male presents to the emergency department with a history of a sore throat for the past 4 days. He felt slightly feverish 4 days ago and noticed some slight swelling in his neck. He has not lost any weight, and had a good appetite up until he started having a sore throat. He has not had any recent contact with anyone who is sick. He denies any upper respiratory infection symptoms. He does not have any headaches and visual changes. Upon physical examination his neck is supple with multiple cervical lymphadenopathies that are not tender. His complete blood count shows a total white blood count (WBC) of 284.5×10^9/L (reference range 4–10) with 10% blasts; platelet count 48×10^9/L (reference range 150–400). His serum creatinine is 144 umol/L (reference is 54–146), potassium 3.3 mmol/L (3.5–5.1), Uric acid 517 umol/L (190–541). Bone marrow biopsy has 60% blasts.

His diagnosis is AML.

Is this patient at risk for tumor lysis syndrome?

What are the prognostic factors for this patient?

What is the role of pediatric treatment protocols for this patient?

Patient Encounter 1, Part 2

The patient is admitted to the inpatient hematology service in the hospital. Mutational analysis is negative for *FLT3* and *NPM1* mutations. He is started on a pediatric research protocol consisting of cytarabine, daunorubicin, and etoposide.

Would this patient benefit from midostaurin?

Would this patient benefit from an allogeneic stem cell transplant?

Patient Encounter 1, Part 3

He receives two induction chemotherapy regimens and two intensification regimens. Less than a year after his initial diagnosis he develops worsening anemia and thrombocytopenia concerning for relapsed AML.

Would he be a candidate for azacitidine?

Table 95–6

Risk Category According to Cytogenetic Abnormalities Present

	Risk Category		
Disease	**Good Risk**	**Intermediate Risk**	**High Risk**
AML	t(8;21) (q22;q22); inv(16); t(15;17); t(9;11), trisomy 21	Normal karyotype; trisomy 8; 1 1q23; del(7q); del(9q); trisomy 22	Complex karyotype; –5; –7; del (5q); inv(3P)
Probability of relapse	25% or less	50%	70% or more
4-Year survival	70% or more	40%–50%	20% or less
ALL	Hyperdiploidy; t(12;21), trisomy 4, 10, 17		t(9;22); t(8;14); t(4;11); t(17;19), hypodiploid, near haploid
Probability of relapse	< 10%	< 20%	30%–40%
4-Year survival	> 80%	> 60%	40%–50%

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia.

Adapted from Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatr Clin North Am. 2008;55(1):1–20.

these values with event-free survival (EFS). For a patient with detectable MRD less than 0.1% at the end of induction, EFS is 88% at 3 years. Conversely, a patient with high MRD (> 1%) has a 3-year EFS of only 30%.[13] Assessment of MRD is also emerging as an important indicator of disease recurrence in the adult population and in patients with AML.

▶ *Prognostic Factors in AML*

The major prognostic factors in newly diagnosed AML are age, subtype, chromosome status, ethnicity, and body mass index.

Older adults with AML (> 60 years), compared with younger patients with the same disease, have a dismal prognosis and represent a distinct population in terms of disease biology, treatment-related complications, and overall survival (OS). Older patients with secondary AML have an even poorer prognosis. Older patients also have a higher incidence of unfavorable chromosomal abnormalities, such as aberrations of chromosomes 5, 7, or 8, FLT_3-internal tandem duplication (ITD) and fewer abnormalities that are associated with a more favorable outcome, such as t(8;21) or inv(16) (Table 95–6).[5,13]

Clinical Presentation and Diagnosis of ALL[3,6,11]

General

- Typically, patients have symptoms for 1 to 3 months before presentation. These include fatigue, fever, and pallor, but patients generally are in no obvious distress.

Symptoms

- The patient may present with weakness, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- Anemia usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Patients often present with bone pain secondary to expansion of the marrow cavity from leukemic infiltration.
- CNS involvement is common at diagnosis.

Signs

- Temperature may be elevated secondary to an infection associated with a low WBC count.
- Petechiae and bleeding are indicative of thrombocytopenia.
- Patients may present with organ involvement, such as peripheral adenopathy, hepatomegaly, and splenomegaly.
- T-lineage ALL may present with a mediastinal mass.

Laboratory Tests

- CBC with differential is performed.
- The anemia is usually normochromic and normocytic. Approximately 50% of children present with platelet counts of less than $50 \times 103/mm^3$ (50×10^9/L). The WBC count may be normal, decreased, or high. About 20% of patients have WBC counts over $100 \times 10^3/mm^3$ (100×10^9/L), which places them at risk for leukostasis.
- Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.
- Electrolytes: Potassium and phosphorus often are elevated. Calcium usually is low.
- Coagulation disorders: Elevated prothrombin time, partial thromboplastin time, D-dimers; hypofibrinogenemia.

Other Laboratory Tests

Flow cytometric evaluation of bone marrow and peripheral blood is performed to characterize the type of leukemia as well as to detect specific chromosomal rearrangements. The bone marrow at diagnosis usually is hypercellular, with normal hematopoiesis being replaced by leukemic blasts. At diagnosis, an LP is performed to determine if CNS leukemia is present.

Clinical Presentation and Diagnosis of AML[3,6,11]

General

- Patients may have symptoms of AML for 1 to 3 months before presentation. These include fatigue, fever, and pallor, but patients generally are in no obvious distress.

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- The patient may present with weakness, bone pain, malaise, bleeding, and weight loss.
- Neutropenic patients are often febrile and highly susceptible to infection.
- Anemia usually presents as pallor, tiredness, and general fatigue.
- Patients with thrombocytopenia usually present with bruising, petechiae, and ecchymosis.
- Chloromas (localized leukemic deposits named after their color) may be seen, especially in the periorbital regions and as skin infiltrates.
- Gum hypertrophy is indicative of AML M4 and AML M5 subtypes.
- Disseminated intravascular coagulation may be present in all AML subtypes, but is common in AML M3 and is associated with generalized bleeding or hemorrhage.
- Lymphadenopathy, massive hepatosplenomegaly, and bone pain are not as common in AML as in ALL.

Signs

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- Petechiae and bleeding are indicative of thrombocytopenia.

Laboratory Tests

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- The anemia is usually normochromic and normocytic.
- Approximately 50% of children present with platelet counts of less than $50 \times 10^3/mm^3$ ($50 \times 10^9/L$).
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- Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.
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Other Diagnostic Tests

Flow cytometric evaluation of bone marrow and peripheral blood to characterize the type of leukemia as well as to detect specific chromosomal rearrangements. The bone marrow at diagnosis usually is hypercellular, with normal hematopoiesis being replaced by leukemic blasts. The presence of greater than 20% blasts in the bone marrow is diagnostic for AML. At diagnosis, an LP is performed to determine if CNS leukemia is present. The CNS is involved at diagnosis in approximately 15% of patients.[14]

Recent studies suggest that ethnicity may be an important predictor of outcome in children with AML. Investigators found that African Americans treated with chemotherapy had a significantly worse outcome than whites, perhaps suggesting race-related pharmacogenetic differences. Body mass index may also affect the prognosis of children with AML. Underweight patients and overweight patients were less likely to survive than normal weight patients because of a greater risk of treatment-related deaths.[15] Current clinical trials in adults and pediatrics strongly suggest that patients with detectable MRD at the end of induction therapy or consolidation is strongly associated with the risk of relapse.[14]

TREATMENT

Desired Outcome

The primary objective in treating patients with acute leukemia is to achieve a continuous complete remission (CCR). **Remission** is defined as the absence of all clinical evidence of leukemia with the restoration of normal hematopoiesis. For both ALL and AML, remission induction is achieved with the use of myelosuppressive chemotherapy that initially induces a state of bone marrow aplasia as the leukemic cells die followed by a slow return and proliferation of normal cells. After this period, hematopoiesis is restored. Failure to achieve remission in the first 7 to 14 days of therapy is highly predictive of later disease recurrence. This again represents the growing importance of MRD in prognosis and treatment.

Nonpharmacologic Therapy

This year, roughly 1.7 million people will be diagnosed with cancer in the United States. With improvements in detection and treatment, approximately two-thirds of those diagnosed with the disease can expect to be alive in 5 years. With improving longevity, the cumulative adverse effects of both the disease and treatment are becoming an increasingly important issue. "Late-effects" data show that both adult and pediatric cancer survivors are at greater risk for developing second malignancies, cardiovascular disease, diabetes, and osteoporosis than those in the general population. With respect to the growing population of pediatric cancer survivors, data confirm that they are eight times more likely than their siblings to have a severe or life-threatening chronic health condition. For example, the survivors of pediatric ALL have an increased risk of obesity, osteopenia, and associated comorbidities. Thus, it is important to provide supportive care and counseling related to nutrition, smoking cessation, and exercise as a part of their active treatment. Health care professionals should think beyond the immediate treatment-related issues of their patients and provide appropriate, active assistance to promote healthy lifestyles and encourage patients to take active roles in pursuing general preventive health strategies.[15]

Pharmacologic Therapy: ALL

The treatment for ALL consists of five main elements: remission induction (the initial tumor reduction leading to

morphologic remission), CNS-directed treatment, intensive postremission consolidation regimens, interim maintenance/delayed intensification followed by a prolonged maintenance phase. The total duration of treatment is 2 to 3 years (Table 95–7).

► *Remission Induction*

LO 5

KEY CONCEPT The initial treatment for acute leukemias is called induction. The purpose of induction is to induce a remission, a state in which there is no identifiable leukemic cells in the bone marrow or peripheral blood with light microscopy.

Table 95–7

Representative Chemotherapy Regimens for Adult ALL

Remission Induction		CNS Prophylaxis		Consolidation		Maintenance
Drug and Dose	**Days**	**Prophylaxis**	**Days**	**Drug and Dose**	**Days**	**Drug, Dose, and Timing**
German or Hoelzer Regimen (Adult)[a]						
PRED (po) 60 mg/m^2	1–28	Cranial irradiation		DEX (po) 10 mg/m^2	1–28	MP (po) 60 mg/m^2 daily and
VCR (IV) 1.5 mg/m^2[b]	1, 8, 15, 22	MTX (IT) 10 mg/m^2[c]	31, 38, 45, 52	VCR (IV) 1.5 mg/m^2[b]	1, 8, 15, 22	MTX (po/IV) 20 mg/m^2 weekly, weeks 10–18 and 29–130
DNR (IV) 25 mg/m^2	1, 8, 15, 22			DOX (IV) 25 mg/m^2	1, 8, 15, 22	
ASP (IV) 5000 units/m^2	1–14			CTX (IV) 650 mg/m^2[d]	29	
CTX (IV) 650 mg/m^2[d]	29, 43, 57			Ara-C (IV) 75 mg/m^2	31–34, 38–41	
Ara-C (IV) 75 mg/m^2	31–34, 38–41, 45–48, 52–55			TG (po) 60 mg/m^2	29–42	
MP (po) 60 mg/m^2	29–57					
CALGB 8811 (Adult)[e]						
Course I (4 Weeks)				Course II: Early Intensification (4 Weeks)		Course V (Continues until 24 months from diagnosis)
CTX (IV) 1200 mg/m^2	1			MTX (IT) 15 mg	1	VCR (IV) 2 mg day 1 monthly
DNR (IV) 45 mg/m^2	1, 2, 3			CTX (IV) 1000 mg/m^2	1	
VCR (IV) 2 mg	1, 8, 15, 22			MP (po) 60 mg/m^2	1–14	PRED (po) 60 mg/m^2 days 1–5 monthly
PRED (po) 60 mg/m^2	1–21			Ara-C (SC) 75 mg/m^2	1–4, 8–11	
ASP (SC) 6000 units/m^2	5, 8, 11, 15, 18, 22			VCR (IV) 2 mg	15, 22	MTX (po) 20 mg/m^2 days 1, 8, 15, 22 monthly
				ASP (SC) 6000 units/m^2	15, 18, 22, 25	MP (po) 60 mg/m^2 days 1–28 monthly
Induction chemotherapy for patients 60 years old or older, use:						
CTX (IV) 800 mg/m^2	1					
DNR (IV) 30 mg/m^2	1–3					
PRED (po) 60 mg/m^2	1–7					
Course III (12 Weeks)	1, 8, 15, 22, 29	Cranial irradiation		Course IV: Late Intensification (8 Weeks)		
MTX (IT) 15 mg	1–70			DOX (IV) 30 mg/m^2	1, 8, 15	
MP (po) 60 mg/m^2	36, 43, 50, 57, 64			VCR (IV) 2 mg	1, 8, 15	
MTX (po) 20 mg/m^2				DEX (po) 10 mg/m^2	1–14	
				CTX (IV) 1000 mg/m^2	29	
				TG (po) 60 mg/m^2	29–42	
				Ara-C (SC) 75 mg/m^2	29–32, 36–39	

[a]Holzer D, Thiel E, Ludwig WD, et al. Follow-up of the first two successive German multicentre trials for adult ALL (01/81 and 2/84). Leukemia. 1993;7(Suppl 2):130–134.

[b]Maximum single dose, 2 mg.

[c]Maximum single dose, 15 mg.

[d]Maximum single dose, 1000 mg.

[e]Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphocytic leukemia. Cancer and leukemia Group B study 8811. Blood. 1995;85:2025–2037.

ASP, asparaginase; C, cytarabine; CALGB, Cancer and Leukemia Group B; CTX, cyclophosphamide; DEX, dexamethasone; DNR, daunorubicin; DOX, doxorubicin; IT, intrathecal; MP, mercaptopurine; MTX, methotrexate; po, oral; PRED, prednisone; SC, subcutaneous; TG, thioguanine; VCR, vincristine.

Adapted from Leather HL, Bickert B. Acute leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 6th ed. New York, NY: McGraw-Hill; 2005:2191–2213.

Patient Encounter 2, Part 1

An 8-year-old male returns to the emergency room after completion of his third course of antibiotics for a presumed ear infection. His father states that he has been more lethargic lately and that he has bruising that cannot be explained. On physical examination, he appears pale and has significantly splenomegaly.

The pediatrician orders a CBC with differential which reveals a normochromic, normocytic anemia with a hemoglobin of 6 g/dL (60 g/L, 3.6 mmol/L; normal 11.7–15.7 g/dL, 117–150 g/L, 7.3–9.7 mmol/L), hematocrit of 18% (0.18; normal 35%–47%, or 0.35–0.47), and white blood cell (WBC) count of $2.6 \times 10^3/\mu L$ ($2.6 \times 10^9/\mu L$). The differential on the WBC count reveals 75% (0.75) lymphocytes (normal 20%–40%, or 0.2–0.4), 20% (0.2) neutrophils (normal 55%–62%, or 0.55–0.62), and 5% (0.05) lymphoblasts (normal 0%). Based on this information, a bone marrow aspirate and biopsy are performed, which reveal 85% (0.85) lymphoblasts. A lumbar puncture is also performed, which shows no evidence of leukemia.

What chemotherapy drugs should this patient receive as part of his ALL induction?

a. Dexamethasone, vincristine, and pegaspargase
b. Prednisone, vincristine, pegaspargase, daunorubicin
c. Daunorubicin, vincristine, pegaspargase
d. Dexamethasone, vincristine, pegaspargase, daunorubicin

What is the role of CNS prophylaxis?

KEY CONCEPT Current induction therapy for ALL typically consists of vincristine, L-asparaginase, and a steroid (prednisone or dexamethasone). An anthracycline is added for higher risk patients. Although induction treatment produces 95% CR in children, it declines to no more than 60% in patients older than 60 years of age.

Adults, unlike children, are universally considered to be at high risk for relapse; therefore, their induction regimens include an anthracycline (daunorubicin or doxorubicin) in addition to the standard steroid and vincristine treatment that have been the backbone of treatment for this disease for the last 40 years.[16,17] Dexamethasone often replaces prednisone because of its longer half-life and better CNS penetration.[17] Although dexamethasone possesses more favorable pharmacologic characteristics than prednisone, its use may be associated with more aseptic osteonecrosis of the femoral and humoral heads as well as an increase in life-threatening infections and septic deaths.[17]

Patient Encounter 2, Part 2

This patient had a bone marrow aspiration performed on days 8 and 29 that showed morphologic remission. The MRD on day 29 was less that 0.01%. This patient completed his induction therapy and started consolidation.

What is the role of MRD?

▶ CNS Prophylaxis

LO 6

KEY CONCEPT Leukemic invasion of the CNS is an almost universal event in patients even in those whose cerebrospinal fluid (CSF) cytology shows no apparent disease. Thus, all patients with ALL and AML leukemia receive intrathecal (IT) chemotherapy. Although this is often referred to as "prophylaxis," it more realistically represents treatment. CNS prophylaxis relies on IT chemotherapy (eg, methotrexate, cytarabine, and corticosteroids), systemic chemotherapy with dexamethasone and high-dose methotrexate, and craniospinal irradiation (XRT) in selected high-risk patients.[16] Cranial radiation use diminished substantially after the efficacy of IT treatment was evident, and the toxicities associated with radiation; learning disabilities, growth retardation, and secondary malignancies (particularly with the use of 6-mercaptopurine), were recognized. IT therapy has replaced cranial XRT as CNS prophylaxis for all except the very high-risk patients and those with T-cell ALL who are at higher risk of CNS disease.

Inexplicably, the treatment of CNS leukemia has not impacted the OS of adults as it has for childhood ALL. With IT chemotherapy alone, the incidence of CNS relapse in adults is 9% to 13% compared with less than 3% in children.[5,12]

▶ Postremission Consolidation Regimens

LO 6

Consolidation After completion of induction and restoration of normal hematopoiesis, patients begin consolidation. The goal of consolidation is to administer dose-intensive chemotherapy to reduce the burden of residual leukemic cells. It is in this and subsequent treatment phases that the remaining leukemic burden is eliminated. Several regimens use agents and schedules designed to minimize the development of drug cross-resistance. Consolidation is an effective strategy to prevent relapse in children with ALL, but its benefits in adults are less clear.

In children, the intensity of the consolidation treatment is determined by the child's risk classification and the degree of cytoreduction during induction (MRD). Patients who respond slowly to induction therapy (as determined by bone marrow examination early in induction) are at higher risk of relapse and are treated with more aggressive regimens.[18]

Reinduction (Delayed Intensification and Interim Maintenance) The typical duration of Interim Maintenance is approximately 8 weeks. Treatment usually consists of low intensity therapy added to continue remission and to lower cumulative toxicity. The Berlin-Frankfurt-Munster (BFM) Study Group introduced a treatment element called delayed intensification (or reinduction) therapy. This therapy consisted of repetition of the initial remission induction therapy administered approximately 3 months after remission. This regimen, similar to consolidation, has been adopted as a component of treatment for children by virtually all institutions.[12]

Intensification regimens vary in their aggressiveness and drug regimens depending on the patient's risk group and immunophenotype. For example, the use of high-dose methotrexate (5 g/m^2) appears to improve outcome in patients with T-cell ALL. The use of intensive asparaginase treatment in T-cell ALL patients also has improved outcomes significantly.[17]

▶ Maintenance

LO 6

The purpose of maintenance therapy is to further eliminate leukemic cells and produce an enduring CCR. The two most

important agents in maintenance chemotherapy are a combination of oral methotrexate and 6-mercaptopurine. Improved outcome is associated with increasing 6-mercaptopurine doses to the limits of individual tolerance based on absolute neutrophil count (ANC). The benefit of adding intermittent "pulses" of vincristine and a steroid (usually dexamethasone) to the antimetabolite backbone remains unclear, but it is common practice in most modern treatment regimens.[17] The goal is to induce a moderate immunosuppression and leukemic cell kill.

6-Mercaptopurine is a key agent in maintenance therapy. It has a complex metabolism and is initially metabolized by thiopurine methyltransferase (TPMT).[19] TPMT activity is variable with about 90% of patients having normal activity, about 10% having intermediate activity, and fewer than 1% having very low or no activity. Genetic polymorphisms in *TPMT* are inherited in an autosomal recessive fashion and have a profound influence on 6-mercaptopurine tolerance.[20,21]

TPMT screening is recommended for children starting therapy with 6-mercaptopurine. Children who possess alleles that have diminished activity require 6-mercaptopurine dose reductions of 50% to 90% to prevent severe immunosuppression and infection. Despite these reductions, these children have equivalent OS when compared with those receiving full-dose 6-mercaptopurine. The optimal duration of maintenance therapy in both children and adults is unknown, but most regimens are given for 2 to 3 years; extension of the regimen beyond 3 years has not shown any additional benefit.

ALL in Infants and Young Children

Infants and children younger than 1 year of age account for approximately 5% of all children with ALL and have the worst outcome of any group with this disease. These patients have several poor prognostic features at diagnosis, including hyperleukocytosis, hepatomegaly, splenomegaly, and CNS leukemia.[9]

A characteristic finding in up to 70% in this group is a chromosomal translocation involving the *MLL* gene located at 11q23. There are multiple possible rearrangements of this gene with other chromosomes, and all confer a poor prognosis. In vitro, blasts of these patients showed greater drug resistance to prednisolone and L-asparaginase than those from other patients, although they are more sensitive to cytarabine.[22] Based on this information, several studies are testing the efficacy of intensified chemotherapy that includes high-dose cytarabine. Another achievement is the prevention of CNS relapse using IT cytarabine in conjunction with high-dose systemic cytarabine. This combination has eliminated the need for cranial XRT in this young population. Even with major advances in cure rates for the general pediatric ALL population, in whom survival is 80% or more, the long-term survival of infants is only about 40% (Table 95–8).

ALL in Adolescents and Young Adults

As noted previously, age is an important prognostic factor in ALL. Adolescents and adult patients have generally been shown to have poorer survival than children. However, the group of patients between late adolescence and age 30 years (adolescents and young adults) have a substantially better outcome than older adult patients, but worse outcomes when compared to pediatric patients. When treated with pediatric protocols the disease-free survival is 60% to 70%, compared historically to 30% to 45%.[23]

Table 95–8

Representative Chemotherapy Regimens for Pediatric ALL

Induction (1 month)
IT cytarabine on day 0
Prednisone 40 mg/m^2/day or dexamethasone 6 mg/m^2/day po for 28 days
Vincristine 1.5 mg/m^2/dose (maximum, 2 mg) IV weekly for four doses
Pegaspargase 2500 units/m^2/dose IM for one dose or asparaginase 6000 units/m^2/dose IM Monday, Wednesday, and Friday for six doses
IT methotrexate weekly for two to four doses

Consolidation (1 month)
Mercaptopurine 50–75 mg/m^2/dose po at bedtime for 28 days
Vincristine 1.5 mg/m^2/dose (maximum, 2 mg) IV on day 0
IT methotrexate weekly for one to three doses
Patients with CNS or testicular disease may receive radiation

Interim Maintenance (one or two cycles) (2 months)
Methotrexate 20 mg/m^2/dose po at bedtime weekly
Mercaptopurine 75 mg/m^2/dose po daily on days 0–49
Vincristine 1.5 mg/m^2/dose (maximum, 2 mg) IV on days 0 and 28
Dexamethasone 6 mg/m^2/day po on days 0–4 and 28–32

Delayed Intensification (one or two cycles) (2 months)
Dexamethasone 10 mg/m^2/day po on days 0–6 and 14–20
Vincristine 1.5 mg/m^2/dose (maximum, 2 mg) IV weekly for three doses
Pegaspargase 2500 units/m^2/dose IM for one dose
Doxorubicin 25 mg/m^2/dose IV on days 0, 7, and 14
Cyclophosphamide 1000 mg/m^2/dose IV on day 28
Thioguanine 60 mg/m^2/dose po at bedtime on days 28–41
Cytarabine 75 mg/m^2/dose SC or IV on days 28–31 and 35–38
IT methotrexate on days 0 and 28

Consolidation Option (2- to 3-week intervals for six courses on weeks 5–24)
Mercaptopurine 50 mg/m^2/dose po at bedtime
Prednisone 40 mg/m^2/day for 7 days on weeks 8 and 17
Vincristine 1.5 mg/m^2/dose (maximum, 2 mg) IV on the first day of weeks 8, 9, 17, and 18
Methotrexate 200 mg/m^2/dose IV + 800 mg/m^2/dose over 24 hours on day 1 of weeks 7, 10, 13, 16, 19, and 22
IT methotrexate on weeks 5, 6, 9, 12, 15, and 18

Late Intensification (weeks 25–52)
Methotrexate 20 mg/m^2/dose IM weekly or 25 mg/m^2/dose po every 6 hours for four doses every other week
Mercaptopurine 75 mg/m^2/dose po at bedtime
Prednisone 40 mg/m^2/day po for 7 days on weeks 25 and 41
Vincristine 1.4 mg/m^{2}w/dose (maximum, 2 mg) IV on the first day of weeks 25, 26, 41, and 42
IT methotrexate on day 1 of weeks 25, 33, 41, and 49

Maintenance (12-week cycles)
Methotrexate 20 mg/m^2/dose po at bedtime or IM weekly with dose escalation as tolerated
Mercaptopurine 75 mg/m^2/dose po at bedtime on days 0–83
Vincristine 1.5 mg/m^2/dose (maximum, 2 mg) IV on days 0, 28, and 56
Dexamethasone 6 mg/m^2/day po on days 0–4, 28–32, and 56–60
IT methotrexate on day 0

IM, intramuscular; IT, intrathecal; po, oral; SC, subcutaneous.

Adapted from Leather HL, Bickert B. Acute leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 6th ed. New York, NY: McGraw-Hill; 2005:2458–2511.

Patient Encounter 3

A 13-year-old Caucasian male presents with a 4-week history of intermittent fevers, loss of appetite, headaches, and weight loss. A few days prior to presentation, he had a brief nose bleed, mild abdominal pain, and an episode of emesis. Patient's father noted a bruise on his left arm about 4 days prior. Physical examination reveals pallor, cervical lymphadenopathy, and hepatosplenomegaly. Electrolytes are within normal limits. A CBC shows a hemoglobin of 7.8 g/dL (78 g/L, 4.8 mmol/L; reference range 11.7–15.7 g/dL, 117–157 g/L, 7.26–9.74 mmol/L), hematocrit of 24% (0.24; reference range 35%–47% or 0.35–0.47), and a WBC count of 140 $\times 10^3$/mm^3 (140 $\times$ 10^9/L). The differential on the WBC count reveals 45% (0.45) lymphoblasts (reference range 0). Flow cytometry reveals B-cell ALL. A diagnostic lumbar puncture (LP) is performed which is negative for CNS leukemia. During the LP, the patient receives intrathecal cytarabine.

What are the prognostic factors for this patient?

What is the role of flow cytometry in identifying ALL?

The pediatric regimens used to treat this group of patients contain the BFM backbone: steroids, vincristine, asparaginase, and CNS prophylaxis.[24] The reasons for improved survival in this age group are not entirely clear, and multiple factors are likely to play a role. Among the likely explanations is that pediatric protocols use more aggressive and prolonged postremission consolidation therapy before maintenance. Other proposed explanations are the potential differences in disease biology in this versus older age patients, more intense CNS prophylaxis, and the greater degree of social support and better compliance fostered in a pediatric environment. Current and planned trials are focusing on the potential of extending this treatment approach to patients age 40 years and possibly older.

ALL in Adults

The incidence of ALL in adults ages 30 to 60 years is only 2 per 100,000 persons per year compared with almost 10 per 100,000 in children. The conventional risk factors such as high WBC counts, older age, and CNS disease hold true in adults as in children. However, the significance of cytogenetic and molecular markers that are so important in children seems to be less predictive of outcome in adults. An exception is the adverse prognostic factor, the presence of the *BCR-ABL* translocation (Ph$^+$) just as in childhood ALL. This occurs in 15% to 30% of adults and is even more common in patients older than 60 years of age.[24] The use of second-generation tyrosine kinase inhibitors, potent inhibitors of the Ph$^+$-associated BCR-ABL tyrosine kinase, has now become a standard of practice for all patient groups with Ph$^+$ disease.[7,25] Results show that the combination of these agents with conventional chemotherapy improves remission rates as well as OS compared with the use of conventional chemotherapy alone.[7,8,26]

Currently, induction and consolidation regimens in adults are similar to pediatric regimens. Aggressive postinduction regimens are not as well tolerated in this population, particularly in patients older than 60 years and are associated with a much higher incidence of toxicity and treatment-related deaths.[7] Some investigators are studying "moderate-dose" consolidation regimens that are better tolerated, although long-term efficacy data is lacking. Even though remissions are achieved in 80% to 90% of adult patients, 5-year disease-free survivals (DFSs) are only in the 30% to 40% range. Among elderly patients, the outcome is even poorer with no more than 20% having long-term survival.

Relapsed ALL

Relapse is the recurrence of leukemic cells at any site after remission has been achieved. Leukemic blasts are much more drug resistant than the blasts at initial diagnosis.[1] KEY CONCEPT Bone marrow relapse is the major form of treatment failure in 15% to 20% of patients with ALL. Most relapses have the same immunophenotype and cytogenetic changes seen of the original disease. Extramedullary sites of relapse include the CNS and the testicles.[24] Extramedullary relapse, although once common, has decreased to 5% or less because of effective prophylaxis. Site of relapse and the length of the first remission are important predictors of second remission and OS. Marrow relapses occurring less than 18 to 24 months into first remission are associated with a poor survival, but longer periods of remission (> 36 months) have a much higher chance of survival.[26] Treatment strategies for relapsed ALL include chemotherapy or allogeneic hematopoietic stem cell transplant (allo-HSCT). Even though patients undergoing allo-HSCT are less likely to relapse, treatment-related toxicity leads to a higher incidence of morbidity and mortality compared with chemotherapy alone.[6] Clofarabine, a next-generation deoxyadenosine analogue, has shown considerable activity in children and adults with refractory acute leukemias. Blinatumomab, a monoclonal antibody (MAB) that targets CD19, was recently approved for Ph negative relapsed or refractory ALL in adults and pediatric patients.[27]

LO 2

Treatment of AML

As with ALL, the primary aim in treating patients with AML is to induce remission and thereafter prevent relapse. Treatment of AML is divided into two phases: induction and consolidation. The prognosis of children with AML has improved dramatically over the past 30 years. Rates of complete remission as high as 80% to 90% and OS rates of 60% are reported.[28] This improvement is a result of better understanding of the biology of AML and the development of molecular targets that are used in combination with conventional chemotherapy.[14]

KEY CONCEPT The current induction therapy for AML usually consists of a combination of cytarabine, daunorubicin, and etoposide. The second phase of treatment for AML is called consolidation. The purpose of this phase is to further enhance remission with more cytoreduction.[14]

▶ *Remission Induction*

The goal of induction chemotherapy in AML is essentially identical to that in ALL—"empty" the bone marrow of all hematopoietic precursors and allow repopulation with normal cells. The combination of an anthracycline (eg, daunorubicin, doxorubicin, or idarubicin) and the antimetabolite cytarabine forms the backbone of AML induction therapy. The most common induction regimen (7 + 3) combines daunorubicin for 3 days with cytarabine on days 1 to 7.[13] The remission rate for this combination is approximately 80% in children and younger adults but declines to 60% in patients older than 60 years of age.[5,13] Adding gemtuzumab ozogamicin to induction therapy for older patients improved relapsed rates and OS, but no improvement in

response rates were demonstrated. Midostaurin, an oral multitarget kinase inhibitor, was recently approved by the FDA for treatment of FLT3 positive AML. It is added on days 8 to 21 of the convention 7+3 induction chemotherapy and also on days 8 to 21 of high-dose cytarabine consolidation.[29]

▶ *Postremission Chemotherapy*

In AML, postremission chemotherapy is often referred to as consolidation therapy. Several cycles of intensive postremission chemotherapy combining non–cross-resistant agents given every 4 to 6 weeks substantially improves DFS. Without postremission treatment, all patients would relapse within several weeks. This is analogous to the consolidation and other phases of postremission chemotherapy in ALL. The use of high-dose cytarabine in postremission therapy seems to be important for improving survival, but the most effective dose has yet to be determined.[14] Although the optimal number of courses remains to be determined, at least four are probably required.[13]

Allogeneic Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is the most effective treatment for AML. Its promising benefit must be weighed against the potential risk of transplantation related sequelae. HSCT has become a less attractive option as the results of increasingly intensive chemotherapy and postrelapse salvage therapy have improved.[14]

The availability of human leukocyte antigen (HLA)-matched sibling donors determines whether patients undergo HSCT as postremission treatment. To facilitate this process, it is important to obtain HLA typing on all younger patients and siblings shortly after diagnosis. Patients who do not have an HLA-matched sibling proceed to postremission therapy with chemotherapy alone.

Complications and benefits of allogeneic HSCT are described in Chapter 98. Transplant-related mortality following matched-sibling allo-HSCT is 20% to 30% in most series. Complications from transplantation increase with age; therefore, patients older than 60 years of age rarely receive a myeloablative allo-HSCT. Because the average age of AML patients is 65 years, most patients with this disease are not candidates for this form of therapy. For older patients up to 70 years of age, a reduced-intensity (mini or nonmyeloablative allogeneic) transplant may be an option. These transplants use less intensive preparative regimens and rely on the allogeneic graft-versus-leukemia (GVL) effect to eliminate their disease.[13]

The role of HSCT, particularly whether it should be performed during the first CR or reserved for second remission, remains the most controversial issue in pediatric AML. In certain institutions, HSCT is often reserved for patients that are considered high risk.[14] Some types of AML patients may be curable with conventional-dose chemotherapy alone.

Autologous Hematopoietic Stem Cell Transplantation

Because the majority of AML patients lack an HLA-identical donor, investigators began to consider the use of the patient's own bone marrow, obtained while in CR, as a source of hematopoietic regeneration. However, relapse continues to be a problem secondary to the presence of residual disease in the graft. Despite the reduced morbidity and mortality associated with auto-HSCT, this type of transplant does not compare favorably to standard postremission chemotherapy.[13]

▶ *CNS Therapy*

The prevalence of CNS disease at diagnosis of AML is approximately 15%.[14] Features associated with the risk of CNS leukemia include hyperleukocytosis, monocytic, or myelomonocytic leukemia (FAB M4 or M5), and young age. Adequate CNS prophylaxis is an essential component of therapy. Patients with CNS disease at diagnosis can be cured with IT therapy alone without the use of cranial XRT. In most cases, IT cytarabine with or without methotrexate and systemic high-dose cytarabine provide effective treatment.

AML in Infants

AML in infants younger than 12 months of age shows clinical and biological characteristics different from those of older children. The disease phenotype is more commonly monoblastic or myelomonoblastic (M4, M5), and the patients usually present with hyperleukocytosis. Extramedullary involvement is common, often involving skin and other organs. As in infant ALL, there is a high incidence of translocations involving the *MLL* gene in infant AML. The number of infant AML trials reported is limited, but the EFS of this population is similar to that of older children with AML. This is in marked contrast to the outcomes for infants with ALL for whom the EFS is much lower than in older children.[30]

AML in the Elderly

AML is the most common acute leukemia in the elderly. Compared with younger patients with the same disease, older adults have a poor prognosis and represent a distinct population with regard to the biology of their disease. Older adults have a lower incidence of favorable chromosomal aberrations and a higher incidence of unfavorable aberrations.[5,13] Fms-like tyrosine kinase 3 (*FLT3*) which is an AML oncogene plays an important role in AML pathogenesis and was associated with a poor outcome. *FLT3*-ITD is common in adults, but is only found in 12% of the pediatric population.[14] Older patients also have more comorbidities, such as type 2 diabetes, obesity, and other physiologic limitations. Thus, the poor prognosis of AML in this population is only partly the result of unfavorable biology.

In older adults, in contrast to children, AML is more likely to arise from a proximal bone marrow–stem cell disorder, such as MDS, or present as a secondary, prior treatment-related leukemia. These forms of AML are notoriously poorly responsive to conventional chemotherapy and thus have a lower CR rate and poorer survival.[26]

As previously noted, age is an important prognostic factor. Older adults are not as tolerant of or as responsive to remission induction and consolidation chemotherapy as younger patients. Furthermore, long-term survival for patients older than 60 years is only 5% to 15% compared with 30% DFS for younger adults.[5,13]

Relapsed AML

Even though 75% to 85% of patients with AML achieve a remission, only about 50% survive. Patients who relapse usually respond poorly to additional treatment and have a shorter duration of remission. This is probably related to drug resistance induced during induction and certain chromosomal abnormalities.

Even though there is no standard therapy for relapse, most studies have shown that high-dose cytarabine-containing regimens have considerable activity in obtaining a second remission. Cytarabine has been used in combination with mitoxantrone, etoposide, fludarabine, 2-chlorodeoxyadenosine, and (more recently) clofarabine.[5,13] For patients unable to tolerate intensive chemotherapy, low dose cytarabine and the hypomethylating agent, azacitidine, are also options for relapsed disease.[31]

After a patient has achieved a second remission with conventional chemotherapy, allo-HSCT is the therapy of choice.

For patients without an HLA-matched sibling, a matched unrelated donor (MUD) or cord blood transplant may be a reasonable alternative. The combination of myeloablative high-dose chemotherapy and the GVL effect is thought to offer the best chance of survival in AML.

Complications of Treatment

LO 7

▶ *Tumor Lysis Syndrome*

Tumor lysis syndrome (TLS) is an oncologic emergency that is characterized by metabolic abnormalities resulting from the death of blast cells and the release of large amounts of purines, pyrimidines, and intracellular potassium and phosphorus. Uric acid, the ultimate breakdown product of purines, is poorly soluble in plasma and urine. Deposition of uric acid and calcium phosphate crystals in the renal tubules can lead to acute renal failure. Many patients with acute leukemia, especially those with a high tumor burden, are at risk for TLS during the first several days of chemotherapy. Measures to prevent TLS include aggressive hydration to increase urine output, and allopurinol to reduce uric acid production. Hyperhydration and potentially using a diuretic to increase urine output is generally an effective method of dealing with this issue. However, on some occasions, the use of rasburicase is indicated. Rasburicase is a urate oxidase that catalyzes the oxidation of uric acid to allantoin, which is much more soluble than uric acid and excreted more easily.[32] Given its high cost, rasburicase generally is restricted to patients with high WBC counts ($> 50 \times 10^3/mm^3$, $50 \times 10^9/L$) and uric acid levels greater than 8 mg/dL (476 μmol/L).

▶ *Infection*

Infection is a primary cause of death in acute leukemia patients. Both the disease and aggressive chemotherapy cause severe myelosuppression, placing the patient at risk for sepsis.

The therapy for AML is extremely myelosuppressive. Children with AML have a 10% to 20% induction mortality rate secondary to infection and bleeding complications. Therefore, patients receiving induction therapy usually are hospitalized for the first 4 to 6 weeks of therapy. The induction therapy for ALL is far less myelosuppressive, and these patients recover their neutrophil counts quicker and usually do not require prolonged hospitalizations.[6]

It is important to recognize that symptoms and signs of infection may be absent in a severely immunosuppressed or neutropenic patient. Fever (> 38.3°C [100.9°F]) in a neutropenic patient is a medical emergency. Because the progression of infection in neutropenic patients can be rapid, empirical antibiotic therapy is started whenever a fever is documented. Currently, the most commonly used initial antibiotic agent is cefepime, a fourth-generation cephalosporin that has good antipseudomonal coverage as well as adequate coverage against *Streptococcus viridans* and pneumococci.[33]

Disseminated fungal infections most commonly caused by Candida and Aspergillus species can be life threatening in children with AML. From the results of clinical trials in adults, many pediatric institutions recommend antifungal prophylaxis with voriconazole, posaconazole, micafungin, or caspofungin. Fluconazole and itraconazole are not considered ideal, because they are not effective against aspergillus species and other molds.[33]

Trimethoprim–sulfamethoxazole is started in all patients with any acute leukemia for the prevention of *Pneumocystis jiroveci* pneumonia (PJP). Patients normally continue this therapy for 6 months after completion of treatment. The use of additional antibiotic prophylaxis is not encouraged because of concerns for antibiotic resistance.

LO 7

Of note is that up to 10% of patients seem to exhibit excessive myelosuppression with trimethoprim–sulfa antibiotics (presumably the result of the antifolate trimethoprim in combination with other systemic cytotoxic agents). Changing to another anti-PJP agent such as dapsone or inhaled pentamidine may help to alleviate this problem.

▶ *Secondary Malignancies*

Secondary malignancies are a risk of the successful treatment of a prior cancer or the use of cytotoxic agents in a variety of autoimmune diseases. The chemotherapy agents used, especially alkylating agents and topoisomerase II inhibitors, predispose patients to secondary hematopoietic neoplasms. As the aggressiveness of treatment and the number of survivors of AML increase, the risk of secondary neoplasms also may rise. There are two different types of second malignancies: acute leukemia, which is generally myeloid in origin, or MDS. There are also reports of secondary solid tumors, especially within regions of prior radiation exposure. The latency period between the end of treatment and the development of a secondary leukemia is generally in the range of 5 to 10 years. For those patients who develop secondary solid malignancies, the latency may be as long as 10 to 20 years.

The incidence of second cancers attributed to alkylators peaks 4 to 6 years after exposure and plateaus after 10 to 15 years. Higher cumulative doses and older age at the time of treatment are risk factors for this type of cancer.

Epipodophyllotoxins (etoposide and others) can induce a second malignancy characterized by balanced chromosomal translocations and short latency periods (2–4 years). The risk of this leukemia is related to schedule (dose intensity) and the concomitant use of other agents (L-asparaginase, alkylating agents, and possibly antimetabolites). The prognosis for topoisomerase II inhibitor–related secondary leukemia is extremely poor. Only about 10% of these patients survive after salvage chemotherapy, and only 20% survive after HSCT.

Ionizing radiation therapy is also a cause of secondary malignancies. These secondary tumors generally develop within or adjacent to the previous radiation field. These cancers often have a prolonged latency, typically 15 or more years, but shorter latencies (5–14 years) are known. Higher doses of radiation and younger age are associated with an increased risk of secondary malignancy.

Unlike children, adults may have other factors that predispose them to secondary malignancies. Lifestyle choices such as tobacco use, alcohol use, and diet are implicated in influencing the development of secondary neoplasms in the adult population.

Now that 80% or more of children survive their primary cancers, the incidence of secondary neoplasms may increase. Recognizing this potential, many treatment regimens for children are being modified appropriately to reduce exposure to alkylators, topoisomerase inhibitors, and radiation. Children in long-term follow-up are screened for secondary malignancies and other disease and treatment-related disabilities that accompany childhood cancer. Similar screening and educational opportunities are not as established in adult survivors.

▶ *Late Effects*

With increased success in pediatric clinical trials, the OS rate for pediatric cancers has increased markedly over the last 35 years. For some diseases (acute lymphoblastic leukemia, Wilms tumor, low-grade and common germ cell tumors), the OS rate is now

at or above 80%. KEY CONCEPT Despite this significant increase in survival, many patients, particularly pediatric cancer survivors, have disease-related or treatment-related disabilities. As many as 50% to 60% of these survivors are estimated to have at least one chronic or late-occurring complication of treatment.[34] In leukemia, the intensified use of methotrexate may be responsible for some sporadic neurotoxicity seen in children and adults. Likewise, the use of pharmacologic doses of glucocorticoids has been associated with avascular necrosis of bone in older children and adults. High cumulative doses of anthracyclines can cause irreversible cardiomyopathy. Cranial XRT is now less frequently used for CNS leukemia prophylaxis but can cause neuropsychological and neuroendocrine abnormalities that may lead to obesity, short stature, or precocious puberty.[4] As newer and more intensive treatments enter clinical trials, close observation for long-term side effects will assume even greater importance.

LO 8

Supportive Care

Because of the need for repeated venous access, a central venous catheter or infusion port is placed before starting treatment. These devices are useful not only for delivery of chemotherapy but also to support patients during periods of myelosuppression. Infection and bleeding complications are the primary causes of mortality in patients with leukemia.

Platelet transfusions are a common tool to prevent hemorrhage. Patients with uncomplicated thrombocytopenia can be transfused when the platelet count falls below $10 \times 10^3/mm^3$ ($10 \times 10^9/L$). Patients who are either highly febrile or actively bleeding may require transfusions at higher levels. Red blood cell transfusions generally are not necessary for a hemoglobin concentration greater than 8 g/dL (80 g/L, 4.97 mmol/L).

There is much controversy regarding the routine use of colony-stimulating factors (CSFs) (eg, granulocyte colony-stimulating factor [G-CSF] and granulocyte-macrophage colony-stimulating factor [GM-CSF]) in neutropenic patients. Even though several clinical trials have shown the time to ANC recovery is decreased with a CSF, none have demonstrated that CSFs statistically influence infection-related mortality. At present, the use of CSFs (G-CSF most commonly) generally is limited to those chemotherapy regimens that place the patient at highest risk for prolonged neutropenia.

OUTCOME EVALUATION

Developing strategies for the treatment and monitoring of acute leukemias begins with risk stratification. Understanding the likely risk of relapse determines the aggressiveness and length of therapy. Remission status and MRD after the induction phase of treatment must be closely observed. Failure to obtain morphologic bone marrow remission by day 28 is a very adverse prognostic sign and dictates further induction treatment. For those who have a morphologic remission, quantification of MRD has become an increasingly important prognostic factor. Levels of residual less than 0.01% appear to be associated with better outcomes.

A clinician is generally charged with developing a plan to educate patients and families about their drugs and doses. This is a critical responsibility; it is imperative that the patients and their families understand why they are receiving their medications and how to take them. Frank, open discussion (with the family or patient in possession of their prescriptions) goes a long way toward preventing errors that occur as a result of "assuming" that they understand their medications. If modifications are necessary secondary to toxicity or inadequate response, establish a plan for treatment change. Remember that individual patients often do not fit the "average" patient profile, and dose modifications are frequently needed. The practitioner should be familiar with dosing ranges, WBC count, and other parameters that indicate appropriate treatment response. Based on response to prior phases of treatment, the clinician should recognize potential toxicities in subsequent phases of treatment with the same or different drugs at similar or different doses.

Patient Care Process

Collect Information:

- Using the medical record collect the pertinent information on the presenting symptoms that made the patient seek out a health care provider.
- Perform a medication history, including over the counter and herbal medications.
- Speak with patient, or patient's family in the instance of a pediatric patient, and assess patient or family's socioeconomic situation to evaluate ability to obtain prescription medications and/or resources for transplantation if necessary.

Assess the Information:

- Review patient's medication history prior to admission, making sure all medications have a diagnosis and are necessary.
- Review patient's medications for drug interactions with antifungals and oral chemotherapy regimens.
- Review the patient's medical history looking for any medical condition that might predispose the patient to adverse effects from chemotherapy and supportive care medications, for example, look for a history of prolonged QT interval, or heart failure.
- Speak to the patient about any risk factors that may predispose them to adverse effects.
- Ascertain the patient's understanding of the process for the treatment of acute leukemias and the need for compliance in prophylactic medications.

Develop a Care Plan:

- If patient has baseline hepatic, renal, QT prolongation, or other cardiac issues, anticipate the need for dose modifications or changes in therapy.
- If there is a barrier to acquiring medications, develop a plan early in the patient's treatment to ensure that the patient can get the medications needed when discharged.
- Review and discuss the importance of being compliant with prophylactic medications with the patient or patient's family.

(*Continued*)

Patient Care Process (*Continued*)

- Educate patient and patient's families about adverse effects of treatment for leukemia, and what supportive care medications will help in preventing and treating the adverse effects.

Implement the Care Plan:

- When the patient is discharged from the hospital and seen at a clinic appointment, perform a medication history and reeducate about the need for all of the medications and the importance of compliance.
- Review all new laboratory and cardiac data to make sure all medications are dosed appropriately.
- Review medication list for drug interactions.
- Review side effect management with patient and patient's family, reeducating on need for home medications to treat side effects.
- Suggest nonpharmacological ways to minimize adverse effects.
- If patient is not tolerating or unable to manage adverse effects at home, work with providers to implement a new strategy.

Follow-up: Monitor and Evaluate:

- At each clinic visit review medication list with patient.
- Check for drug interactions with new medications.
- Review hepatic, renal, and any changes in clinical status; reduce dose or eliminate medications based on those results.
- Review effectiveness of symptom management plan with patient and patient's family.
- Reeducate as needed.

Abbreviations Introduced in This Chapter

ALL	Acute lymphocytic/lymphoblastic leukemia
allo-HSCT	Allogeneic hematopoietic stem cell transplant
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ANLL	Acute nonlymphocytic leukemia
BFM	Berlin-Frankfurt-Munster
CCR	Continuous complete remission
CD	Cluster determinant
CR	Complete remission
CSF	Cerebrospinal fluid
CSF	Colony-stimulating factor
DFS	Disease-free survival
EFS	Event-free survival
FISH	Fluorescent in situ hybridization
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVL	Graft-versus-leukemia
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplantation
ITD	Internal tandem duplication
MAB	Monoclonal antibody
MDS	Myelodysplastic syndrome
MRD	Minimal residual disease
MUD	Matched unrelated donor
OS	Overall survival
Ph^+	Philadelphia chromosome
TLS	Tumor lysis syndrome
XRT	Irradiation

REFERENCES

1. Bhojwani D, Pui CH. Relapsed childhood acute lymphoblastic leukemia. Lancet. 2013;14:205–2017.
2. Ribera JM, Oriol A. Acute lymphoblastic leukemia in adolescents and young adults. Hematol Oncol Clin North Am. 2009;23:1033–1042.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
4. Campana D, Pui CH. Childhood leukemia. In: Abeloff MD, Armitage JO, Niederhuber JE, et al., eds. Clinical Oncology, 4th ed. Philadelphia: Elsevier; 2008:2139–2169.
5. Applebaum FR. Acute myeloid leukemia in adults. In: Abeloff MD, Armitage JO, Niederhuber JE, et al., eds. Clinical Oncology, 4th ed. Philadelphia: Elsevier, 2008:2215–2134.
6. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatr Clin North Am. 2008;55(1):1–20.
7. Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. Cancer. 2010;116:1165–1176.
8. Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia. J Clin Oncol. 2011;29:532–543.
9. Silverman LB. Acute lymphoblastic leukemia in infancy. Pediatr Blood Cancer. 2007;49:1070–1073.
10. Teachy DT, Hunger SP. Predicting relapse risk in childhood acute lymphoblastic leukaemia. Br J Haematol. 2013;162:606–620.
11. Mandrell BN, Pritchard M. Understanding the clinical implications of minimal residual disease in childhood leukemia. J Pediatr Oncol Nurs. 2006;23:38–44.
12. Bickert-Poon B, Hatfield Seung A. Acute leukemias. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York City: McGraw-Hill; 2014.
13. Shipley JL, Butera JN. Acute myelogenous leukemia. Exp Hematol. 2009;37:649–658.
14. Rubnitz Je, Gibson B, Smith FO. Acute myeloid leukemia. Hematol Oncol Clin North Am. 2010;24:35–63.
15. Rubnitz JE, Gibson B, Smith FO. Acute myeloid leukemia. Pediatr Clin North Am. 2008;55:21–51.
16. Hoelzer D, Gokbudet N. Acute lymphoid leukemia in adults. In: Abeloff MD, Armitage JO, Niederhuber JE, et al., eds. Clinical Oncology, 4th ed. Philadelphia: Elsevier; 2008:2191–2213.
17. Rabin KR, Poplack DG. Management strategies in acute lymphoblastic leukemia. Oncology. 2011;15:328–347.
18. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2010;24:1–18.
19. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009;360:2730–2741.
20. Karran P, Attard N. Thiopurines in current medical practice: molecular mechanisms and contributions to therapy related cancer. Nat Rev Cancer. 2008;8:24–36.

21. Wang L, Weinshilboum R. Thiopurine S-methyltransferase pharmacogenetics: insights challenges and future directions. Oncogene. 2006;25:1629–1638.
22. Pui CH, Relling MV, Campana D, et al. Childhood acute lymphoblastic leukemia. Rev Clin Exp Hematol. 2002;6:161–180.
23. Curran E, Stock W. How I treat acute lymphocytic leukemia in older adolescents and young adults. Blood. 2015;125:3702–3710.
24. Larson S, Stock W. Progress in the treatment of adults with acute lymphoblastic leukemia. Curr Opin Hematol. 2008;15:400–407.
25. Ribera JM, Oriol A. Acute lymphoblastic leukemia in adolescents and young adults. Hematol Oncol Clin North Am. 2009;23:1033–1042.
26. Jabbour E, O'Brien S, Konopleva M, Kantarijan H. New insights into the pathophysiology and therapy of adult acute lymphocytic leukemia. Cancer. 2015;121:2517–2528.
27. Blyncto package insert. Amgen Pharmaceuticals, Thousand Oaks, CA. August 2017.
28. Dohner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. NEJM. 2015;373:1136–1152.
29. Stone RM, Mandrekai BL, Laumann SK, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3+ mutation. NEJM. 2017;1056:1–10.
30. Ishii E, Kawasaki H, Isoyama K, Eguchi-Ishimae M, Eguchi M. Recent advances in the treatment of infant acute myeloid leukemia. Leuk Lymphoma. 2003;44:741–748.
31. Gemuenden C, Benz R, Senn O, Goede JS, Manz MG, Gerber B. Efficacy of azacitidine in de novo and relapsed acute myeloid leukemia: a retrospective comparative study. Clin Lymphoma Myeloma Leuk. 2015;15:811–815.
32. Howard SC, Jones DP, Pui C. The tumor lysis syndrome. N Engl J Med. 2011;364:1844–1854.
33. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002;34:730–751.
34. Nathan PC, Wasilewski-Masker K, Janzen LA. Long-term outcomes in survivors of childhood acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2009;23:1065–1082.

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96 Chronic Leukemias and Multiple Myeloma

Amy M. Pick

LEARNING OBJECTIVES

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

LO

1. Explain the role of the Philadelphia chromosome in the pathophysiology of chronic myelogenous leukemia (CML).
2. Identify the clinical signs and symptoms and laboratory findings associated with CML, chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).
3. Discuss first- and second-line treatment options for CML, including options for those patients with drug-resistant disease.
4. Describe the clinical course of CLL and distinguish which patients may be observed and who require treatment.
5. Outline the treatment options available for CLL, noting treatment differences based on variations in the tumor's molecular profile.
6. Describe the clinical presentation and symptoms of MM.
7. Recommend the appropriate treatment for patients with MM, recognizing the importance of combination therapy and the role of autologous hematopoietic stem cell transplant.

INTRODUCTION

Several diseases comprise chronic leukemia. The two most common forms are chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL). The slower progression of the disease contrasts it from acute leukemia, with the survival of chronic leukemia often lasting several years without treatment. This chapter covers CML and CLL. The chapter also discusses the hematologic cancer MM.

CHRONIC MYELOGENOUS LEUKEMIA

CML is a hematologic cancer that results from an abnormal proliferation of an early myeloid **progenitor** cell. The clinical course of CML has three phases: chronic phase (CP-CML), accelerated phase (AP-CML), and **blast** crisis (BP-CML), with 90% of patients diagnosed in chronic phase.[1] Criteria for these phases are largely based on the percent blasts in the peripheral blood or bone marrow. Chemotherapy can be used to control white blood cell (WBC) counts in the chronic phase, but as CML slowly progresses, the cancer becomes resistant to treatment. Blast crisis resembles acute leukemia, and immediate aggressive treatment is required.

EPIDEMIOLOGY AND ETIOLOGY

There were an estimated 8430 new cases of CML diagnosed in 2018, accounting for 14% of all adult leukemias.[2] The incidence of CML increases with age, with the median age of diagnosis being 65 years.[3] In most newly diagnosed cases, the etiology cannot be determined, but high doses of ionizing radiation and exposure to solvents such as benzene are recognized risk factors.

PATHOPHYSIOLOGY

Cell of Origin

CML arises from a defect in an early progenitor cell. The pluripotent (noncommitted) stem cell is implicated as the origin of the disease; therefore, multiple cell lineages of hematopoiesis may be affected, including myeloid, erythroid, megakaryocyte, and (rarely) lymphoid lineages. These cells remain functional in CP-CML, which is why patients in this phase are at low risk for developing infections.

Ph Chromosome

LO 1

KEY CONCEPT The Philadelphia chromosome (Ph) results from a translocation between chromosomes 9 and 22, leaving a shortened chromosome 22. The Ph results in the formation of an abnormal fusion gene between the breakpoint cluster region and the Abelson proto-oncogene (*BCR-ABL*), which encodes an overly active tyrosine kinase. The loss of control of tyrosine kinase activity causes abnormal cellular proliferation and inhibition of apoptosis.[1] Molecular tools such as quantitative reverse transcriptase-polymerase chain reaction (Q-PCR) and fluorescence in situ hybridization (FISH) are used in the detection and monitoring of *BCR-ABL* transcripts found in CML.[4]

Clinical Presentation and Diagnosis of CML[5]

Signs and Symptoms

- 30%–50% are asymptomatic at diagnosis
- Symptoms may include fatigue, fever, weight loss, and bleeding
- Organomegaly consisting of splenomegaly and hepatomegaly

Diagnostic Procedures

- Peripheral blood
- Bone marrow biopsy (percentage of blasts)
- Cytogenetic studies (presence of Ph and additional chromosomal abnormalities)
- Molecular testing (Q-PCR to detect *BCR-ABL1* transcripts)

Laboratory Findings

- Peripheral blood
  - Leukocytosis (most present with WBC count > 100 × 10^9/L [100 × 10^3/mm^3])
  - Thrombocytosis (~50% of patients in chronic phase)
  - Anemia
  - Basophilia
  - Presence of blasts
  - Elevated uric acid
- Bone marrow
  - Hypercellularity with presence of blasts
  - Cytogenetics including the presence of Ph

Poor Prognostic Factors

- Older age
- Splenomegaly
- High percent blasts in the blood (ie, AP- or BP-CML at time of diagnosis)
- Abnormal platelet count (high or low)
- Additional chromosomal abnormalities (ie, clonal evolution)

TREATMENT

Desired Outcome

The primary goal in the treatment of CML is to achieve a clinical response with tyrosine kinase inhibitor (TKI) therapy. Ideally, this is a deep, long-lasting molecular response which is achievable for many patients with CP-CML.[6] A complete molecular response is defined as undetectable *BCR-ABL* transcripts by the international scale.[7] International standardization of molecular response reflects a percentage of *BCR-ABL1* compared to control gene.[4] Approximately 50% to 70% of patients with CML will achieve a major molecular response (> 3 $\log_{10}$ reduction in *BCR-ABL1* transcripts) and another 10% to 20% will achieve an even deeper molecular response.[8] Additional goals include achieving a complete hematologic and cytogenetic response. A complete hematologic response is defined as a normalization of peripheral blood counts and complete cytogenetic response being the elimination of the Ph.[7] A cure from CML can only come from complete eradication of the Ph clone.

General Approach to Treatment

There have been significant advances in the treatment of CML since the discovery of the Ph in 1960. The success of therapy is largely dependent on the clinical phase of the disease. Treatment decisions are based on patient's age, phase of CML, and comorbidities. The National Comprehensive Cancer Network (NCCN) provides recommendations on the therapeutic treatment approach.[7] Nearly all patients with CML are initially treated with a TKI. Depending on the clinical phase, newer generation TKIs or omacetaxine may be options for patients who fail to respond or do not tolerate initial TKI therapy. Hydroxyurea may be used after diagnosis to rapidly reduce high WBC counts and prevent potentially serious complications (respiratory and neurologic) associated with large numbers of circulating neutrophils. Hydroxyurea, though, does not alter the disease process. TKIs can also reduce peripheral WBC counts over several weeks; therefore, many patients are started on a TKI alone. **Allogeneic** hematopoietic stem cell transplant (HSCT) is the only curative therapy for CML and is reserved for patients with TKI resistance. **Figure 96–1** illustrates one approach for clinically managing newly diagnosed CP-CML patients.

Nonpharmacologic Therapy

▶ *Hematopoietic Stem Cell Transplantation*

LO 3

KEY CONCEPT Allogeneic HSCT is the only curative treatment option for CML; however, the impressive outcomes with TKIs have limited the role of transplant. Allogeneic HSCT may be considered for the rare patient with *BCR-ABL* mutations that are resistant to or who fail TKI therapy. Transplant should also be considered for patients who present in BP-CML or who progress on a TKI with advanced disease.[7] There are significant risks and long-term complications with allogeneic HSCT including early mortality and **graft-versus-host disease**. For patients who do not achieve a complete molecular response or have a relapse, the infusion

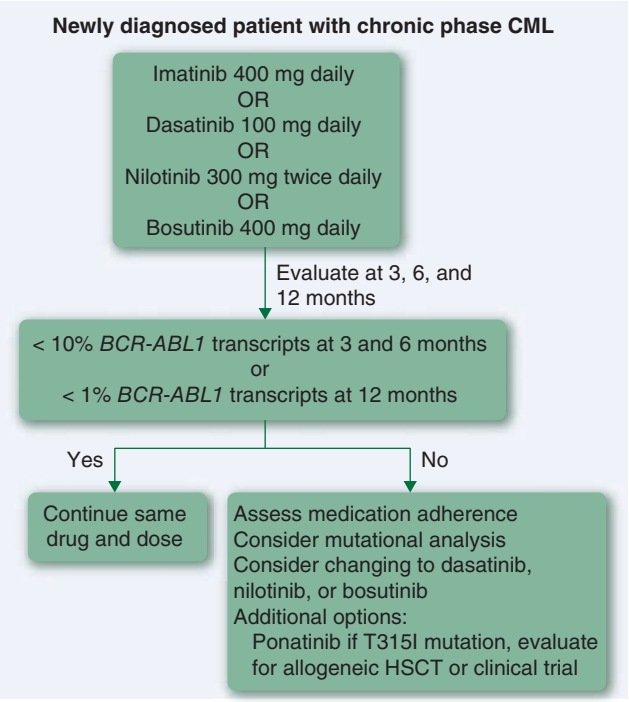

FIGURE 96–1. Algorithm for TKI therapy in newly diagnosed patient with CP-CML. (Data from NCCN.)

of donor lymphocytes may place the patient back into a durable remission.[7]

Pharmacologic Therapy

LO 2

The treatment of CML has dramatically changed since the introduction of TKIs. KEY CONCEPT Nearly all patients with CML are initially treated with a TKI. These oral agents do not cure CML but produce long-term response in the vast majority of patients. Four TKIs (imatinib, dasatinib, nilotinib, and bosutinib) may be used may be used as first-line therapy for newly diagnosed CP-CML.[7]

▶ *Imatinib Mesylate (Gleevec)*

Imatinib mesylate (Gleevec) is a first-generation TKI and was the first TKI to show efficacy in the treatment of CML. Imatinib inhibits phosphorylation of various proteins involved in cell proliferation by binding to the adenosine triphosphate–binding pocket of *BCR-ABL*.[9] The almost 11 year follow-up data show that the use of imatinib in CP-CML results in an estimated overall survival of 83.3%, a complete cytogenetic response of 82.8%, and an estimated event-free survival of 79.6%.[10] Lower response rates are reported in accelerated phase and BP-CML.[9] Disease progression is typically attributed to imatinib primary or secondary resistance.[1,7] The *ABL* kinase mutation *T315I* is one mechanism of secondary resistance that results in reactivation of *BCR-ABL* activity. The *T315I* mutation renders imatinib and the second-generation TKIs ineffective; therefore, alternative therapy with agents that overcome this mutation (ie, ponatinib) must be selected.[4] Imatinib is generally well tolerated. Common side effects include myelosuppression, gastrointestinal disturbances, and myalgias. Dosing and additional adverse effects may be found in Table 96–1.

Table 96–1

Drugs Used in CML

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Bosutinib (Bosulif)	Diarrhea, nausea vomiting, thrombocytopenia, neutropenia, increased liver function tests, fluid retention	Dose: 400–500 mg po once daily depending on phase Dose may be increased to 600 mg po once daily if complete hematologic response not seen at 8 weeks or complete cytogenetic response by 12 week Take with food Drug interactions: metabolized by CYP 3A4; inhibitor and substrate of P-glycoprotein	CrCl 30–50 mL/min (0.50–0.83 mL/s): 500 mg daily and may decrease to 400 mg if cannot tolerate CrCl < 30 mL/min (0.50 mL/s): 300 mg daily	Any baseline liver impairment: 200 mg daily
Dasatinib (Sprycel)	Thrombocytopenia, neutropenia, headache, rash, edema, pleural effusions	Dose: 100 mg po once daily for chronic phase CML or 140 mg po daily for accelerated phase or blast crisis Avoid concomitant medications that prolong the QT-interval; low levels of potassium and magnesium should be corrected before initiating therapy Drug interactions: metabolized by CYP 3A4 Dasatinib exhibits pH-dependent absorption; avoid medications that alter gastric pH (eg, H_2 antagonists and PPIs)	No reductions	No reductions
Imatinib mesylate (Gleevec)	Neutropenia, thrombocytopenia, diarrhea, rash, nausea, edema, fatigue, arthralgias, myalgias, headache, increased liver function tests, congestive heart failure (rare)	Dose range: 400–800 mg po per day depending on phase Take with meals and a full glass of water Drug interactions: metabolized by CYP 3A4; weak inhibitor of CYP 2D6 and 2C9 Avoid taking with acetaminophen to reduce hepatic toxicity Diarrhea usually responds to loperamide	CrCl 20–39 mL/min (0.33–0.66 mL/s): 50% reduction in dose CrCl < 20 mL/min (0.33 mL/s): use with caution	Mild to moderate impairment: no adjustment Severe impairment: reduce dose by 25% Discontinue imatinib if liver transaminases are > 5 × upper limit of normal or if serum bilirubin > 3 × upper limit of normal
Nilotinib (Tasigna)	Thrombocytopenia, neutropenia, elevated bilirubin, elevated serum lipase	Dose: 400 mg po twice daily Take on an empty stomach Black-box warning for QT prolongation; avoid concomitant medications that prolong the QT interval; low levels of potassium and magnesium should be corrected before initiating therapy Drug interactions: metabolized by CYP 3A4; competitive inhibitor of CYP 2C8, 2C9, 2D6, and UGT1A1 Pharmacogenomic testing of UGT1A1 polymorphisms can be used to identify patients who may have hyperbilirubinemia	No reductions	Child-Pugh class A, B, or C: 200 mg po twice daily for chronic phase CML; may increase to 300 mg if tolerating nilotinib therapy; discontinue nilotinib if experiencing grade 3 or 4 elevations in bilirubin or liver transaminases

(*Continued*)

Table 96–1

Drugs Used in CML (*Continued*)

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Omacetaxine mepesuccinate (Synribo)	Myelosuppression, hyperglycemia	Dose: 1.25 mg/m^2 subcutaneous injection twice daily × 14 days, repeat every 28 days until hematologic response achieved Maintenance therapy: 1.25 mg/m^2 subcutaneous injection twice daily × 7 days every 28-day cycle Drug interactions: P-glycoprotein substrate	No reductions	No reductions
Ponatinib (Iclusig)	Arterial and venous thromboembolisms, hepatotoxicity, congestive heart failure, pancreatitis, gastrointestinal bleeding, fluid retention, myelosuppression, fatigue, headaches	Dose: 45 mg daily Black-box warnings for thromboembolism stroke, myocardial infarction, hepatotoxicity, and heart failure Monitor CBC, lipase and liver function tests Drug interactions: metabolized by CYP 3A4,2C8, 2D6 competitive inhibitor of P-glycoprotein	No reductions	Child-Pugh class A, B, or C: 30 mg daily Hold ponatinib if liver transaminases are > 3 × upper limit of normal May resume but reduce dose when < 3 × upper limit of normal

CML, chronic myeloid leukemia; CrCl, creatinine clearance; po, oral; PPI, proton pump inhibitor.

▶ *Advanced-Generation TKIs*

LO 3

KEY CONCEPT Dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), and ponatinib (Iclusig) are advanced generation TKIs that may overcome imatinib resistance or intolerance. These inhibitors are anywhere from 10 to 325 times more potent than imatinib in inhibiting *BCR-ABL* and overcome most *BCR-ABL* mutations that lead to imatinib resistance.[1] Of the four, only ponatinib can overcome the *T315I* mutation.[4]

Bosutinib, dasatinib, and nilotinib are indicated for first-line therapy in CP-CML. Studies suggest bosutinib, dasatinib, and nilotinib are superior to imatinib in achieving faster and deeper cytogenetic and molecular responses.[11–14] Fewer patients may progress to accelerated or blast phase on bosutinib, dasatinib, or nilotinib compared to imatinib although there are no differences in overall survival reported between the agents. Common side effects are similar to those of imatinib and may be found in Table 96–1. A significant and potentially severe side effect of pleural effusions has been reported with the use of imatinib and dasatinib but not with the use of nilotinib.[10] Additional side effects of nilotinib include QT prolongation and increases in indirect bilirubin.[1]

Ponatinib is a third-generation multikinase inhibitor that overcomes the *BCR-ABL* domain mutation *T315I*. Ponatinib was initially approved for the treatment of patients in all phases that were resistant or intolerant to prior TKI therapy. In postmarketing analysis, an increase in serious arterial thrombotic events was shown in 24% of patients.[15] The revised label indicates the use of ponatinib in patients harboring the *T315I* mutation or have failed multiple prior TKIs. Rare yet serious adverse effects include heart failure, liver failure, and death, which are black-box warnings.[6] Ponatinib is available through a Risk Evaluation and Mitigation Strategy (REMS) program.

▶ *Omacetaxine Mepesuccinate*

Omacetaxine mepesuccinate (Synribo) is a semisynthetic formulation of homoharringtonine. Omacetaxine reversibly inhibits protein synthesis thereby causing cell death.[16] Unlike TKIs, the mechanism of action affects both normal and malignant hematopoietic cells. Omacetaxine is a subcutaneous injection indicated for patients in CP- or AP-CML who are resistant or intolerant to two or more TKIs.[6] It may also be used in patients with the *T315I* mutation. Nonhematologic adverse reactions may be found in Table 96–1. Clinicians should note omacetaxine may cause hyperglycemia, requiring monitoring, particularly in patients with diabetes.[6,16]

OUTCOME EVALUATION

Successful treatment for CML depends on an optimal response to TKI therapy (ie, hematologic, cytogenetic, and molecular). Nearly all newly diagnosed CP-CML patients will be placed on a TKI and will remain on TKI therapy for an indefinite amount of time. First-line treatment options include imatinib, bosutinib, dasatinib, and nilotinib. Which agent to use depends on several factors, including disease risk score, age, comorbid conditions, medication safety profile, and financial accessibility. Patients should be counseled on the importance of medication adherence. Patients should understand that poorer outcomes may result if they are not adherent to daily TKI therapy. The NCCN guidelines provide response criteria.[7] Molecular response at 3, 6, and 12 months is assessed, as it has been associated with improved progression free and overall survival.[7,17] If patients fail to achieve these milestones, a change in therapy is recommended. If TKI treatment failure occurs, patients should undergo *BCR-ABL* domain mutation testing and be evaluated for patient adherence and possible drug interactions. Second-line CP-CML therapy should be selected based on mutational analysis with second-generation TKIs (utilized). These agents may also be used in patients who have AP-CML. Ponatinib may be considered if the *T315I* mutational status is present with an understanding that it is associated with serious vascular effects. Omacetaxine, allogeneic stem cell transplantation, and clinical trials are options for those patients that do not respond to a TKI. Some patients will not respond to treatment and will progress to BP-CML where they

Patient Encounter 1

A 38-year-old Hispanic female presents to her primary care physician with complaints of "feeling tired over the past couple months" and "occasional abdominal pain". Her past medical history consists of poorly type 2 diabetes. Her A1C is 10.8% despite treatment on metformin 1 g twice daily and 30 units of glargine (weight: 100 kg). She also takes OTC omeprazole for GERD. A CBC is drawn and shows the following:

Total WBC: 104×10^9/L (104×10^3/mm^3) (5% [0.05] blasts, 75% [0.75] segs, 20% [0.20] lymphs)

Hgb/Hct: 9.7 g/dL (97 g/L; 6.014 mmol/L)/29% (0.29)

Platelets: 190×10^9/L (190×10^3/mm^3)

The patient is referred to an oncologist for further workup. A bone marrow biopsy is performed and reveals hypercellular marrow with 5% (0.05) blasts. Cytogenetics are positive for t(9:22) via FISH.

What information is suggestive of CP-CML?

Which specific treatment do you recommend for initial treatment and why?

Identify your treatment goals for this patient.

What drug information and patient counseling will you provide to the patient?

Identify factors that may contribute to this patient's having a suboptimal response.

Assuming this patient has a suboptimal response to your initial therapy, what would you recommend for second-line therapy?

will receive treatment for acute leukemia. Although its use is limited, allogeneic transplant offers the only cure for CML and may be useful in patients with advanced disease who have failed other options.

CHRONIC LYMPHOCYTIC LEUKEMIA

EPIDEMIOLOGY AND ETIOLOGY

CLL is the most common type of leukemia diagnosed in adults, accounting for 30% of all adult leukemias. It was estimated that in 2018, 20,940 new cases were diagnosed in the United States.[2] The median age at diagnosis is 70 years with the incidence increasing with age.[18] The etiology of CLL is unknown, but hereditary factors may have a role, with family members of CLL patients having a twofold to sevenfold increased risk of CLL.[19]

PATHOPHYSIOLOGY

Cell of Origin

CLL is characterized by small, relatively incompetent B lymphocytes that accumulate in the blood and bone marrow over time. The lack of apoptotic mechanisms, including BCL-2 overexpression, leads to the persistence and accumulation of B lymphocytes.[20] The exact cell of origin is controversial but has been described as an antigen-activated B lymphocyte.[19] Chromosomal abnormalities have been identified in 80% cases of CLL and often correlate with progressive disease.[21] Numerous tyrosine kinases appear to be involved in CLL, including the activation of Bruton tyrosine kinase (BTK).[20] Detection of some of these markers may predict clinical course and prognosis and may influence treatment decisions.[19,22]

Clinical Course

LO 4

KEY CONCEPT CLL can have a variable clinical course with survival ranging from months to decades. Patients are classified as low, intermediate, or high risk. Approximately 90% of patients are diagnosed with asymptomatic, low-risk CLL, where the median survival times exceed 10 years.[23] The typical low-risk patient is an asymptomatic elderly patient who is diagnosed on routine blood draw. Intermediate risk is associated with lymphadenopathy and has median survival times of about 7 years. High-risk patients with anemia have median survival times of only 2 years.[24] The typical high-risk patient is a symptomatic middle-aged patient. Some patients with slightly elevated B lymphocytes may not meet the diagnostic criteria for CLL and may be diagnosed with monoclonal B-lymphocytosis (MBL). The progression from MBL to CLL is approximately 1.1% per year.[25]

Clinical Presentation and Diagnosis of CLL

Signs and Symptoms (50% Are Asymptomatic at Diagnosis)[19]

- Lymphadenopathy
- Organomegaly consisting of splenomegaly and hepatomegaly
- Fatigue, weight loss, night sweats, fevers
- Chronic infections caused by immature lymphocytes

Diagnostic Procedures

- Peripheral blood smear
- Bone marrow biopsy
- Cytogenetic studies
- Molecular testing

Laboratory Findings

- Peripheral-blood
  - Leukocytosis (WBC count > 100×10^9/L [100×10^3/mm^3])
  - Lymphocytosis (absolute lymph count > 5×10^9/L [5×10^3/mm^3])
  - Anemia
  - Thrombocytopenia
  - Hypogammaglobulinemia
- Bone marrow
  - Hypercellular with increased mature lymphocytes
- Molecular markers
  - Cytogenetic abnormalities

Poor Prognostic Factors

- Lymphocytosis with accompanying:
  - Anemia (hemoglobin ≤ 11.0 g/dL [110 g/L; 6.83 mmol/L])
  - Thrombocytopenia (platelets < 100×10^9/L [100×10^3/mm^3])
  - ZAP-70, CD49d, and CD38 antigen expression
  - Cytogenetics such as deletions of chromosomes 17p and 11q
  - *TP53* and *IgVH* mutations

PROGNOSTIC FACTORS

Two staging systems, Rai and Binet, have been developed to help practitioners determine the overall prognosis of patients with CLL. They are comparable systems and are useful to broadly determine good, intermediate, and poor prognostic disease.[24] Risk stratification criteria included in these systems are lymphadenopathy, splenomegaly, hepatomegaly, and cytopenias. Increasingly, biological markers of the disease such as deletions of chromosome 17p (del(17p)) and 11q (del(11q)) and mutational status of immunoglobulin heavy chain variable region gene (IgVH) are being used to predict the likely clinical course.[20,26] Patients with del(17p) tend to have a poor response to therapy. These biological markers are not included in the Rai or Binet staging systems.

TREATMENT

Desired Outcomes

The primary goals in the treatment of CLL are to provide palliation of symptoms and achieve a long-term remission. Because the current treatments for CLL are not curative, reduction in tumor burden and improvement in disease symptoms are reasonable end points, particularly in older patients. A complete response (CR) to therapy can be defined as a resolution of lymphadenopathy and organomegaly, normalization of peripheral blood counts, and elimination of lymphoblasts in the bone marrow.

Nonpharmacologic Therapy

LO 4

KEY CONCEPT Asymptomatic early stage CLL can be observed without treatment until evidence of disease progression. Past studies with chlorambucil suggest that chemotherapy does not improve overall survival in early stage CLL although there is question whether this remains true with the development of newer therapies. In addition, deferring therapy until a patient becomes symptomatic does not alter overall survival.[23,26] For this reason, the notion of "watch and wait" is considered reasonable for older patients with low risk disease. Several factors will influence this approach, including life expectancy, disease characteristics, and ability to tolerate therapy.[23,26]

▶ *Hematopoietic Stem Cell Transplantation*

The use of HSCT in CLL is limited. Allogeneic HSCT offers longer disease-free remissions in patients with poor prognosis than autologous HSCT but is associated with higher treatment morbidity and mortality. Several factors must be considered before allogeneic HSCT. The lack of a donor, older age, and poor performance status make transplant an uncommon procedure in this population. Allogeneic HSCT remains an option for younger patients with aggressive disease who have failed prior therapies.[24,26]

Pharmacologic Therapy

The treatment options for CLL have significantly expanded in the past decade. Combination chemoimmunotherapy is typically initiated in the symptomatic patient. There are numerous agents that can be used in combination as initial therapy. The NCCN guidelines provide recommendations on first-line and subsequent therapies based on mutational status.[24] Many of the chemotherapy regimens have not been compared directly with one another, so there is not one preferred regimen. Selection of the appropriate chemotherapy depends on the individual patient, the tumor's molecular abnormalities (particularly with or without del(17p)), and the practitioner's preference. Chemoimmunotherapy has shown limited success in patients with del(17p); however, recently, the immunomodulatory agent lenalidomide has shown promise as maintenance therapy for patients with del(17p) CLL following first-line therapy.[23,27]

Figure 96–2 illustrates one approach for initial therapy in newly diagnosed patients with CLL.

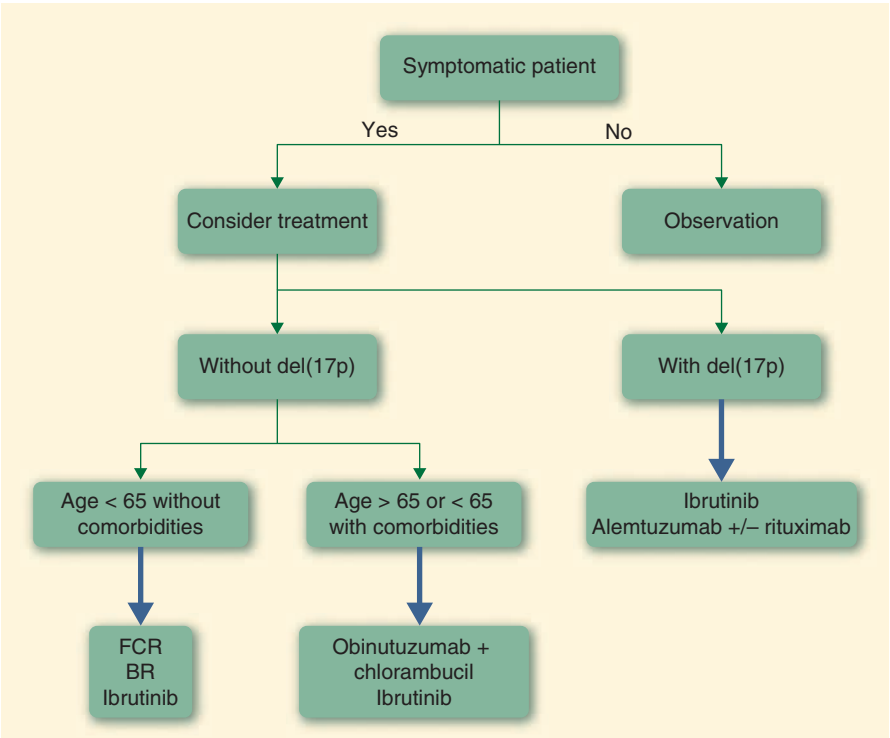

FIGURE 96–2. Selected treatment approach for primary therapy in newly diagnosed CLL patients. (B, bendamustine; C, cyclophosphamide; F, fludarabine; R, rituximab.) (Data from NCCN.)

▶ Cytotoxic Chemotherapy

Historically, chlorambucil (Leukeran), an oral alkylating agent, was considered the standard treatment for CLL. Today, the treatment for CLL has changed with the development of the purine analogs. There are three purine analogs used in the treatment of CLL: fludarabine (Fludara), pentostatin (Nipent), and cladribine (Leustatin) with fludarabine being the most studied. KEY CONCEPT Fludarabine-based chemoimmunotherapy is commonly used as first-line therapy for younger patients with CLL without a del(17p) mutation.[19,26,27]

Randomized clinical trials have shown that fludarabine is superior to chlorambucil in achieving higher response rates and producing a longer duration of response.[24,26] Although fludarabine is one of the most effective agents in the treatment of CLL, it is rarely used as a sole agent. Instead fludarabine is given in combination with cyclophosphamide and rituximab (FCR) to improve response rates.[24,26,27]

Fludarabine is associated with more toxicities than chlorambucil, including myelosuppression and prolonged immunosuppression. Resultant infectious complications may occur during the periods of prolonged immunosuppression. Clinicians should consider antibacterial and antiviral prophylaxis for *Pneumocystis* and varicella zoster when using fludarabine-based therapy.[24] Chlorambucil in combination with anti-CD20 monoclonal antibody remains a practical option for symptomatic elderly patients and those with comorbidities.[26]

Bendamustine (Treanda) is an alkylating agent used in the treatment of CLL. The combination of bendamustine and rituximab was shown to have a lower median progression-free survival (PFS) compared to FCR in younger patients, but less toxicities.[24,27] Bendamustine in combination with an anti-CD20 monoclonal antibody in an option for those patients without a del(17p) mutation who cannot tolerate the toxicities of FCR, including patients older than 65 or with comorbities.[24,26,27]

▶ Monoclonal Antibodies

KEY CONCEPT Combination chemoimmunotherapy with anti-CD20 monoclonal antibodies are widely used in the treatment of CLL. Rituximab (Rituxan) is a naked chimeric monoclonal antibody directed against the CD20 antigen on B-lymphocytes.[28] Similar to other B-cell malignancies, CLL expresses CD20 antigens. Dose escalation studies suggest higher doses are required than those used in non-Hodgkin lymphoma.[29] The higher dose required in CLL is probably a combined effect of lower CD20 antigen expression and higher concentrations of soluble CD20 antigen than in non-Hodgkin lymphoma.[29] Rituximab is given in combination with other therapies since these combinations result in higher CRs than rituximab alone.[28] The most common side effects of rituximab include infusion reactions consisting of fever, chills, hypotension, nausea, vomiting, and headache.[24] Premedication with diphenhydramine and acetaminophen is recommended to minimize infusion reactions.

Ofatumumab (Arzerra) and obinutuzumab (Gazyva) are two additional anti-CD20 monoclonal antibodies. Ofatumumab is a CD20 antigen-directed monoclonal antibody that is often used in combination with chlorambucil in patients with untreated CLL who cannot tolerate fludarabine-based therapy.[30] Obinutuzumab is different than the other anti-CD20 monoclonal antibodies having a higher binding affinity to the CD20 epitope and causing direct cell death.[30] The combination of obinutuzumab and chlorambucil was shown to have a clinically meaningful improvement in PFS compared to rituximab and chlorambucil in untreated CLL in patients without del(17p). This regimen is often used in combination with chlorambucil for the treatment of previously untreated CLL in patients without del(17p) who are not able to tolerate purine analogs. Table 96–2 lists some of the adverse effects seen with the anti-CD20 monoclonal antibodies.

▶ Small Molecule Inhibitors

KEY CONCEPT An understanding of the B-cell receptor signaling pathways of CLL has led to the approval of oral targeted therapies. Many of these therapies have improved the median overall survival of CLL.[27] Ibrutinib (Imbruvica) is an inhibitor of BTK which is an essential enzyme in the B-cell receptor pathway and may be used as first-line therapy for all patients, including patients with del(17p) and age older than 65.[23,24] The overall response rate as a single-agent in patients with relapsed CLL was 71%, an impressive percentage for this subset of patients.[31] Additional positive studies expanded ibrutinib's indications to first-line therapy. Idelalisib (Zydelig) targets phosphatidylinositol-3-kinase (PI3-K), an essential lipid kinase that is a regulator of the B-cell receptor pathway and involved in cellular survival and proliferation.[32] Idelalisib has been studied as monotherapy as well as combination therapy with rituximab in patients with relapsed disease.[32] Nonhematologic side effects for both drugs may be found in Table 96–2. Black-box warnings for idelalisib include hepatotoxicity, colitis, pneumonitis, and intestinal perforation. Most patients experience a transient increase in absolute lymphocyte count when initiating ibrutinib or idelalisib.[24] The lymphocytosis will persist for several weeks and then subside. Continuation of therapy is warranted and does not suggest disease progression.

Venetoclax (Venclexta) is a small molecular inhibitor that targets B-cell lymphoma 2 (BCL-2) protein and is approved for patients with relapsed/refractory CLL in patients with del (17p).[23,24] Adverse effects for venetoclax include tumor lysis syndrome, in which prophylaxis with allopurinol or rasburicase and oral hydration is recommended, and prolonged neutropenia, which may require growth factor support.[24]

▶ Chemoimmunotherapy

Combination chemoimmunotherapy is the standard for younger patients with symptomatic CLL in patients without del(17p).[24] The specific drug regimen is often selected based on age and cytogenetics. There are numerous first-line options for patients without del(17p). Combination therapy generally consists of an anti-CD20 antibody in combination with chemotherapy. The combination of fludarabine, cyclophosphamide, and rituximab (FCR) is often utilized in those that can tolerate chemotherapy.[24] A 2013 multiple-treatment meta-analysis was not able to show a significant survival benefit of one regimen compared to another.[33]

OUTCOME EVALUATION

Successful outcomes depend on the appropriate treatment selection for a specific patient. Risk-versus-benefit should be determined in the treatment of older CLL patients. Because CLL is incurable, watch and wait is a reasonable approach for those with indolent, asymptomatic disease. Treatment can then begin when the patient becomes symptomatic. Aggressive chemoimmunotherapy with fludarabine is often reserved for younger patients with high-risk CLL, with the goal being prolonged disease-free survival. A desirable response to therapy includes a reduction in lymphocytes, decrease in stage of the disease, and resolution of symptoms. Supportive care, including herpes virus and *Pneumocystis* prophylaxis, may be required depending on the treatment chosen.

Table 96–2

Drugs Used in CLL

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Bendamustine (Treanda)	Myelosuppression, fever, nausea, vomiting, infusion reactions, tumor lysis syndrome	Consider using allopurinol for tumor lysis syndrome during first few cycles of therapy	CrCl < 40 mL/min (0.67 mL/s): do not use	Mild impairment: use with caution Moderate to severe impairment: do not use
Chlorambucil (Leukeran)	Myelosuppression; allergic reactions (skin rash); secondary malignancies	Take on an empty stomach because food decreases absorption Dose range: 4–10 mg po daily	No reductions	No reductions
Fludarabine (Fludara)	Myelosuppression; prolonged immunosuppression, resulting in secondary infectious complications; edema; neurotoxicity	Dose: 20 mg/m^2 IV daily for 5 days Often given in combination	CrCl 30–70 mL/min (0.50–1.17 mL/s): 20% reduction of dose (IV and po) CrCl < 30 mL/min (0.50 mL/s): do not use IV; reduce dose of oral by 50%	No reductions
Ibrutinib (Imbruvica)	Risk of bleeding, neutropenia, thrombocytopenia	Dose: 420 mg po once daily Avoid the use of concomitant CYP 3A4 inhibitors/inducers Drug metabolism: CYP 3A4 and 2D6	No reductions in CrCl > 25 mL/min (0.42 mL/s) Insufficient data in < 25 mL/min (0.42 mL/s)	Insufficient data exists; interruption if hepatotoxicity occurs
Idelalisib (Zydelig)	Black-box warnings: severe hepatotoxicity, diarrhea, colitis, pneumonitis, intestinal perforation Serious allergic reactions	Given in combination with rituximab Dose: 150 mg po twice daily Drug metabolism: CYP 3A4; strong inhibitor of 3A4, 2C8, 2C9, 2C19	No reductions in CrCl > 15 mL/min (0.25 mL/s) Insufficient data in < 15 mL/min (0.25 mL/s)	Insufficient data exists
Obinutuzumab (Gazyva)	Infusion reactions, reactivation of hepatitis B, progressive multifocal encephalopathy, tumor lysis syndrome, neutropenia	Premedicate with acetaminophen, IV antihistamine, and an IV steroid to alleviate infusion-related reactions Consider antimicrobial, antiviral, and antifungal prophylaxis Hold antihypertensives 12 hours prior, during, and after due to the risk of hypotension	No reductions in CrCl > 30 mL/min (0.50 mL/s) Insufficient data in < 30 mL/min (0.50 mL/s)	No reductions
Ofatumumab (Arzerra)	Severe infusion-reactions: bronchospasm, edema, fever, chills, rigors, hypotension; prolonged myelosuppression	Premedicate with acetaminophen, IV antihistamine, and an IV steroid to alleviate infusion-related reactions Rate of infusion should be increased gradually to minimize reactions Monitor for reactivation of hepatitis B	No reductions	No reductions
Rituximab (Rituxan)	Infusion reactions: fever, chills, rigors, hypotension	Premedicate with acetaminophen, diphenhydramine with or without a steroid to alleviate infusion related reactions Rate of infusion should be increased gradually to minimize reactions Monitor for reactivation of hepatitis B	No reductions	No reductions
Venetoclax (Venclexta)	Tumor lysis syndrome requiring hydration and anti-hyperuricemics, neutropenia, thrombocytopenia, infections	Initial dose: 20 mg po once daily × 7 days; then increased weekly over 5 weeks to a max dose of 400 mg po once daily Drug metabolism: do not coadminister with a strong CYP3A inhibitor and caution with strong/moderate CYP3A inducers	No reductions in CrCl > 30 mL/min (0.50 mL/s) Insufficient data in < 30 mL/min (0.50 mL/s)	No reductions for mild to moderate; insufficient data exists for severe

CrCl, creatinine clearance; IV, intravenous; po, oral; PCP, pneumocystits pneumonia; SC, subcutaneous.

Patient Encounter 2

A 77-year-old man presents to his health care provider with complains of a "lump in his neck". Past medical history includes an acute myocardial infarction and benign prostatic hypertrophy. Physical examination reveals cervical lymph node enlargement and splenomegaly. Blood work reports the following:

WBC: 30×10^9/L (30×10^3/mm^3)

Hgb: 11.2 g/dL (112 g/L; 6.944 mmol/L)

Platelets: 182×10^9/L (18.2×10^3/mm^3)

Peripheral Smear: Lymphocytosis with small, mature-appearing cells suggestive of chronic lymphocytic leukemia

FISH analysis: del(17p)

Identify your treatment goals for this patient.

How does the del(17p) influence your treatment approach?

What treatment do you recommend and what would you monitor?

Would your treatment options change if this patient were asymptomatic? If so, what would be your new treatment?

MULTIPLE MYELOMA

Multiple myeloma is a malignancy of the plasma cell and is characterized by an abnormal production of a monoclonal protein in the bone marrow. Features of the disease include bone lesions, anemia, and renal insufficiency. MM is an incurable disease; however, advancements in the treatment of myeloma have significantly extended survival.

EPIDEMIOLOGY AND ETIOLOGY

Multiple myeloma is the second most common hematologic malignancy. It is estimated that approximately 30,770 new cases would be reported in 2018, accounting for approximately 2% of all cancers.[2] The median age at diagnosis is 69 years, and fewer than 2% are diagnosed before the age of 40 years.[34] The incidence of myeloma is highest in African Americans, lowest in Asians, and occurs more frequently in men than women.[35] The etiology of MM remains largely unknown although a exposure to ionizing radiation and genetic factors have been implicated.[35]

PATHOPHYSIOLOGY

The pathogenesis of MM is quite complex with multiple-step models created to postulate the process. Myeloma must be distinguished from a condition called monoclonal gammopathy of unknown significance (MGUS), which is characterized by a monoclonal immunoglobulin without malignant plasma cells, and smoldering myeloma, which lacks clinical manifestations from the high monoclonal immunoglobulin. Yearly, about 1% of patients with MGUS will develop MM. Chromosomal abnormalities and changes in gene expression lead to cell cycle dysregulation and appear to be involved early in the disease process.[36] The pathophysiology of MM involves complex bone marrow microenvironment and cytokine interactions. Interleukin-6, tumor necrosis factor, vascular endothelial growth

Clinical Presentation and Diagnosis of Multiple Myeloma

Signs and Symptoms

- "CRAB"
  - "C"—hyperCalcemia
  - "R"—Renal failure (serum creatinine > 2 mg/dL [177 µmol/L])
  - "A"—Anemia (fatigue)
  - "B"—Bone disease (pain, lesions, fractures)
- Weight loss
- Recurrent infections

Diagnostic Procedures

- Laboratory
  - CBC, chemistry panel, β_2-microglobulin
  - Peripheral blood smear
  - Serum protein electrophoresis and immunofixation
  - Urine protein electrophoresis and immunofixation
  - Serum free light chains
- Radiologic evaluation (MRI, bone densitometry)
- Bone marrow biopsy
- Cytogenetic studies
- Molecular testing

Laboratory Findings

- Peripheral blood
  - Monoclonal protein (M protein) in serum (usually IgG or IgA)
  - High β_2-microglobulin
  - Low platelets and hemoglobin
  - High creatinine, urea, lactate dehydrogenase, C-reactive protein, and calcium
  - Rouleaux formation
- Urinalysis
  - Urinary free light chains (Bence-Jones Protein)
- Bone marrow
  - Plasma cells (10% or more)
  - Abnormal cytogenetics
- Radiologic findings
  - Bone lesions, fractures, osteoporosis

Poor Prognostic Factors

- High serum β_2-microglobulin and low serum albumin
- Elevated C-reactive protein
- Elevated lactate dehydrogenase
- IgA isotype
- Low platelet count
- Chromosome 13 deletions and other cytogenetic abnormalities

factor, and stromal-derived factor-1 support the establishment and proliferation of myeloma cells.[36,37] The understanding of these interactions has led to novel agents used in the treatment of MM.

PROGNOSTIC FACTORS

Prognostic factors for myeloma include tumor-, treatment-, and patient-related factors. The International Staging System is used to predict outcomes after therapy. Staging is stratified based on the levels of serum β_2-microglobulinemia and serum albumin. High β_2-microglobulinemia and low albumin are poor prognostic factors and are indicative of high tumor load.[38] Although cytogenetic abnormalities are not included in the International Staging System, many abnormalities are associated with poor outcomes. The Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) classification incorporates tumor biology to stratify patients according to their disease risk.[39] Chromosomal changes are being used to predict high-risk patients with perhaps the most important being deletions of the long arm of chromosome 13 and translocation of chromosomes 4 and 14.[40] Older patients, renal impairment, and other comorbidities also predict for poorer outcomes.[33]

TREATMENT

Desired Outcomes

The primary goal in the treatment of MM is to prolong progression free and overall survival while minimizing complications associated with the disease.[40] A watch and wait approach is an option for patients with smoldering myeloma who have no lytic lesions in the bone. When symptoms occur, treatment is required. The treatment of MM often includes induction, transplantation, and maintenance therapy. All patients should be evaluated early on to see if they are transplant eligible candidates. Autologous stem cell transplantation prolongs overall survival in patients who can tolerate high-dose chemotherapy. Regardless of transplant eligibility, all patients will be placed on primary therapy to reduce tumor burden. Maintenance therapy following transplant with lenalidomide is being used to prolong the duration of response. Almost all patients become refractory to primary treatment, requiring the use of salvage therapies. Figure 96–3 illustrates possible treatment approaches for transplant-eligible and transplant-ineligible patients.

Patient Encounter 3, Part 1

A 68-year-old woman presents to the emergency room after a fall in her home. Her past medical history includes controlled hypertension and osteoporosis. She notes severe bilateral hip pain. Workup reveals:

Radiology: X-ray of right and left hips: Pathologic fracture of right hip; Osteolytic lesions in both right and left hip

Labs: Hemoglobin: 8.4 g/dL (84 g/L; 5.208 mmol/L); platelets: 220×10^9/L (220×10^3/mm^3); corrected calcium: 11.8 mg/dL (2.95 mmol/L); serum creatinine: 2.3 mg/dL (203 µmol/L); serum IgG: 6200 mg/dL (42 g/L) (normal: 620–1500 mg/dL) (6.2–15 g/L); serum IgM: 80 mg/dL (8 g/L) (normal: 50–200 mg/dL [0.5–2 g/L]); bone marrow: 72% plasma cell infiltrates

What signs and symptoms are suggestive of multiple myeloma?

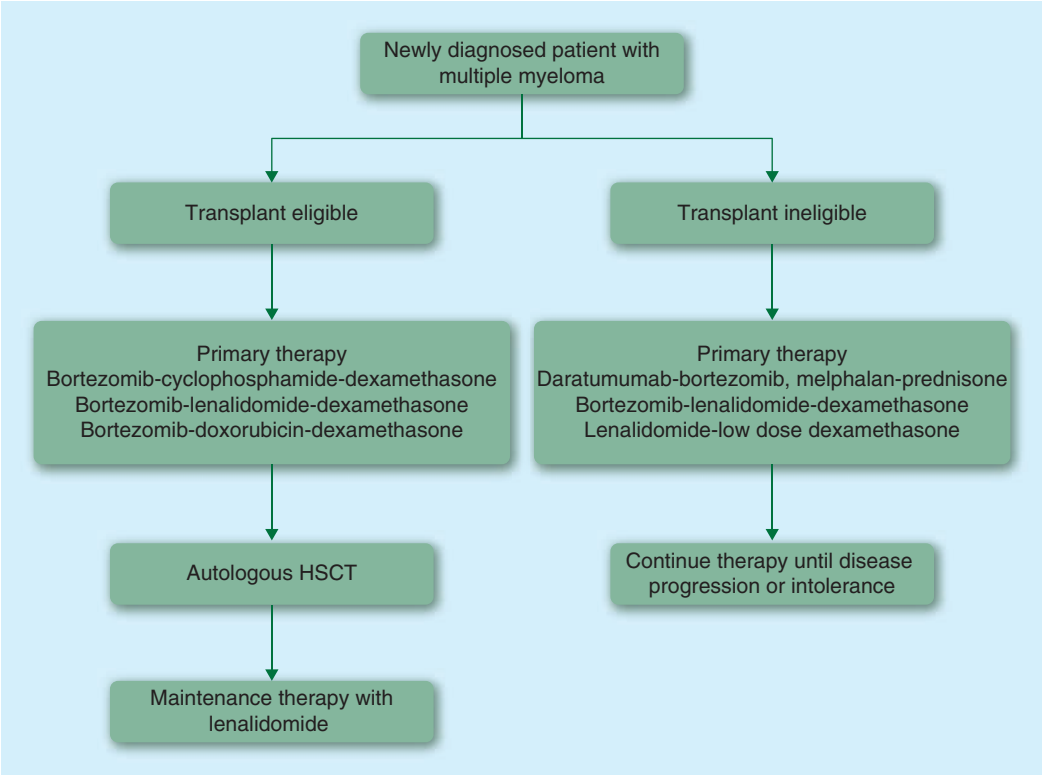

FIGURE 96–3. Possible approach for treatment in newly diagnosed patients with multiple myeloma. (HSCT, hematopoietic stem cell transplantation.) (Data from NCCN.)

Nonpharmacologic Therapy

▶ *Autologous Hematopoietic Stem Cell Transplantation (HSCT)*

LO 7

KEY CONCEPT Autologous hematopoietic stem cell transplantation results in higher response rates and extends PFS compared with those who receive conventional chemotherapy.[37,40] Autologous HSCT remains the standard of care and should be considered in all patients who can tolerate high-dose chemotherapy.[40] High-dose melphalan is the most common preparative regimen. Two sequential transplants (tandem transplants) improve overall survival in patients who do not have a good partial response after one transplant.[37] The use of maintenance therapy after autologous transplantation with lenalidomide may be used in select patients to extend PFS.[40,41]

Pharmacologic Therapy

See Table 96–3. Symptomatic MM requires treatment. There are five main classes of drugs used in the treatment of MM: alkylating agents, anthracyclines, corticosteroids, immunomodulatory agents, and proteasome inhibitors. A three-drug regimen is often utilized in the treatment of myeloma.

▶ *Conventional-Dose Chemotherapy*

The use of conventional-dose chemotherapy with alkylating agents or anthracyclines has declined with the advent of

Table 96–3

Drugs Used in Multiple Myeloma

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Bortezomib (Velcade)	Constipation; decreased appetite; asthenia; fatigue; fever; thrombocytopenia; dose related, reversible peripheral neuropathy	Dose: 1.3 mg/m^2 IV bolus or SC twice weekly for 2 weeks; week 3 off; repeat Concentration for IV is 1 mg/mL and 2.5 mg/mL for SC Consider herpes zoster prophylaxis with daily acyclovir	No reductions	Bilirubin > 1.5 × the upper limit of normal: reduce dose to 0.7 mg/m^2
Carfilzomib (Kyprolis)	Neutropenia, thrombocytopenia, cardiac toxicity including cardiac arrest, congestive heart failure, infusion-reactions, tumor lysis syndrome	Dose: 20 mg/m^2 IV bolus on days 1, 2, 8, 9, 16, and 16; days 17–28 off; repeat every 28 days Patients with a BSA greater than 2.2 m^2 should have dose calculated based on 2.2 m^2 Premedicate with dexamethasone 4 mg to reduce infusion-related reactions Hydration with normal saline prior to carfilzomib is recommended	No reductions	May need to dose reduce or hold dose depending on degree of hepatic dysfunction
Daratumumab (Darzalex)	Infusion-reactions, diarrhea, nausea, vomiting, respiratory concerns including cough and dyspnea, infection	Dose: 16 mg/kg IV weekly on weeks 1–8, every other week starting week 9–24 and every 4 weeks starting week 25 Premedicate with acetaminophen, steroid, and antihistamine to reduce infusion-related reactions Bronchodilators may be needed Antiviral prophylaxis should be initiated and continued for 3 months post-last dose Corticosteroid should be started for 2 days following each infusion	No reductions	Mild/moderate: No reductions Severe: Insufficient data exists
Dexamethasone	Hyperglycemia, edema, adrenal cortical insufficiency	Dose given po once daily	No reductions	No reductions
Doxorubicin (Adriamycin)	Myelosuppression; alopecia; cumulative dose-limiting toxicity: myocardium damage	Given in combination with lenalidomide and dexamethasone	No reductions	Bilirubin 1.2–3 mg/dL (21–51 µmol/L): 50% reduction in dose Bilirubin 3.1–5 mg/dL (53–85 µmol/L): 75% reduction in dose Bilirubin > 5 mg/dL (85 µmol/L): use with caution
Elotuzumab (Empliciti)	Infusion-reactions, infections including opportunistic, diarrhea, secondary malignancies	Given in combination with lenalidomide and dexamethasone Premedicate with acetaminophen, ranitidine, diphenhydramine and dexamethasone to reduce infusion-related reactions	No reductions	Mild: No reductions Moderate/severe: Insufficient data exists

(*Continued*)

Table 96–3

Drugs Used in Multiple Myeloma (*Continued*)

Drug	Adverse Effects	Comments	Renal Dosing	Hepatic Dosing
Ixazomib (Ninlaro)	Neutropenia, thrombocytopenia, rash, peripheral neuropathy, drug-induced hepatotoxicity	Dose: 4 mg po on days 1, 8, and 15 in combination with lenalidomide 25 mg po on days 1–21 and dexamethasone 40 mg po on days 1, 8, 15, and 28. Repeat every 28 day cycle Thromboprophylaxis is recommended with this regimen	CrCl > 30 mL/min (0.50 mL/s): no adjustments CrCl < 30 mL/min (0.50 mL/s): reduce dose to 3 mg	Mild: no reductions Moderate/severe: reduce dose to 3 mg
Lenalidomide (Revlimid)	Possible birth defects neutropenia, thrombocytopenia, DVT, PE, pruritus, fatigue	Dose: 25 mg taken with water once daily Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use Enrollment into monitoring program required	CrCl 30–60 mL/min (0.50–1.00 mL/s): 10 mg/day CrCl < 30 mL/min (0.50 mL/s): 15 mg every 48 hours Dialysis and CrCl < 30 mL/min (0.50 mL/s): 5 mg every 24 hours given after dialysis	No reductions
Melphalan (Alkeran)	Myelosuppression, secondary malignancies, pulmonary fibrosis, sterility, alopecia	Dose given po once daily IV formulation used for stem cell transplantation	No recommendation but may consider an initial dose reduction	No reductions
Pomalidomide (Pomalyst)	Severe birth defects, DVT, neutropenia	Dose: 4 mg po daily on days 1–21; off 21–28 and repeat Drug metabolism: CYP 1A2 and 3A4	Do not use if SCr > 3 mg/dL (265 µmol/L)	Do not use if bilirubin > 2 mg/dL (34 µmol/L) and AST/ALT > 3 × the upper limit of normal
Thalidomide (Thalomid)	Severe birth defects, peripheral neuropathy, DVT, somnolence, constipation	Titrate initial doses; doses are taken nightly Women of childbearing age must use two forms of contraception Pregnancy test must be taken before and during use Enrollment into monitoring program required	No reductions	No reductions

DVT, deep venous thrombosis; IV, intravenous; PE, pulmonary embolism; po, oral; SC, subcutaneous.

immunomodulators and proteasome inhibitors. The combination of melphalan and prednisone (MP) was once the most common initial treatment combination for myeloma. Today, MP is no longer recommended due to cytopenias and inferior effectiveness.[40] The anthracycline doxorubicin may be incorporated into treatment regimens, with the combination of doxorubicin, bortezomib, and dexamethasone selected for primary therapy in patients who are transplant eligible.[40]

▶ *Immunomodulatory Drugs*

LO 7

KEY CONCEPT The immunomodulatory drug lenalidomide (Revlimid) is often used in combination therapy for the treatment of MM. The precise mechanism of action is unknown, but its antimyeloma activity may be attributable to its antiangiogenic and anticytokine properties.[42] Response rates are improved when an immunomodulatory agent is added to a treatment regimen. Thalidomide was the first immunomodulatory agent to be studied with impressive responses (87%) in combination with a steroid and bortezomib.[43] Today lenalidomide has largely replaced thalidomide due to high potency and a more favorable safety profile over thalidomide.[40] The combination of lenalidomide, bortezomib, and dexamethasone has emerged as one of the most commonly used primary regimens in the treatment of transplant-eligible and transplant-ineligible patients with myeloma.[40,43,44] Low-dose dexamethasone with lenalidomide offers improved overall survival compared with high-dose dexamethasone.[40] Lenalidomide may also be used in combination dexamethasone and the other proteasome inhibitors, carfilzomib or ixazomib.[40,44] Lenalidomide lacks many of the common side effects seen with thalidomide. Significant adverse effects of lenalidomide include myelosuppression and VTEs. VTE prophylaxis is recommended in patients at high risk for thrombosis.[40] Stem cells should be collected shortly after starting lenalidomide because CD34-positive stem cell counts tend to decrease with prolonged lenalidomide exposure.[40] Maintenance lenalidomide after autologous HSCT is widely utilized. Although it has been associated with an increase in PFS, there has also been an increase in the incidence of secondary malignancies.[40,45]

▶ *Proteasome Inhibitors*

LO 7

Bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro) are **proteosome** inhibitors approved for the treatment of MM. Proteosome inhibitors induce myeloma cell death by modulating **nuclear factor kappa-B** products, including inflammatory cytokines and adhesion molecules that support myeloma cell growth.[43] These drugs also disrupt the myeloma microenvironment by inhibiting the binding of myeloma cells to the bone marrow stromal cells.[43] Bortezomib-based regimens are frequently used as primary therapy for MM. The response rates with bortezomib have been reported as high as 97%

in newly diagnosed myeloma.[43] Bortezomib has also shown impressive outcomes in patients with high risk disease, making it a preferred agent for these patients. Adverse effects of bortezomib include fatigue, nausea, peripheral neuropathy, and hematologic effects.[43] Subcutaneous bortezomib may be given to patients with preexisting neuropathy to lessen peripheral neuropathy.[40] The incidence of VTE is lower than the immunomodulators; thus, bortezomib does not routinely require prophylactic anticoagulation. However, prophylactic antiviral therapy should be considered to reduce the risk of herpes zoster reactivations.[40]

Carfilzomib and ixazomib are second-generation proteasome inhibitors that are used in the treatment of refractory MM. While carfilzomib is administered intravenously, ixazomib is the first oral proteasome inhibitor and is given in an all orally administered regimen with lenalidomide and dexamethasone. Phase I/II studies have shown promising results with carfilzomib or ixazomib as primary therapy in combination regimens with an immunomodulator and dexamethasone.[40] The adverse effect profile is similar to bortezomib with potentially less neurotoxicity. Clinicians should note that carfilzomib requires monitoring for cardiac and pulmonary toxicities.

▶ *Additional Agents*

Several new drugs have been approved for the treatment of relapsed and refractory MM. The monoclonal antibodies daratumumab (Darzalex) and elotuzumab (Empliciti) target CD38 and signaling lymphocytic activation molecular F7 (SLAMF7), respectively.[46] Both glycoproteins are expressed on MM cells. These monoclonal antibodies are used in combination with dexamethasone and bortezomib or lenalidomide.[40] Panobinostat (Farydak) is an inhibitor or histone deacetylase used in combination with bortezomib and dexamethasone.[40,46] This regimen has significant toxicity consisting of thrombocytopenia, ischemic events, arrhythmias, diarrhea, and peripheral neuropathy.

▶ *Bisphosphonates*

Bone disease is a common manifestation of MM. Bisphosphonates or denosumab should be initiated in symptomatic patients with bone lesions to slow osteopenia and reduce the fracture risk associated with the disease. Pamidronate 90 mg and zoledronic acid 4 mg have equivalent efficacy in the management of osteolytic lesions.[47] The use of zoledronic acid decreases pain and bone-related complications and improves quality of life. Denosumab 120 mg Q4 weeks was recently shown to be noninferior to zoledronic acid 4 mg Q4 weeks and is preferred in patients with renal insufficiency.[40] Osteonecrosis of the jaw is a major concern with bisphosphonate therapy. Risk factors are unclear, but osteonecrosis of the jaw is more common in patients receiving IV administration of bisphosphonates and having dental procedures performed. It is recommended that patients have dental restoration work before starting bisphosphonate therapy. Several consensus guidelines have been published on the use of bisphosphonates and myeloma.[48,49] Recommendations on the duration of therapy and which bisphosphonate to use have largely been left up to the practitioner.[40]

Patient Encounter 3, Part 2

The patient was diagnosed with multiple myeloma.

What treatment options are available for this patient?

What would be an appropriate regimen for primary therapy?

What may be used for maintenance therapy after an autologous stem cell transplantation?

OUTCOME EVALUATION

Newly diagnosed, asymptomatic patients with MM may be observed without treatment. This asymptomatic period may last for months to several years. All patients with MM become symptomatic, and when this occurs, treatment is required. All patients should be evaluated for an autologous stem cell transplant. For patients who are eligible for transplant, induction therapy often consists of lenalidomide, bortezomib, and dexamethasone. Maintenance therapy with lenalidomide may be used posttransplant. There are numerous treatment options for transplant ineligible patients including MPT, MPB, or MPL. Nearly all patients progress at some point, and second-line therapy usually includes bortezomib. Monthly bisphosphonates or denosumab should be given to patients who have bone lesions with the hope of reducing pain and fractures.

Patient Care Process

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements.
- Review medical history, including patient's age, comorbid conditions, and current medications to avoid drug–drug interactions.
- Review laboratory values and physical assessment findings.

Assess the Information:

- Determine whether the patient requires immediate treatment based on laboratory values, physical assessment and medical history.
- Identify whether the patient is taking any medications that could interact with the possible treatment selections for the given cancer.
- Discuss with the patient the financial costs of the possible treatment and determine if one agent is more cost-effective than another.
- If goals are not achieved, assess whether a change in medication is warranted or if nonadherence is suspected.
- If the patient experiences intolerance to therapy including any severe adverse effects, a change in medication may be warranted.

Develop a Care Plan:

- Select the most appropriate treatment based on the assessment findings for the patient.
- Consider whether additional supportive care medications are needed such as prophylactic antimicrobials, growth factors, or anticoagulants.

(*Continued*)

Patient Care Process (*Continued*)

- Discuss the importance of medication adherence and long-term outcomes.
- Address any concerns about the selected medication including cost and management of adverse effects.
- Identify the required monitoring and determine treatment outcomes and goals.

Implement the Care Plan:

- Educate the patient on the selected drug therapy, medication administration, importance of adherence, potential adverse effects, and how to manage and report adverse effects that occur.
- Address any patient concerns about the selected drug therapy and its management.

Follow-up: Monitor and Evaluate:

- Drug therapy should be frequently monitored to assess treatment efficacy and safety.
  - For CML, follow-up should be scheduled every 3 months to determine whether molecular, cytogenetic, and hematologic goals of therapy are being met.
  - For CLL, follow-up should include a review of symptoms and laboratory findings including lymphocytes and hemoglobin.
  - For MM, monitor myeloma monoclonal protein in urine and serum, renal function, hemoglobin, and platelets.
- Review medication adherence.
- If patients continue to have disease progression or have relapsed disease, another regimen should be utilized.
- Out of office follow-up (ie, phone calls) may be helpful to reinforce the importance of adherence and to identify and manage any adverse effects.

Abbreviations Introduced in This Chapter

AP	Accelerated phase
BP	Blast phase/crisis
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CP	Chronic phase
CR	Complete response
FISH	Fluorescence in situ hybridization
HSCT	Hematopoietic stem cell transplantation
MGUS	Monoclonal gammopathy of unknown significance
Ph	Philadelphia chromosome
Q-PCR	Quantitative polymerase chain reaction
TKI	Tyrosine kinase inhibitor
WBC	White blood cell

REFERENCES

1. Santos FPS, Ravandi F. Advances in treatment of chronic myelogenous leukemia—new treatment options with tyrosine kinase inhibitors. Leuk Lymphoma. 2009;50:16–26.
2. Cancer Facts & Figures 2018. American Cancer Society. Available from: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html. Accessed July 30, 2018.
3. Cancer Stat Facts: Leukemia – Chronic Myeloid Leukemia (CML). National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Available from: https://seer.cancer.gov/statfacts/html/cmyl.html. Accessed July 30, 2018.
4. Aguayo A, Couban S. State-of-the-art in the management of chronic myelogenous leukemia in the era of the tyrosine kinase inhibitors: evolutionary trends in diagnosis, monitoring, and treatment. Leuk Lymphoma. 2009;50(suppl 2):1–8.
5. Apperley JF. Chronic myeloid leukaemia. Lancet. 2015;385:1447–1459.
6. Branford S. Molecular monitoring in chronic myeloid leukemia — how low can you go? Hematology Am Soc Hematol Educ Program. 2015;156–163.
7. Chronic Myelogenous Leukemia. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Accessed July 30, 2018.
8. Holyoake TL, Vetrie D. The chronic myeloid leukemia stem cell: stemming the tide of persistence. Blood. 2017;129(12):1595–1606.
9. Kantargian HM, Cortes J, La Rosee P, Hochhaus A. Optimizing therapy for patients with chronic myelogenous leukemia in chronic phase. Cancer. 2010;116:1419–1430.
10. Hochlaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med. 2017;376(10):917–927.
11. Khan DL, Bixby DL. BCR-ABL inhibitors: updates in the management of patients with chronic phase chronic myeloid leukemia. Hematology. 2014;19(5):249–258.
12. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010;362:2260–2270.
13. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010;362:2251–2259.
14. Cortes JE, Kim DW, Kantarjian HM, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: Results from the BELA trial. J Clin Oncol. 2012;30:3486–3492.
15. Hoy SM. Ponatinib: A review of its use in adults with chronic myeloid leukaemia or Philadelphia chromosome-positive acute lymphoblastic leukaemia. Drugs. 2014;74:793–806.
16. Alvandi F, Kwitkowski VE, Ko CW, et al. U.S. Food and Drug Administration approval summary: omacetaxine mepesuccinate as treatment for chronic myeloid leukemia. Oncologist. 2014;19:94–99.
17. Deininger MW. Molecular monitoring in CML and the prospects for treatment-free remissions. Hematology Am Soc Hematol Educ Program. 2015;2015:257–263.
18. Cancer Stat Facts: Leukemia – Chronic Lymphocytic Leukemia (CLL). National Cancer Institute: Surveillance, Epidemiology, and End Results Program. Available from: https://seer.cancer.gov/statfacts/html/clyl.html. Accessed July 30, 2018.
19. Wierda WG, O'Brien S. Chronic lymphocytic leukemias. In: Devita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology, 9th ed. Philadelphia: Lippincott, 2011.

20. Alsagaby SA, Brennan P, Pepper C. Key molecular drivers of chronic lymphocytic leukemia. Clinical Lymphoma, Myeloma & Leukemia. 2016;16:593–606.
21. Chiorazzi N. Implications of new prognostic markers in chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2012;2012:78–87.
22. Hallek M. Signaling the end of chronic lymphocytic leukemia. Blood. 2013;122(23)3723–3734.
23. Stilgenbauer S. Prognostic markers and standard management of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2015;368–377.
24. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed July 30, 2018.
25. Rawstron AC, Bennett FL, O'Connor SJM, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. N Eng J Med. 2008;359:575–583.
26. Barrientos JC. Sequencing of chronic lymphocytic leukemia therapies. Hematology Am Soc Hematol Educ Program. 2016;128–136.
27. Jain N, O'Brien S. First-line therapy for young patients with CLL. Hematology Am Soc Hematol Educ Program. 2016;146–148.
28. Hallek M. Signaling the end of chronic lymphocytic leukemia. Blood. 2013;122(23):3723–3734.
29. Hillmen P. Advancing therapy for chronic lymphocytic leukemia—the role of rituximab. Semin Oncol. 2004;31(suppl 2): 22–26.
30. Shah A. Obinutuzumab: A novel anti-CD20 monoclonal antibody for previously untreated chronic lymphocytic leukemia. Ann Pharmacother. 2014;48(10):1–6.
31. Byrd JC, Furman RR, Coutre CE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32–42.
32. Furman RR, Sharman JP, Coutre SE. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370(11):997–1007.
33. Terasawa T, Trikalinos NA, Djulbegovic B, Trikalinos TA. Comparative efficacy of first-line therapies for advanced-stage chronic lymphocytic leukemia: a multiple-treatment meta-analysis. Cancer Treat Rev. 2013;39(4):340–349.
34. Cancer Stat Facts: Multiple Myeloma. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Available from: https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed July 30, 2018.
35. Munshi NC, Anderson KC. Plasma cell neoplasms. In: Devita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology, 9th ed. Philadelphia: Lippincott, 2011.
36. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364:1046–1060.
37. Rollig C, Knop S, Bornhauser M. Multiple myeloma. Lancet. 2015;385:2197–2208.
38. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised international staging system for multiple myeloma: A report from International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863–2869.
39. Mikhael JR, Dingli D, Roy V, et al. Management of newly diagnosed symptomatic multiple myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013. Mayo Clin Proc. 2013;88(4):360–376.
40. Multiple Myeloma. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed July 30, 2018.
41. Alsina M, Becker PS, Zhong X, et al. Lenalidomide maintenance for high-risk multiple myeloma after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2014; 20:1183–1189.
42. Lacy MQ. New immunomodulatory drugs in myeloma. Curr Hematol Malig Rep. 2011;6:120–125.
43. Painuly U, Kumar S. Efficacy of bortezomib as first-line treatment for patients with multiple myeloma. Clin Med Insights Oncol. 2013;7:53–73.
44. Dispenzieri A. Myeloma: management of the newly diagnosed high-risk patient. Hematology Am Soc Hematol Educ Program. 2016;485–494.
45. McCarthy PL, Holstein SA. Role of stem cell transplant and maintenance therapy in plasma cell disorders. Hematology Am Soc Hematol Educ Program. 2016;504–511.
46. Ocio EM, Richardson PG, Rajkumar SV, et al. New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Groups (IMWG). Leukemia. 2014;28:525–542.
47. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. Cancer. 2003;98:1735–1744.
48. Terpos E, Morgan G, Dimopoulos MA et al. International Myeloma Working Group Recommendations for the Treatment of Multiple Myeloma-Related Bone Disease. J Clin Oncol 2013;31:2347–2357.
49. Kyle Ra, Yee GC, Somerfield MR, et al. American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. J Clin Oncol. 2007;25:2462–2472.

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97 Malignant Lymphomas

Keith A. Hecht and Susanne E. Liewer

LEARNING OBJECTIVES

LO

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

1. Discuss the underlying pathophysiologic mechanisms of the lymphomas and how they relate to presenting symptoms of the disease.
2. Differentiate the pathologic findings of Hodgkin lymphoma (HL), follicular indolent non-Hodgkin lymphoma (NHL), and diffuse aggressive NHL and how this information yields a specific diagnosis.
3. Describe the general staging criteria for the lymphomas and how it relates to prognosis; evaluate the role of the prognostic systems such as the International Prognostic Score for HL, the Follicular Lymphoma International Prognostic Index (IPI), and the IPI for diffuse, aggressive NHL.
4. Compare and contrast the treatment algorithms for early and advanced stage disease for HL.
5. Assess the role of autologous hematopoietic stem cell transplantation for relapsed lymphomas.
6. Delineate the clinical course of follicular indolent and diffuse aggressive NHL and the implications for disease classification schemes and treatment goals.
7. Outline the general treatment approach to follicular indolent and diffuse aggressive NHL for localized and advanced disease.
8. Interpret the current role for monoclonal antibody therapy in NHL.

INTRODUCTION

The malignant lymphomas are a clonal disorder of hematopoiesis with the primary malignant cells consisting of lymphocytes of B-, T-, or natural killer (NK) cell origin. Lymphoma cells predominate in the lymph nodes; however, they can infiltrate lymphoid and nonlymphoid tissues, such as the bone marrow, central nervous system (CNS), gastrointestinal (GI) tract, liver, mediastinum, skin, and spleen. An overview of the lymph node regions is depicted in Figure 97–1. KEY CONCEPT There are two broad classifications of lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), and both contain numerous histologic subtypes that are pathologically distinct disease entities.

The clinical course varies widely among histologies of lymphoma. More aggressive subtypes are highly proliferating cells that require aggressive therapeutic intervention with chemotherapy, radiation therapy, or both. By contrast, certain subtypes of NHL are characterized by a disease course that flares and remits intermittently over a period of years regardless of treatment.

HODGKIN LYMPHOMA

EPIDEMIOLOGY AND ETIOLOGY

Approximately 8500 new cases of HL were estimated to be diagnosed in the United States in 2018, with 1050 deaths attributed to the disease.[1] The incidence of HL is bimodal, with peaks occurring in the third decade of life and in patients over 50 years of age.[2] The precise cause of HL is unknown, but certain associations have been reported and provide insight about possible etiologic factors. Epstein-Barr virus (EBV) has been associated with HL, its viral genome is detected in Reed-Sternberg (RS) cells in up to 40% of cases in developed countries. Other viruses (cytomegalovirus, human herpes viruses, human immunodeficiency virus [HIV], and adenoviruses) have been associated with HL; however, data is conflicting.[3] Other possible risk factors identified include woodworking and a familial history of HL.

PATHOPHYSIOLOGY

LO 1

Pluripotent stem cells in the bone marrow are able to differentiate to both lymphoid and myeloid progenitor cells. Lymphoid progenitor cells undergo normal gene rearrangement to yield either B-cell or T-cell lineage precursor cells. Normal maturation for naive B cells includes expression of cell surface antibody or the cells typically undergo **apoptosis**. These cells are differentiated from other B cells, such as memory cells, by virtue of cell surface antigen ($CD5^+$ or $CD5^-$ and $CD27^-$) and bound antibody (IgM+ and IgD+). When naive B cells recognize antigen with their cell surface antibody, they accumulate in the lymph nodes, spleen, or other lymphoid tissue. The DNA of these B cells is susceptible to three different types of genetic modification: **receptor editing**, somatic hypermutation, and class switching within the germinal center of the lymph node. Germinal centers are microanatomic structures located within lymph nodes that develop with clonal B-cell expansion secondary to antigen stimulation. Under normal circumstances, these genetic changes allow for adaptation of the immune system to the repeated exposure to environmental antigens.

LO 2

The pathophysiology of HL is defined by the presence of the RS cell in a grouping of lymph nodes. The RS cell is a morphologically large cell with a multinucleated structure possessing pronounced eosinophilic nucleoli, thought to be B cell in origin.[4]

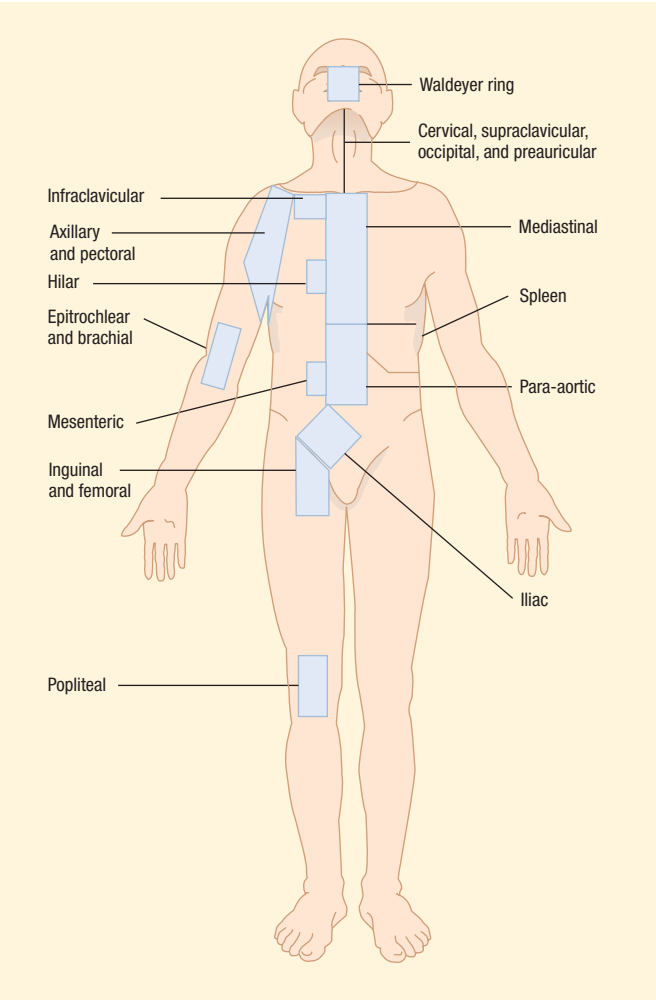

FIGURE 97–1. Representation of the anatomic regions used in the staging of Hodgkin disease. (From Rosenberg SA. Staging of Hodgkin disease. Radiology. 1966;87:146.)

In the affected lymph nodes, the RS cells are contained within an inflammatory background that is believed to be essential for their survival.

RS cells have lost the expression of most B-cell markers. Common cell-surface antigens expressed by RS cells include CD30 and CD15, but other common B-cell antigens, such as CD20 are inconsistently expressed.[4] The Janus kinase-signal transduction and transcription (JAK-STAT) signaling pathway has also been found to be active in HL. Additionally, the overexpression of nuclear factor kappa-B (NF-κB), a proliferative and antiapoptotic transcription factor nuclear factor is believed to contribute to the expansion and survival of RS cells.

HL is classified into disease subtypes based on the number and morphologic appearance of RS cells and the background cellular milieu. These are listed in the World Health Organization (WHO) classification of lymphoid neoplastic diseases in Table 97–1.[5] Nodular sclerosing (75%) is the most common form of classical HL. It is more common in young adults and is marked by the presence of the RS variant cell, the lacunar cell. The second most common form of HL is mixed-cellularity variant (19%), with others accounting for the remainder of cases.[6] Factors identified as negative disease prognostic indicators are listed in Table 97–2.

LO 3

Table 97–1

Abbreviated WHO Classification of Lymphoid Neoplasms

B-Cell Neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell proliferative leukemia
Splenic marginal zone B-cell lymphoma
Hairy cell leukemia
Lymphoplasmacytic lymphoma
Monoclonal gammopathy of undetermined significance
Plasma cell myeloma
Plasmacytoma
Monoclonal immunoglobulin deposition disease
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone lymphoma
Follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL)
Primary DLBCL of central nervous system
Primary cutaneous DLBCL
Lymphomatoid granulmatosis
Primary mediastinal large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Burkitt lymphoma

T-Cell and NK-Cell Neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK cell leukemia
Hydroa vacciniforme-like lymphoproliferative disorder
Adult T-cell lymphoma/leukemia (HTLV1+)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous T-cell lymphoproliferative disorders
Peripheral T-cell lymphoma
Angioimmunoblastic T-cell lymphoma
Follicular T-cell lymphoma
Anaplastic large-cell lymphoma

Hodgkin Lymphoma
Nodular lymphocyte-predominant HL
Classical HL
- Nodular sclerosis HL
- Lymphocyte-rich classical HL
- Mixed cellularity HL
- Lymphocyte depletion HL

Posttransplant Lymphoproliferative Disorders

Histiocytic and Dendritic Cell Neoplasms

AML, acute myeloid leukemia; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

TREATMENT OF HL

Desired Outcome

LO 3

Staging of HL with a standard classification is necessary to guide treatment. The extent and location of involvement, localized or disseminated extranodal disease, and B symptoms are factors in assignment of stage. The Lugano modification

Table 97–2

Negative Prognostic Factors for HL

International Prognostic Score—Advanced HL
Albumin < 4 g/dL (40 g/L)
Hemoglobin < 10.5 g/dL (105 g/L; 6.52 mmol/L)
Male sex
Age > 45 years
Stage IV disease
WBC ≥ 15,000/mm^3 (15 × 10^9/L)
Lymphocytopenia (count < 600/mm^3 [0.6 × 10^9/L], < 8% [0.08] of WBC count, or both)

WBC, white blood cell.

of the original Ann Arbor classification is used in staging lymphomas and is outlined in Table 97–3.[7]

KEY CONCEPT The principal goal in treating HL is to cure the patient of the primary malignancy. HL is sensitive to both radiation and chemotherapy, resulting in an 80% rate of cure with modern therapy. Treatment strategy is generally divided into approaches for early stage I/II disease and stage III/IV advanced disease. Patients with stage I/II disease are further classified into favorable, unfavorable with bulky disease, and unfavorable with nonbulky disease. Regardless of stage, all patients are treated with curative intent. Other treatment goals include:

- Complete resolution of disease symptoms
- Incorporation of supportive care measures to optimize quality of life
- Minimization of acute and long-term treatment-related toxicity

Nonpharmacologic Therapy

Radiation therapy is effective in the treatment of HL and has cured patients of their disease. Historically, patients with favorable early stage I/II disease were treated with radiation alone. However, long-term toxicities associated with this practice have precluded this approach. Current treatment strategies combine radiation with chemotherapy. This has been reported to reduce the irradiated volume and dose as well as the number of cycles of chemotherapy.

Table 97–3

Lugano Staging Classification for Lymphomas (2014 Modification of Ann Arbor Staging)

Stage	Involvement	Extranodal (E) Status
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky	Same as II but with "bulky" disease	
Advanced		
Stage III	Nodes on both sides of diaphragm or nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional noncontiguous extralymphatic involvement	Not applicable

"A" (absence of B-symptoms) or "B" (presence of B-symptoms) is only used for Hodgkin lymphoma.

Clinical Presentation and Diagnosis of Malignant Lymphomas

General

Nonspecific; can range from an asymptomatic patient with a less aggressive lymphoma to a patient who is gravely ill with advanced disease.

KEY CONCEPT Symptoms

- Lymphadenopathy, generally in the cervical, axillary, supraclavicular, or inguinal lymph nodes
- Splenomegaly
- Shortness of breath, dry cough, chest pressure (patients with mediastinal mass)
- GI complications (nausea, vomiting, early satiety, constipation, and diarrhea)
- Back, chest, or abdominal pain

Signs

- Fever[a]
- Night sweats[a]
- Weight loss greater than 10% within last 6 months[a]
- Pruritus

Laboratory Tests

- LDH
- ESR
- Serum chemistries
- CBC with differential

KEY CONCEPT Other Diagnostic Tests

- Physical examination with careful attention to lymph node inspection.
- Imaging—chest x-ray, chest CT, abdominal or pelvic CT; integrated PET and CT are recommended as part of the initial workup.
- Bone marrow biopsy.
- Biopsy of suspected lymph node(s)—either open lymph node biopsy (preferred) or core biopsy; fine-needle aspiration should only be performed if preferred biopsy methods are unobtainable.
- Hematopathology evaluation of biopsy specimen—morphologic inspection, immunohistochemistry for cell surface antigens to characterize lymphoma cells, cytogenetic analysis.

[a]Known collectively as B symptoms.

CBC, complete blood count; CT, computed tomography; ESR, erythroid sedimentation rate; LDH, lactate dehydrogenase; PET, positron emission tomography.

Patient Encounter Part 1: Initial Presentation

A 59-year-old man with a medical history of hypertension and coronary artery disease presents to the oncologist on referral from his primary care provider. He presented to his PCP with swollen lymph nodes and facial swelling. He was in her usual state of health until 2 months ago when he began experienceing "lumpy spots" in his bilateral axillary region and swelling and tenderness in the neck. He states that he has experienced a 20-pound weight loss over the last several months. The PCP referred him for biopsy of palpable cervical lympho node. A fine-needle aspiration was performed that showed a "lymphoproliferative process." Complete blood count revealed a WBC of 3500/mm^3 (3.5 × 10^9/L), hemoglobin of 8.5 g/dL (8.5 g/L; 5.27 mmol/L), and platelets were 137,000/mm^3 (137 × 10^9/L). Lactate dehydrogenase was 353 U/L (5.9 μkat/L). The chemistry panel was unremarkable.

What tests should be performed to confirm a diagnosis of lymphoma and determine its overall stage?

Based on the information provided, what is his International Prognostic Index (IPI), and how does it impact treatment selection?

Historically in the treatment of HL, the radiation fields were large and often included the lungs, liver, heart, and breast. Today, the use of involved-site radiotherapy (ISRT) and involved-node radiotherapy (INRT) limits radiation to the involved area. In addition to the smaller radiation volumes, other organs have reduced exposure.[8] Treatment with radiotherapy produces significant toxicity of acute and delayed onset. Acute effects of irradiation include nausea, anorexia, xerostomia, dysgeusia, pharyngitis, dry cough, fatigue, diarrhea, and rash. These effects are typically transient, resolving shortly after completion of treatment. Delayed effects from radiotherapy are concerning as they may be permanent and present months to years after therapy. Pneumonitis, pericarditis, hypothyroidism, infertility (with pelvic field irradiation), coronary artery disease, deformities in bone and muscle growth in children, herpes zoster reactivation, and **Lhermitte sign** are not uncommon. Patients cured with radiotherapy are at increased risk for new cancers of the breast, lung, and stomach, as well as melanoma and new NHL, depending on the radiation field.

Pharmacologic Therapy

▶ *Early Stage Disease*

KEY CONCEPT Initial treatment of HL includes combination chemotherapy; these regimens are effective and have acceptable long-term toxicities. Combined modality therapy of two to four cycles ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) plus 20 to 30 Gy (Gray, the absorbed radiation dose) of ISRT or two cycles Stanford V chemotherapy plus 30 Gy of ISRT or chemotherapy alone (ABVD) are treatment options for patients with favorable stage I/II HL. Patients with favorable disease have: no B symptoms, an erythrocyte sedimentation rate less than 50 mm/hour, no extralymphatic lesions, and only one or two involved nodal sites. Chemotherapy alone can be considered in patients with a negative PET scan after three cycles of ABVD.[9] When combined modality treatment is favored, ISRT should be initiated for patients who achieve a complete response (CR) or a partial response (PR) to chemotherapy. After completion of ISRT, no further treatment is necessary for patients with a CR; further restaging is required for patients with PR to therapy.

LO 4

ABVD followed by escalated BEACOPP or Stanford V followed by ISRT is recommended for patients with unfavorable, bulky disease. Interim staging after 2–3 cycles of chemotherapy can help guide further treatment, such as two cycles of ABVD are given before interim restaging. Patients with a response to therapy are treated with two additional cycles (total of 4) of ABVD or two cycles of escalated BEACOPP (consider with PR to ABVD) followed by ISRT.[10] Stanford V is administered for three cycles and restaged at the completion of chemotherapy prior to beginning ISRT. ISRT may also be incorporated into ABVD based on provider preference or response to chemotherapy. The use of the Stanford V regimen should be considered for patients with mediastinal disease, bulky disease, B symptoms, or unfavorable nonbulky disease.[11] A list of chemotherapy regimens used in HL is presented in Table 97–4.

▶ *Advanced Disease*

LO 4

Patients with advanced disease can be further classified into two groups based on International Prognostic Score (see Table 97–2). Patients with three or fewer poor prognostic factors are considered to have favorable disease while patients with four or more factors have unfavorable disease. Patients with unfavorable disease may warrant more aggressive treatment.

Trials have focused on the use of multiagent chemotherapy for six to eight cycles. The chemotherapy regimen MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)

Table 97–4

Common Treatment Regimens in HL

ABVD—Every 28 Days
Doxorubicin 25 mg/m^2 IV × 1, days 1 and 15
Bleomycin 10 units IV × 1, days 1 and 15
Vinblastine 6 mg/m^2 × 1, days 1 and 15
Dacarbazine 375 mg/m^2 IV × 1, days 1 and 15

Stanford V
Doxorubicin 25 mg/m^2 IV weeks 1, 3, 5, 7, 9, and 11
Vinblastine 6 mg/m^2 IV weeks 1, 3, 5, 7, 9, and 11
Mechlorethamine 6 mg/m^2 IV weeks 1, 5, and 9
Etoposide 60 mg/m^2 IV weeks 3, 7, and 11
Vincristine 1.4 mg/m^2 IV weeks 2, 4, 6, 8, 10, and 12
Bleomycin 5 mg/m^2 IV weeks 2, 4, 6, and 8
Prednisone 40 mg po every other day for 12 weeks, start taper at week 10

BEACOPP (Escalated)—Every 21 Days
Bleomycin 10 mg/m^2 IV, day 8
Etoposide 200 mg/m^2 IV daily × days 1–3
Doxorubicin 35 mg/m^2, day 1
Cyclophosphamide 1200 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 8
Procarbazine 100 mg/m^2 po daily, days 1–7
Prednisone 40 mg po daily, days 1–14

BEAM (High-Dose with Autologous SCT)[a]
Carmustine 300 mg/m^2 IV × 1 day
Etoposide 100–200 mg/m^2 IV every 12 hours × 4 days
Cytarabine 100–200 mg/m^2 IV every 12 hours × 4 day
Melphalan 140 mg/m^2 IV × 1 day

[a]Used for both Hodgkin lymphoma and non-Hodgkin lymphoma.
IV, intravenous; po, oral; SCT, stem cell transplantation.

Table 97–5

Practical Information for ABVD and CHOP

Regimen	Drug Class	Pharmacokinetics	Unique Toxicities
ABVD			
Doxorubicin	Anthracycline	Hepatic metabolism[a]	Highly emetogenic Cardiomyopathy Maximum cumulative lifetime dose, 550 mg/m^2
Bleomycin	Antitumor antibiotic	Renal clearance[a]	Pulmonary fibrosis Maximum cumulative lifetime dose, 400 units
Vinblastine	Vinca alkaloid	CYP 3A4/5 metabolism[a]	Neuropathy, constipation
Dacarbazine	Alkylating agent	Hepatic metabolism[a]	Myelosuppression
CHOP			
Cyclophosphamide	Alkylating agent	Prodrug; CYP3A4/5, 2D6	Highly emetogenic Hemorrhagic cystitis
Doxorubicin	Anthracycline	Hepatic metabolism	Cardiomyopathy
Vincristine	Vinca alkaloid	CYP3A4/5	Neuropathy, constipation
Prednisone	Corticosteroid	100% oral bioavailability	Hyperglycemia, osteopenia

[a]See dose adjustments (Chapter 88).

is of historical significance because it was the first chemotherapy regimen to cure HL in the 1960s. However, significant toxicity, including sterility and secondary leukemia, led to the development of new regimens. A pivotal phase III trial comparing ABVD, MOPP, and ABVD-MOPP alternating in patients with stage III/IV HL documented a higher CR in the ABVD arms. A recent update of the data shows superior 18-year freedom from progression in the ABVD arms compared to MOPP though a survival advantage was not demonstrated.[12] ABVD is now considered standard therapy for initial treatment of stage III or IV HL. Further information on ABVD may be found in Table 97–5.

LO 4

Additional regimens such as Stanford V and BEACOPP were developed to improve outcomes in patients with advanced HL. Except in patients with high-risk disease (International Prognostic Score > 3) the Stanford V regimen has demonstrated similar response rates to ABVD reported for event-free survival, overall survival, and toxicity.[13] A dose-escalated regimen of BEACOPP (with colony-stimulating factor [CSF] support) was compared with a standard-dose BEACOPP and also COPP (cyclophosphamide substituted for mechlorethamine in MOPP) alternating with ABVD. The dose-escalated BEACOPP was superior to the other arms in both freedom from treatment failure and overall survival at 10 years.[14] However, the escalated BEACOPP regimen is associated with more toxicity including infertility and secondary leukemia. Currently, neither BEACOPP regimen is widely used in the United States but is considered for advanced HL with a high number of poor prognostic factors.

Despite the high success rate in treating HL, approximately 5% to 10% of patients will be refractory to initial treatment and 10% to 30% will relapse after initial response.[15] Patients relapsing after treatment should be offered additional therapy as durable responses have been reported. The duration of remission after chemotherapy remains a vital prognostic factor for likelihood of response to future treatment.[16] For healthy patients, the definitive therapy after relapse is high-dose chemotherapy with autologous stem cell transplantation (SCT).[17] This treatment offers a cure rate up to 50%.

LO 5

Several studies have reported the importance of giving conventional chemotherapy before SCT. The purpose of the initial treatment after relapse is to decrease the tumor bulk before SCT. The safety profile of autologous SCT continues to improve as refinements in supportive care advance. Current estimates of mortality from autologous SCT for HL are approximately 5%. Morbidity associated with preparative regimens in HL, aside from infectious and bleeding complications, includes pulmonary toxicity of bleomycin coupled with carmustine, inducing potentially fatal pulmonary pneumonitis.

Patients who are not candidates for autologous SCT may receive standard salvage chemotherapy, such as etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP) or dexamethasone, cytarabine, and cisplatin (DHAP). Other regimens such as GVD (gemcitabine, vinorelbine, and pegylated liposomal doxorubicin), IGEV (ifosfamide, gemcitabine, and vinorelbine), and GCD (gemcitabine, carboplatin, and dexamethasone) have also been effective. Single agents such as lenalidomide, bendamustine, and everolimus have also shown activity. Brentuximab vedotin is a monoclonal antibody that targets CD-30 and is linked to a microtubule-disrupting agent, monomethylauristatin E. This agent has demonstrated efficacy with sustained responses up to 3 years.[18] Programmed death 1 blocking monoclonal antibodies such as nivolumab and pembrolizumab have also shown benefit in patients with relapsed refractory disease. Clinical trials are ongoing to define the role of these agents.[19,20]

NON-HODGKIN LYMPHOMA

EPIDEMIOLOGY AND ETIOLOGY

Approximately 74,680 cases of NHL were estimated to be diagnosed in the United States in 2018, with an estimated 19,910 deaths. These figures represent a stabilization in the incidence of NHL since 1998 that follows a dramatic increase that nearly doubled the number of cases in the United States since 1950.[1,21] The increase may be related to the development of aggressive NHL in patients with HIV, although the overall increase is independent of HIV disease. The median age for diagnosis is 50 years, although children and young adults may also be affected. The etiology of certain aggressive NHL subtypes is related to specific

endemic geographic factors. Follicular or low-grade lymphoma is more common in the United States and Europe and is relatively uncommon elsewhere. Exposure to various causative agents, such as pathogens or occupational exposure, can be attributed to many different types of lymphoma and may be responsible for differences in regional lymphoma rates. Human T-cell leukemia virus I, human herpesvirus 8, hepatitis C, *Helicobacter pylori*, and EBV have all been implicated in inducing NHL.[22] The incidence of Burkitt NHL is 7 cases per 100,000 people in Africa compared with 0.1 per 100,000 in the United States. Malaria or EBV is thought to contribute to the chronic B-lymphocyte stimulation leading to malignant transformation in Burkitt NHL. Due to the pathogen-related induction of NHL, immunocompromised patients are at increased risk of NHL. Environmental factors have been identified as contributing to the development of NHL. Certain occupations such as wood and forestry workers, butchers, exterminators, grain millers, machinists, mechanics, painters, printers, and industrial workers have a higher prevalence of disease. Industrial chemicals such as pesticides, herbicides, organic chemicals (eg, benzene), solvents, and wood preservatives are also associated with NHL.

PATHOPHYSIOLOGY

LO 2

The pathophysiology of NHL is governed by numerous environmental and genetic events culminating with a monoclonal population of malignant lymphocytes. B cells represent the cells of origin in excess of 90% of cases. Figure 97–2 outlines normal B-cell maturation with accompanying cell-surface antigens. Evolving data are correlating chromosomal mutations with specific disease subtypes. Cytogenetic abnormalities involving translocations of antigen receptor genes are prevalent in NHL. These include T-cell receptor genes in T-cell lymphomas and immunoglobulin genes in B-cell lymphomas. The principal defect appears to be an error in assembly of the regulatory gene

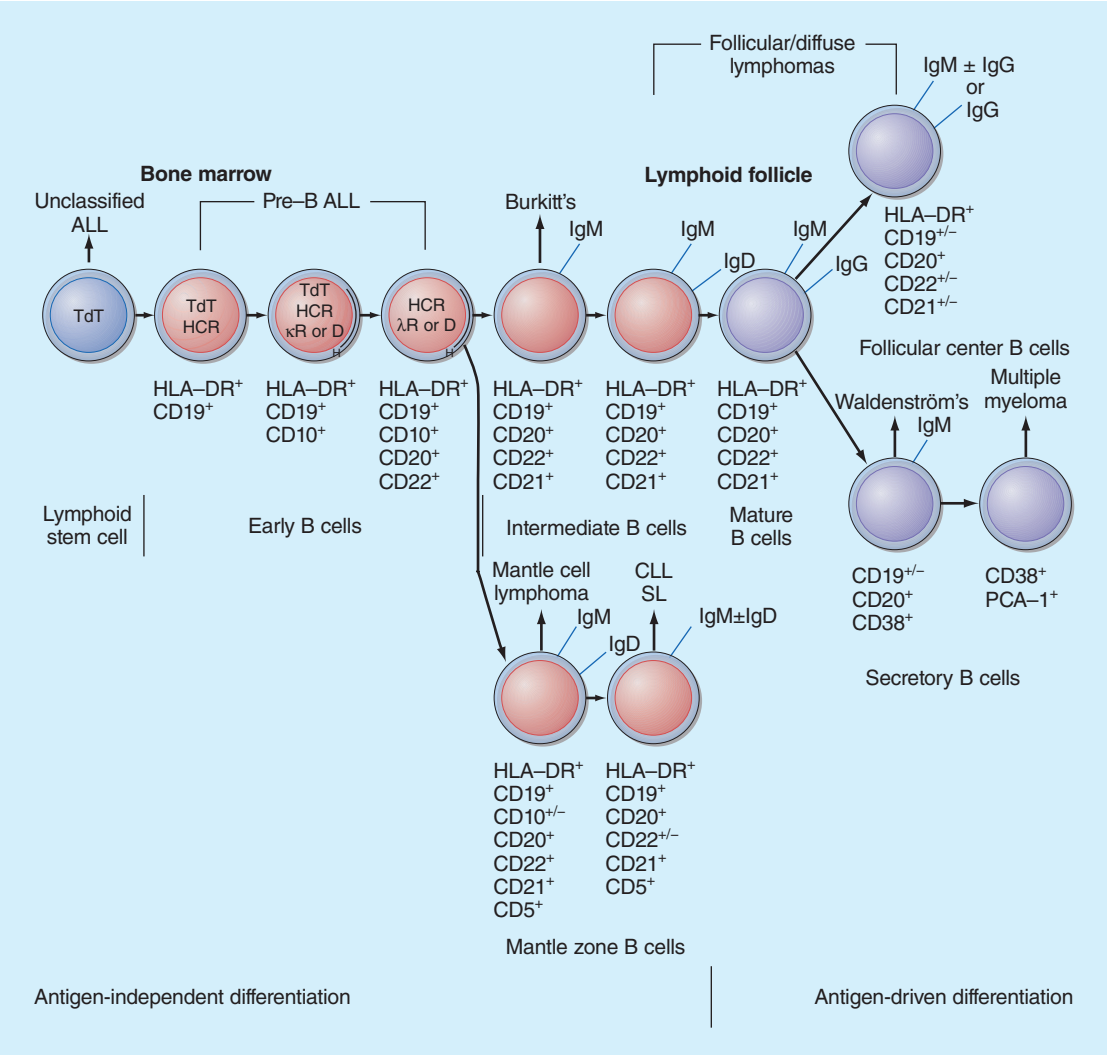

FIGURE 97–2. Pathway of normal B-cell differentiation and relationship to B-cell lymphocytes. (ALL, acute lymphoblastic leukemia; HCR, human chemokine receptor; HLA, human leukocyte antigen; Ig, immunoglobulin; TdT, terminal deoxynucleotidyl transferase.) (From Longo DL. Chapter 134. Malignancies of Lymphoid Cells. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015.)

segment of an antigen receptor gene, resulting in inappropriate binding to an **oncogene**. This results in dysregulation of cell growth and proliferation, leading to the malignant clone of lymphocytes. Oncogenes identified in different lymphomatous diseases include *myc, bcl-1, bcl-2, bcl-3, NF-κB,* and *bcl-6*.[23] Classic translocations for NHL include t(8;14) in Burkitt lymphoma, t(14;18) in follicular lymphomas, t(11;14) mantle cell lymphoma, and t(11;18)/t(1;14) in mucosa-associated lymphoid tissue (MALT).

KEY CONCEPT Characterization of the **morphology** of lymphocytes, the reactivity of other cells in the lymph node, and architecture of the node are essential in obtaining a diagnosis and predicting disease course. The nodal presentation of NHL is divided into two main categories: follicular, corresponding to low-grade disease, and diffuse, corresponding to aggressive disease. A follicular disease pattern in the inspected lymph node is indicative of a more indolent or low-grade progression that has survival measured in years if left untreated. In contrast, a diffuse pattern of lymph node infiltration indicates highly aggressive disease, resulting in death within weeks to months if untreated. Follicular NHL is the most common indolent subtype, comprising 22% of NHL. Diffuse, large B-cell lymphoma (DLBCL) is the most common aggressive histology, comprising 31% of NHL. The cells of origin for follicular NHL tend to be more mature, nondividing lymphocytes, whereas aggressive NHL is derived from rapidly dividing lymphoid precursors. A unique feature of the biology of NHL is that follicular low-grade histologies can undergo further malignant transformation, transforming further into a DLBCL population. This syndrome, also possible as a transition from chronic lymphocytic leukemia to an aggressive lymphoma, is called Richter transformation. Richter transformation involves multiple genetic events, including abnormalities of chromosomes 11 and 12 and tumor suppressor genes.[24]

The classification of NHL has undergone several revisions as the histology, molecular biology, and clinical course have been more precisely defined. Classification schemes such as the Working Formulation categorize disease on aggressiveness into three categories: low grade–survival estimated in years without treatment, intermediate grade–survival estimated in months without treatment, and high grade–survival measured in days to weeks for untreated disease. This scheme is limited in clinical applicability because of the large number of distinct diseases that are not categorized by this classification. A more accepted classification system for lymphoid malignancies was proposed by the WHO. The WHO classification groups lymphomas based on cell of origin (B-cell, T-cell, NK-cell) as shown in Table 97–1. Further description of tumors is based on cell characteristics such as aggressiveness, cell size, and proliferation.[5]

LO 3

Prognostic factors present at diagnosis have been identified for NHL. Age, the presence of B symptoms, performance status, number of nodal and extranodal sites, lactate dehydrogenase (LDH) level, bulky disease (> 10 cm), advanced stage, and β_2-microglobulin concentration have been shown to be important prognostic features in NHL. Table 97–6 shows the International Prognostic Index (IPI), a predictive model for aggressive NHL to be treated with doxorubicin-containing chemotherapy regimens.[25] This index is used as a tool to identify patients who may benefit from a more intense treatment regimen. A similar model, the Follicular Lymphoma International Prognostic Index (FLIPI), is used to help guide treatment decisions in follicular lymphoma.[26]

Table 97–6

Negative Prognostic Factors for NHL

International Prognostic Index—Diffuse, Aggressive NHL

Criteria	Risk Group	Number of Criteria
Age ≥ 60 years		
Stage III/IV disease	Low	0–1
Extranodal disease > 1 site	Low-intermediate	2
ECOG performance status 2 or greater	High-intermediate	3
Serum LDH > 1 × normal limit	High	4–5

Follicular Lymphoma International Prognostic Index

Criteria	Risk Group	Number of Criteria
Age ≥ 60 years		
Stage III/IV disease	Low	0–1
Hemoglobin < 12.0 g/dL (120 g/L; 7.45 mmol/L)	Intermediate	2
Serum LDH > 1 × normal limit	High	≥ 3
Number of nodal sites ≥ 5[a]		

[a]The nodal map used in the Follicular Lymphoma International Prognostic Index is different than the nodal map used in conventional staging.

TREATMENT OF NHL

Desired Outcome

NHL treatment depends primarily on histologic subtype (follicular low grade versus diffuse aggressive) and staging (local stage I/II versus advanced stage III/IV) to guide treatment with observation, chemotherapy, radiation, or chemotherapy and radiation. The Lugano modification of the Ann Arbor staging system for HL is also used in NHL.

LO 6

Treatment goals depend on the specific subtype of NHL. For follicular low-grade NHL, the disease is considered to be incurable. Many patients with follicular lymphoma are older than 60 years of age, making allogeneic SCT impractical due to high treatment-related mortality for older patients.

KEY CONCEPT The treatment goals for low-grade NHL include:

- Observation of the disease until the patient exhibits obvious progression that limits functional capacity or is life threatening
- Treatment that induces remission with manageable toxicity
- Judicious selection of treatment to avoid long-term toxicity
- Prevention of infectious complications

The intent of treatment for patients with aggressive histologies is cure. Some histologic subtypes exhibit a highly aggressive clinical course and are not considered to be curable. These patients are still treated with curative-intent chemotherapy or may be considered for a clinical trial.

Nonpharmacologic Therapy

For patients with low-grade follicular NHL, deferring initial therapy until progression of disease is a standard approach. The median survival time is 6 to 10 years. Some patients may be asymptomatic for several years after diagnosis, making observation a reasonable approach. Radiation therapy has a limited role in NHL relative to HL. NHL is more often a

systemic disease, and radiation typically has been reserved for consolidation after chemotherapy in patients presenting with a large extranodal mass. However, ISRT without chemotherapy is a treatment option for patients with stage I/II follicular lymphoma.

For early-stage diffuse, aggressive NHL, combined-modality therapy was tested versus a longer course of chemotherapy.[27] Overall survival favored the CHOP–radiation arm for 5 years (82% vs 72%). There was a trend toward increased toxicity, particularly hematologic and cardiac toxicity, in the CHOP alone arm. The results of this trial have established combined-modality therapy as first-line treatment for early stage NHL.

Pharmacologic Therapy

▶ *Follicular Low-Grade NHL*

The management of low-grade lymphomas is an area of controversy, especially in patients presenting with early stage disease. Typical indications for treatment include cytopenias, recurrent infections, threatened end-organ function, disease progression over at least 6 months, or patient preference. In these patients, chemotherapy such as fludarabine or bendamustine is typically offered initially. The role of combination regimens is controversial as they have not been shown to improve overall survival compared to single agent chemotherapy. Rituximab, a chimeric monoclonal anibody that binds to CD20 on B lymphocytes, is an essential component of treatment of follicular lymphoma. Clinical trials have demonstrated improved patient outcomes with the combination of rituxan/chemotherapy versus chemotherapy alone for initial treatment of follicular lymphoma.[28] Rituximab is incorporated into most patients' treatment of follicular lymphoma. These regimens are detailed in Table 97–7. Additionally, rituximab was examined as maintenance therapy administered every 8 weeks for 2 years after rituximab-containing multiagent chemotherapy. Compared with observation, rituximab increased 3-year progression-free survival (PFS) (74.9 vs 57.6 months).[29]

Other strategies for treatment of low-grade lymphomas include the combination of monoclonal antibodies directed against CD20 with a radiopharmaceutical attached, a kinase inhibitor active against B-cells, an immunomodulatory agent, and a new monoclonal antibody against CD20. Ibritumomab-yttrium 90 is a monoclonal antibody targeting CD20 that delivers radioactive yttrium. It is indicated for the treatment of relapsed follicular lymphoma or as consolidation after response to initial chemotherapy. Idelalisib is a small molecule that inhibits PI3Kδ kinase found in B-cells, inducing apoptosis and inhibiting chemotaxis. It was approved based on a phase I study in patients who had failed multiple prior therapies. These heavily pretreated patients had an overall response rate of 45%.[30] Lenalidomide is an immunomodulatory agent that has shown promise when combined with rituximab for the treatment of follicular lymphoma.[31,32] Obinutuzumab is a type II anti-CD20 monoclonal antibody. It is currently being evaluated in combination with standard chemotherapy regimens versus rituximab with chemotherapy for the initial treatment of follicular lymphoma. The results have not fully matured; however, after approximately 3 years of follow-up, obinutuzumab containing regimens had a 35% improvement in progression-free survival.[33] High-dose chemotherapy is being evaluated for low-grade follicular NHL, but its role is limited to clinical trials.

Table 97–7

Chemotherapy Regimens for Low-Grade, Follicular NHL

Fludarabine/Rituximab
Fludarabine 25 mg/m^2 IV days 1–5 every 28 days
Rituximab 375 mg/m^2 IV, days 1 and 5 of weeks 1 and 26; single dose 72 hours before fludarabine cycles 2, 4, and 6

Bendamustine/Rituximab—Every 28 Days
Bendamustine 90 mg/m^2 IV days 1 and 2
Rituximab 375 mg/m^2 IV, day 1

R-CVP—Every 21 Days
Rituximab 375 mg/m^2 IV, day 1
Cyclophosphamide 750 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Prednisone 40 mg/m^2 po daily, days 1–5

R-CHOP—Every 21 Days
Rituximab 375 mg/m^2 IV, day 1
Cyclophosphamide 750 mg/m^2 IV, day 1
Doxorubicin 50 mg/m^2 IV, day 1
Vincristine 1.4 mg/m^2 IV, day 1
Prednisone 100 mg/day po, days 1–5

IV, intravenous; po, oral.

▶ *Diffuse, Aggressive NHL*

LO 7

KEY CONCEPT The mainstay of therapy for diffuse, aggressive NHL, such as DLBCL, is anthracycline-based combination chemotherapy, generally consisting of four or more drugs. Therapy options for intermediate- and high-grade NHL generally are segregated between localized (stage I/II) and advanced (stage III/IV) disease. Combined-modality therapy with an abbreviated course of R-CHOP and local radiation is considered a standard of care for stage I/II disease.

The standard therapy for disseminated disease since the 1970s has been CHOP. This regimen conferred a response of 50% to 60%, with long-term survival of approximately 30%. The benefits of CHOP have been confirmed by multiple clinical trials including comparisons to regimens with more agents and varying schedules. None of these other options have improved on CHOP in patients with normal risk DLBCL.[34] There were no significant differences in response rate or overall survival between the groups and severe toxicity and death were higher in the advanced-generation treatment regimens relative to CHOP cementing CHOP as first-line chemotherapy in DLBCL.

LO 8

Rituximab is also routinely used to treat DLBCL. A study randomized patients 60 to 80 years of age with newly diagnosed disease to either CHOP for eight cycles or CHOP plus rituximab (R-CHOP) for eight cycles.[35] Two-year follow-up showed rituximab improved CR (76% vs 63%) and median event-free survival (57% vs 38%) and long-term follow-up confirmed benefit with an improvement in 10-year survival (43% vs 27.6%). Similar findings have been reported in younger patients, making R-CHOP first-line therapy for advanced-stage DLBCL (Table 97–8).

▶ *Special Populations*

There are histologic subtypes of diffuse, aggressive NHL which are less responsive to treatment with conventional regimens such as R-CHOP. Burkitt lymphoma, lymphoblastic lymphoma, mantle cell lymphoma, primary mediastinal large B-cell lymphoma, and primary CNS lymphoma are examples of disease that benefit from more intensive therapy. Regimens such as R-hyper-CVAD, which alternate cycles of rituximab, hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone with rituximab, high-dose cytarabine and methotrexate,[36,37] or EPOCH-R, which contains etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab should be considered alternatives to R-CHOP.

Table 97–8

Treatment Regimens for Diffuse, Aggressive NHL

R-CHOP—Every 21 Days[a]
EPOCH-R—Every 21 Days
Rituximab 375 mg/m² IV, day 1
Etoposide 50 mg/m²/day CIVI, days 1–4
Prednisone 60 mg/m²/day po, days 1–5
Vincristine 0.4 mg/m²/day CIVI, days 1–4
Cyclophosphamide 750 mg/m² IV, day 5
Doxorubicin 10 mg/m²/day CIVI, days 1–4

R-CNOP-Rituximab—Every 21 Days[b]
Rituximab 375 mg/m² IV, day 1
Cyclophosphamide 750 mg/m² IV, day 1
Mitoxantrone 10 mg/m² IV, day 1
Vincristine 1.4 mg/m² IV, day 1
Prednisone 100 mg/day po, days 1–5

R-Hyper-CVAD
Part A: The following drugs given on course 1, 3, 5, and 7
Rituximab 375 mg/m² IV, day 1
Cyclophosphamide 300 mg/m² IV every 12 hours, days 1–3 (with Mesna)
Doxorubicin 50 mg/m² IV, day 1
Vincristine 1.4 mg/m² IV, days 1, 11
Dexamethasone 40 mg/day po, days 1–4 and 11–14
Methotrexate 15 mg intrathecal, day 2
Cytarabine 30 mg intrathecal, day 2
Hydrocortisone 15 mg intrathecal, day 2
Part B: The following drugs are given on courses 2, 4, 6, and 8
Rituximab 375 mg/m² IV, day 1
Methotrexate 1000 mg/m² IV over 24 hours, day 1
Cytarabine 3000 mg/m² IV every 12 hours, days 2 and 3
Leucovorin 25 mg IV × 1; then 25 mg po every 6 hours for seven doses
Methotrexate 15 mg intrathecal, day 2

Bendamustine/Rituximab—Every 28 Days[a]

ESHAP
Etoposide 40 mg/m² IV per day continuous infusion, days 1–4
Cisplatin 25 mg/m² IV per day continuous infusion, days 1–4
Cytarabine 2000 mg/m² IV × 1, day 5
Methylprednisone 250 mg IV every 12 hours, days 1–4

DHAP
Dexamethasone 40 mg po or IV daily, days 1–4
Cisplatin 100 mg/m² IV continuous infusion, day 1
Cytarabine 2000 mg/m² IV every 12 hours for two doses on day 2

ICE
Etoposide 100 mg/m² IV daily, days 1–3
Carboplatin AUC 5 (maximum dose, 800 mg) IV, day 2
Ifosfamide 5000 mg/m² IV continuous infusion × 1 on day 2 (with 100% replacement with Mesna)

[a]Refer to Table 97–8 for regimen.

[b]Data are limited, use only for patients who are unable to receive an anthracycline.

AUC, area under the curve; CIVI, continuous intravenous infusion; IV, intravenous; po, oral.

The presence of *C-Myc* gene rearrangement in addition to either *Bcl-2* or *Bcl-6* gene rearrangements is known as double-hit lymphoma (DHL) and can occur in patients with DLBCL or other high-grade lymphomas. These lymphomas are highly aggressive and have inferior response to R-CHOP.[38] Aggressive chemotherapy regimens such as R-hyper-CVAD and EPOCH-R have been shown to superior outcomes and should be used in the treatment of DHL.[39]

Patients with CNS NHL have disease that is poorly responsive to therapy because of inadequate penetration of standard doses of chemotherapy across the blood–brain barrier. High-dose methotrexate, ranging from 2500 to 8000 mg/m², is a mainstay of therapy. Treatment may also include intrathecal chemotherapy. Drugs that are commonly used intrathecally include methotrexate, cytarabine (conventional formulation and liposomal products), and corticosteroids.

The recognition of *H. pylori* colonization and MALT has spurred the more aggressive treatment of this organism with antibiotics. In patients with localized disease, aggressive, combination therapy for *H. pylori* has been shown to induce MALT remission. Patients with advanced disease may require chemotherapy with R-CHOP.

Patients with HIV-related lymphoma represent a therapeutic dilemma considering many have high-grade NHL. A common presentation includes extranodal disease, frequently in the GI tract, CNS, or bone marrow. Because of the aggressive nature of HIV-related lymphoma, aggressive chemotherapy regimens such as Hyper-CVAD and EPOCH are recommended. Antiretroviral therapy is important to improving patients' ability to tolerate chemotherapy and should be initiated before chemotherapy. The use of CSFs to promote white blood cell counts is also recommended. Rituximab should be added to chemotherapy for CD20 positive lymphomas in patients with an adequate CD4 count.

With more than half of patients with NHL expected to relapse, salvage therapy plays a major role in the attempt to treat recurrence. Multiple drug regimens such as ESHAP and DHAP can induce a CR, but long-term cure with these regimens is less than 10%. When salvage regimens are used, rituximab is frequently added to the regimen. Further salvage therapy can induce remissions with subsequent relapses; however, the chance for a CR is further diminished.

High-dose chemotherapy with autologous SCT has been studied as an alternative to standard dose regimens in the setting

Patient Encounter Part 2: Treatment Selection

Complete evaluation revealed stage IV diffuse large B-cell lymphoma that is positive for gene rearrangement in *c-Myc* and negative for *Bcl-2/Bcl-6* gene rearrangements. Therapy is scheduled to begin immediately.

What therapy (or therapies) is (are) most appropriate for this patient?

At this time, is this patient an appropriate candidate for stem cell transplant?

What other information (eg, laboratory studies, diagnostic tests) is needed prior to initiating chemotherapy?

Patient Encounter Part 3: Creating a Care Plan

Based on the information presented, create a care plan for this patient, including the goals of therapy, antineoplastic therapy plan, and necessary supportive care.

LO 5

of first relapse.[40] The best-studied indication for SCT is for patients with intermediate- or high-grade disease that fails to respond to first-line therapy. A 3- to 5-year survival of greater than 40% is achieved in patients who have good performance status and disease that demonstrates a significant response to one or two cycles of salvage chemotherapy. The procedure-related mortality rate has ranged from 5% to 10% in published reports. However, as with HL, with improvements in SCT techniques and better supportive care, the mortality rate continues to decline. The role of allogeneic SCT in this setting is limited because of donor availability, the older age of patients, and the high treatment-related morbidity and mortality. Outcomes between autologous and allogeneic transplant appear similar.

OUTCOME EVALUATION

Treatment response in lymphomas is measured using the response evaluation criteria in solid tumors (RECIST), a uniform criterion assessing tumor response developed by the National Cancer Institute. Lymphomas may have residual masses after completion of treatment, adding to the difficulty in establishing a definitive remission from treatment. Historically, imaging scans using positron emission tomography (PET) or computed tomography (CT) have been used to evaluate patient with lymphomas. Now, PET combined with CT (PET-CT) is recommended to evaluate patients with lymphoma for staging as well as for response assessment.[41]

Long-term follow-up monitors patients for continued disease remission with careful examination of the original areas of involvement and repeated follow-up imaging. Patients also require long-term monitoring for toxicities of their treatment.

Due to the high sensitivity to therapy of many lymphomas, most patients treated for lymphoma with chemotherapy or radiation notice a regression of palpable lymphadenopathy within days. This also necessitates implementation of tumor lysis syndrome precautions with aggressive intravenous hydration and allopurinol. Rasburicase should be considered for patients with moderate to high tumor burdens. Most chemotherapy treatments for lymphoma have a significant risk of infectious complications. Combination regimens for both HL and NHL are associated with rates of severe leukopenia and/or neutropenia ranging from 20% to 100% of patients. Consideration must be given to supportive care with prophylactic CSFs or antibiotics. Most chemotherapy regimens discussed in this section are highly emetogenic. Antiemetic regimens are available to control

Patient Care Process

Collect Information:

- Take a thorough medication history with particular attention to nonprescription or herbal medications.
- Review medical history with an emphasis on identifying causative factors of lymphoma and preexisting medical conditions that can affect chemotherapy.

Assess the Information:

- Evaluate home medications to identify any potential drug interactions with chemotherapy.
- Review findings of diagnostic tests including laboratory values, imaging results, pathology results, cancer diagnosis, and genetic profile of the malignancy.
- Determine the stage and prognostic index for the patient.
- Before initiation of treatment, assess patient for risk of tumor lysis syndrome.

Develop a Care Plan:

- Identify the optimal treatment regimen for the patient incorporating diagnosis, stage, and prognostic indicators (Tables 97–4, 97–7, 97–8)
- Verify chemotherapy regimen doses with a standardized reference and assess for dose adjustment based on height, weight, and body surface area and organ dysfunction (renal or hepatic).
- Assess appropriateness of supportive care for the chemotherapy regimens including need for prophylactic antiemetics and use of colony-stimulating factors.

Implement the Care Plan:

- Provide patient education regarding common toxicities associated with chemotherapy such as nausea/vomiting, mucositis, myelosuppression, and alopecia.
- For doxorubicin-containing regimens, maintain records of the cumulative doxorubicin dosage received by the patient to monitor for cardiac toxicity risk.
- For bleomycin-containing regimens, maintain records of the cumulative bleomycin dosage received by the patient to monitor for pulmonary fibrosis.
- Educate patients regarding the short- and long-term complications associated with radiation therapy.
- Provide contact numbers for patient in the event of a fever and a response plan if the patient is considered to be at risk for neutropenic fever.

Follow-up: Monitor and Evaluate:

- Schedule regulatory laboratory tests including complete blood count and blood chemistries to monitor for chemotherapy toxicities and tumor lysis syndrome.
- Use RECIST criteria to determine patient's response to therapy by reviewing PET-CT scan following completion of therapy.
- Develop a plan to monitor for long-term complications of chemotherapy such as cardiotoxicity and secondary malignancies.

chemotherapy-induced nausea and vomiting well for most standard-dose regimens.[42]

Advances in the treatment of lymphoma have increased the number of long-term survivors. Identification of long-term complications of lymphoma therapy is vital to patient follow-up and may influence treatment decisions in newly diagnosed patients. Outcomes associated with the treatment of HL make up the majority of data. However, advances in NHL treatment have provided more information regarding long-term toxicities. Two leading causes of death associated with lymphoma treatment are secondary malignancies and cardiovascular disease. The use of combined modality of irradiation with doxorubicin-based therapy has been reported to increase the risk of cardiac dysfunction. Treatment-related pulmonary toxicity, hypothyroidism, and infertility have been associated with lymphoma therapy as well. Lymphoma survivors have an increased risk for developing myelodysplasia, acute myelogenous leukemia, and various solid tumors.[43]

A limitation of rituximab is severe, potentially fatal infusion-related reactions. Deaths have been reported resulting from the profound hypotension and circulatory collapse, particularly with the first dose. The package labeling recommends premedication with acetaminophen and diphenhydramine before each infusion. The initial infusion should be given slowly, at 50 mg/hour and may be increased as tolerated to a maximum of 400 mg/hour. In the absence of infusion reactions, subsequent doses may be started at a higher rate and titrated more aggressively. Rituximab has also caused reactivation of hepatitis B. Patients at high risk for hepatitis B should be screened and monitored carefully for reactivation of hepatitis. If hepatitis occurs, rituximab should be discontinued, and patients should be treated appropriately. Other associated toxicities of rituximab include fever, chills, headache, asthenia, nausea, vomiting, angioedema, bronchospasm, and skin reactions. KEY CONCEPT Rituximab is an effective treatment option for patients with various forms of NHL as long as patients are monitored appropriately.[44]

Abbreviations Introduced in This Chapter

Bcl-1	Important in the regulation of mitosis
Bcl-2	A regulator of apoptosis
Bcl-3	A regulator of nuclear transcription factor
Bcl-6	Regulates cell differentiation
c-Myc	Regulator of gene transcription
ABVD	Doxorubicin, bleomycin, vinblastine, and dacarbazine
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CT	Computed tomography
CSFs	Colony-stimulating factors
CVP	Cyclophosphamide, vincristine, and prednisone
DHL	Double-hit lymphoma
EBV	Epstein-Barr virus
FLIPI	Follicular lymphoma international prognostic index
HL	Hodgkin lymphoma
IPI	International Prognostic Index
IPS	International Prognostic Score
LDH	Lactate dehydrogenase
MALT	Mucosa-associated lymphoid tissue
MOPP	Mechlorethamine, vincristine, procarbazine, and prednisone
NHL	Non-Hodgkin lymphoma
PET	Positron emission tomography
RECIST	Response evaluation criteria in solid tumors
RS	Reed-Sternberg
SCT	Stem cell transplantation

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.
2. Caporaso NE, Goldin LR, Anderson WF, Landgren O. Current insight on trends, causes, and mechanisms of Hodgkin's lymphoma. Cancer J. 2009;15:117–123.
3. Ansell SM. Hodgkin lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016;91: 434–442.
4. Tiacci E, Doring C, Brune V, et al. Analyzing primary Hodgkin and Reed-Sternberg cells to capture the molecular and cellular pathogenesis of classical hodgkin lymphoma. Blood. 2012;120:4609–4620.
5. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–2390.
6. Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA Cancer J Clin. 2016;66:443–459.
7. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–3068.
8. Specht L, Yahalom J, Illidge T, et al. Modern radiation therapy for Hodgkin lymphoma: field and dose guidelines from the international lymphoma radiation oncology group (ILROG). Int J Radiat Oncol Biol Phys. 2014;89:854–862.
9. Radford J, Illidge T, Counsell N, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med. 2015;372:1598–1607.
10. Raemaekers JMM, André MPE, Federico M, et al. Omitting radiotherapy in early positron emission tomography–negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2014;32:1188–1194.
11. Advani RH, Hoppe RT, Baer D, et al. Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial. Ann Oncol. 2013;24:1044–1048.
12. Canellos GP, Niedzwiecki D, Johnson JL. Long-term follow-up of survival in Hodgkin's lymphoma. N Engl J Med. 2009;361:2390–2391.
13. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. J Clin Oncol. 2009;27:5390–5396.
14. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. J Clin Oncol. 2009;27:4548–4554.
15. Alinari L, Blum KA. How I treat relapsed classical Hodgkin lymphoma after autologous stem cell transplant. Blood. 2016;127:287–295.
16. Hertzberg M. Relapsed/refractory Hodgkin lymphoma: what is the best salvage therapy and do we need RIC-AlloSCT? Hematol Oncol Clin North Am. 2014;28:123–147.
17. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. 1993;341:1051–1054.
18. Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125:1236–1243.

19. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372:311–319.
20. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol. 2016;34:3733–3739.
21. Roman E, Smith AG. Epidemiology of lymphomas. Histopathology. 2011;58:4–14.
22. Smedby KE, Ponzoni M. The aetiology of B-cell lymphoid malignancies with a focus on chronic inflammation and infections. J Intern Med. 2017;282(5):360–370.
23. Kuppers R, Klein U, Hansmann ML, Rajewsky K. Cellular origin of human B-cell lymphomas. N Engl J Med. 1999;341:1520–1529.
24. Montgomery ND, Mathews SP. Transformation in low-grade B-cell neoplasms. Surg Pathol Clin. 2016;9:79–92.
25. International non-Hodgkin's lymphoma prognostic factors project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329:987–994.
26. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004;104:1258–1265.
27. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med. 1998;339:21–26.
28. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2007;99:706–714.
29. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet. 2011;377:42–51.
30. Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-delta, as therapy for previously treated indolent non-Hodgkin lymphoma. Blood. 2014;123:3406–3413.
31. Fowler NH, Davis RE, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. Lancet Oncol. 2014;15:1311–1318.
32. Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (alliance). J Clin Oncol. 2015;33:3635–3640.
33. Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized phase 3 GALLIUM study. Blood. 2016;128(22):6.
34. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med. 1993;328:1002–1006.
35. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the groupe d'etudes des lymphomes de l'adulte. Blood. 2010;116:2040–2045.
36. Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with rituximab-HyperCVAD alternating with rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. Br J Haematol. 2010;150:200–208.
37. Wasterlid T, Brown PN, Hagberg O, et al. Impact of chemotherapy regimen and rituximab in adult Burkitt lymphoma: a retrospective population-based study from the Nordic lymphoma group. Ann Oncol. 2013;24:1879–1886.
38. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30:3452–3459.
39. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. Br J Haematol. 2015;170:504–514.
40. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333:1540–1545.
41. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. J Clin Oncol. 2014;32:3048–3058.
42. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;35:3240–3261.
43. Ng AK, LaCasce A, Travis LB. Long-term complications of lymphoma and its treatment. J Clin Oncol. 2011;29:1885–1892.
44. Armitage JO, Carbone PP, Connors JM, Levine A, Bennett JM, Kroll S. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. J Clin Oncol. 2003;21:897–906.

98 Hematopoietic Stem Cell Transplantation

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LEARNING OBJECTIVES

LO

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

1. Explain the rationale for using hematopoietic stem cell transplant (HSCT) to treat cancer.
2. Compare the different types of HSCTs, specifically (a) the types of donors (ie, autologous and allogeneic), (b) the source of hematopoietic cells (ie, umbilical cord, peripheral blood progenitor cells, and bone marrow), and (c) the type of preparative regimen (ie, myeloablative and nonmyeloablative).
3. Develop a plan for monitoring and managing engraftment of hematopoiesis.
4. List the nonhematologic toxicity to high-dose chemotherapy used in myeloablative preparative regimens, specifically busulfan-induced seizures, hemorrhagic cystitis, gastrointestinal toxicities, and sinusoidal obstruction syndrome.
5. Explain graft-versus-host disease (GVHD).
6. Recommend a prophylactic and treatment regimen for GVHD.
7. Choose an appropriate regimen to minimize the risk of infectious complications in HSCT patients.
8. Evaluate the long-term health care of HSCT survivors.

INTRODUCTION

KEY CONCEPT

Hematopoietic stem cell transplantation (HSCT) is a procedure used primarily in the treatment of hematologic malignancies via high-dose chemotherapy and/or a graft-versus-tumor effect. HSCT may be either autologous, where a patient receives their own bone marrow, or allogeneic, where the patient receives bone marrow from a donor. As an alternative to bone marrow, hematopoietic stem cells may be obtained from the peripheral blood progenitor cells (PBPCs) or umbilical cord blood (UCB). Bone marrow and PBPCs contain pluripotent stem cells and postthymic lymphocytes, which are responsible for long-term hematopoietic reconstitution, called engraftment and immune recovery.[1]

LO 1

The rationale of an autologous transplant is to administer a **myeloablative preparative regimen** and eradicate the patient's malignancy. Collecting the bone marrow or PBPCs prior to administering high-dose chemotherapy essentially protects the collected PBPCs from the effects of chemotherapy and can restore hematopoiesis. Allogeneic transplants use donor PBPCs to rescue the patient after myeloablative chemotherapy with an added advantage of the donor cells generating an immunologic response toward the recipient's residual tumor, called the **graft-versus-tumor effect**. Unfortunately, **graft-versus-host disease** (GVHD) where the donor cells generate an immunologic response toward the recipient's normal tissue also occurs.

The type of HSCT performed depends on a number of factors, including the type and status of disease, availability of a compatible donor, patient age, performance status, and organ function. Examples of diseases treated with HSCT are listed in Table 98–1.

EPIDEMIOLOGY AND ETIOLOGY

In 2015, approximately 14,000 autologous HSCTs and 8000 allogeneic HSCTs were performed in the United States. The most common indications for HSCT were multiple myeloma (MM) and lymphoma; acute myeloid leukemia accounted for 70% of all allogeneic transplants. The annual number of transplants continues to steadily increase due to the use of alternative donors and the use of transplant expanding to older patients.[3]

The use of allogeneic PBPCs is increasing; from years 2007 through 2011, almost 80% of allogeneic HSCTs performed worldwide used PBPCs as the source of hematopoietic cells rather than bone marrow in adult patients.[3] Autologous PBPC use has increased and essentially has replaced bone marrow as a graft source in many transplant centers. From years 2007 through 2011, approximately 99% of autologous HSCTs in adults and 94% in children used PBPCs as the source of hematopoietic cells.[3]

PATHOPHYSIOLOGY

KEY CONCEPT

Autologous HSCT, or infusion of a patient's own hematopoietic cells, allows for the administration of higher doses of chemotherapy, radiation, or both to treat the malignancy or autoimmune disorder. In this setting, the hematopoietic cells "rescue" the recipient from otherwise dose-limiting hematopoietic toxicity, allowing higher doses of chemotherapy to be safely administered. Autologous HSCT is used to treat intermediate- and high-grade non-Hodgkin lymphoma (NHL), MM, autoimmune diseases, and relapsed or refractory Hodgkin lymphoma.[1,2] Patients do not benefit from an immunologic graft-versus-tumor effect while undergoing an autologous transplant;

Table 98–1

Diseases Commonly Treated with HSCT

	Autologous Graft	Allogeneic Graft
Cancers	Multiple myeloma Non-Hodgkin lymphoma Hodgkin disease Neuroblastoma Germ cell tumors	Acute myeloid leukemia Acute lymphoblastic leukemia Chronic myeloid leukemia Myelodysplastic syndrome Myeloproliferative disorders Non-Hodgkin lymphoma Hodgkin disease Chronic lymphocytic leukemia Multiple myeloma
Other Diseases	Autoimmune diseases Amyloidosis	Aplastic anemia Paroxysmal nocturnal hemoglobinuria Fanconi anemia Thalassemia major Sickle cell anemia Severe combined immunodeficiency Inborn errors of metabolism

instead, the administration of high-dose chemotherapy followed by an autologous stem cell transplant in chemotherapy-sensitive malignancies relies on the preparative regimen alone to eradicate the malignant disease. Autologous HSCT circumvents the need for histocompatible donors, is associated with a lower mortality rate, and is not restricted to younger patients.[3]

KEY CONCEPT **Allogeneic HSCT** involves the transplantation of hematopoietic cells obtained from a different person's (donor) bone marrow, peripheral blood, or umbilical cord blood to the recipient. Unless the donor and the recipient are identical twins (referred to as a *syngeneic HSCT*), they are dissimilar genetically. In allogeneic transplant, the donor and recipient share common cell surface antigens called human leukocyte antigens (HLA). These antigens are encoded by a group of genes called the major histocompatibility complex (MHC).[1]

The transplanted donor stem cells are immunologically active, and thus there is potential for bidirectional graft rejection. When host-versus-graft reactions occur, cytotoxic T cells and natural killer (NK) cells belonging to the host (recipient) recognize MHC antigens of the graft (donor hematopoietic stem cells) as foreign and this leads to a rejection response. When GVHD occurs, immunologically active cells in the graft recognize host MHC antigens and elicit an immune response. When host-versus-graft effects occur in allogeneic HSCT, they are referred to as *graft failure* or *rejection,* which results in ineffective hematopoiesis (ie, adequate absolute neutrophil count [ANC] and/or platelet counts were not obtained). Allogeneic HSCT is used to treat both nonmalignant conditions and hematologic malignancies such as acute and chronic leukemias.[1]

LO 2 For both allogeneic and autologous transplants, hematopoietic cells are infused after the administration of a combination of chemotherapy and/or radiation, termed the conditioning or preparative regimen. KEY CONCEPT A myeloablative preparative regimen involves the administration of sublethal doses of chemotherapy to the recipient to eradicate residual malignant disease. The recipient will not regain his or her own hematopoiesis and will be at risk for substantial life-threatening nonhematologic toxicity.[4] LO 2 For those undergoing an autologous HSCT, their hematopoietic cells must be harvested and stored before the myeloablative preparative regimen is administered. After the administration of the myeloablative preparative regimen, these hematopoietic cells serve as a rescue intervention to reestablish bone marrow function and avoid long-lasting, life-threatening bone marrow aplasia. In the setting of an allogeneic HSCT, the preparative regimen is designed to suppress the recipient's immunity, eradicate residual malignancy, or create space in the marrow compartment. Improved survival outcomes have been observed with both autologous and allogeneic HSCT when the hematologic malignancy is in complete remission at the time of HSCT.[3] At most HSCT centers, age younger than 65 years and normal renal, hepatic, pulmonary, and cardiac function are considered eligibility requirements for myeloablative allogeneic HSCT.

LO 2 The recognition of graft-versus-tumor effect, which likely is caused by cytotoxic T lymphocytes in the donor stem cells in those undergoing an allogeneic HSCT transplant, led to investigations with reduced intensity conditioning, in which less toxic preparative regimens are used in the hope of expanding the availability of HSCT to recipients whose medical condition or age prohibits use of myeloablative regimens. Reduced intensity regimens may still be myeloablative; purely nonmyeloablative regimens also have been introduced for certain disease states and are less toxic than myeloablative and reduced intensity regimens.

A myeloablative, or reduced intensity, or **nonmyeloablative preparative regimen** may be used for allogeneic HSCT; only myeloablative preparative regimens are used for autologous HSCT.

Histocompatibility

LO 2 **Histocompatibility** differences between the donor and the recipient necessitate immunosuppression after an allogeneic HSCT because considerable morbidity and mortality are associated with graft failure and GVHD. Rejection is least likely to occur with a syngeneic donor. In patients without a syngeneic donor, initial HLA typing is conducted on family members because the likelihood of complete histocompatibility between unrelated individuals is remote. Siblings are the most likely individuals to be histocompatible within a family; however, only 30% of patients will have an HLA-matched sibling donor. Having a matched-sibling donor is no longer a requirement for allogeneic HSCT because improved immunosuppressive regimens and the National Marrow Donor Program have allowed an increase in the use of unrelated or related matched or mismatched HSCTs. Establishment of the National Marrow Donor Program has helped to increase the pool of potential donors for allogeneic HSCT.[5] Through this program, an HLA-matched unrelated volunteer donor might be identified. Recipients of an unrelated graft are more likely to experience graft failure and acute GVHD relative to recipients of a matched-sibling donor. Due to the amount of patients without a matched donor, alternative strategies have been investigated such as mismatched unrelated donors, related haploidentical donors, and UCB stem cell products. Mismatched unrelated donors involve one or more HLA-locus mismatch and are high risk for GVHD. A related haploidentical donor refers to a complete half mismatch to the recipient (matched at 3 of 6 or 4 of 8 HLA loci); these donors are parents, children, or siblings. Haploidentical transplants are high risk for graft rejection and GVHD; however, recent advances including the use of posttransplant cyclophosphamide have led to an increase in the use of haploidentical donors for patients without an HLA-matched option.[6,7]

The degree of HLA mismatching is correlated with the risk of acute GVHD, graft rejection, and mortality. An optimal donor for transplantation will be an HLA match at the HLA-A, HLA-B,

HLA-C, and HLA-DRB1 loci (an 8/8 HLA match). There is an increase in the risk of GVHD and posttransplant mortality with each mismatch.[8] Determination of histocompatibility between potential donors and the patient is completed before allogeneic HSCT. Initially, HLA typing is performed using blood samples and compatibility for class I MHC antigens (ie, HLA-A, HLA-B, and HLA-C) is determined through serologic and DNA-based testing methods. In vitro reactivity between donor and recipient also can be assessed in mixed-lymphocyte culture, a test used to measure compatibility of the MHC class II antigens (ie, HLA-DR, HLA-DP, and HLA-DQ). Most clinical and research laboratories are also performing molecular DNA typing using polymerase chain reaction (PCR) methodology to determine the HLA allele sequence.[9]

Stem Cell Sources

KEY CONCEPT Bone marrow, PBPCs, and UCB can serve as the source of hematopoietic cells. The optimal cell source differs based on the donor and recipient characteristics.

LO 2

Hematopoietic stem cells are obtained from bone marrow or peripheral blood. The technique for harvesting hematopoietic cells depends on the anatomic source (ie, bone marrow or peripheral blood). A surgical procedure is necessary for obtaining bone marrow. Multiple aspirations of marrow are obtained from the anterior and posterior iliac crests until a volume with a sufficient number of hematopoietic stem cells is collected (ie, 600–1200 mL of bone marrow). The bone marrow then is processed to remove fat or marrow emboli and usually is infused intravenously into the patient similar to a blood transfusion.

The shift to the use of PBPCs over bone marrow for HSCT is primarily because of the more rapid engraftment and decreased health care resource use. For an autologous transplant, the harvest occurs before administering the preparative regimen; therefore, autologous hematopoietic cells must be cryopreserved and stored for future use.

Allogeneic cells are usually harvested just prior to the HSCT and administered to the recipient without cryopreservation; however, they are sometimes collected and cryopreserved as well. The bone marrow may need additional processing if the donor and recipient are ABO incompatible, which occurs in up to 30% of HSCTs. Red blood cells (RBCs) may need to be removed before infusion into the recipient to prevent immune-mediated hemolytic anemia and thrombotic microangiopathic syndromes.

Transplantation with PBPCs essentially has replaced bone marrow transplantation (BMT). PBPCs are obtained by administering a mobilizing agent(s) followed by apheresis, which is an outpatient procedure similar to hemodialysis. Hematopoietic growth factors (HGFs) alone or in combination with myelosuppressive chemotherapy are used for **mobilization** of autologous PBPCs with similar results.[10,11] HGFs are also used to mobilize donor PBPCs for allogeneic transplants, although chemotherapy is not used in this setting.

LO 2

UCB offers an alternative stem cell source to patients requiring an allogeneic transplant who do not have an acceptable matched related or unrelated donor. When allogeneic hematopoietic cells are obtained from UCB, the cord blood is obtained from a consenting donor in the delivery room after birth and delivery of the placenta. The UCB is processed, a sample is sent for HLA typing, and the cord blood is frozen and stored for future use. Numerous UCB registries exist, with the goal of providing alternative sources of allogeneic stem cells. UCB offers the advantage of being readily available, and has provided a stem cell source to a more diverse patient population, in addition to a low risk of GVHD.[12,13] Limitations include an increased risk of graft failure, delayed immune reconstitution leading to an increase in infections, and the inability to use donor-lymphocyte infusions in the event of relapse.[6,14] The prospective use of dual umbilical cord units and ex vivo expansion of umbilical cord units to obtain adequate engraftment are methods currently under exploration.

TREATMENT

Desired Outcome

KEY CONCEPT Engraftment is defined as the point at which a patient can maintain a sustained ANC of greater than 500 cells/mm^3 (0.5×10^9/L) and a sustained platelet count of 20,000/mm^3 (20×10^9/L) or more lasting 3 or more consecutive days without transfusions[15] and is the desired short-term outcome in a transplant. The desired long-term outcome with HSCT is to cure the patient of his or her underlying disease while minimizing the short- and long-term morbidity associated with HSCT.

Nonpharmacologic Therapy

▶ *Harvesting, Preparing, and Transplanting Autologous and Allogeneic Hematopoietic Cells*

Autologous Transplants The number of hematopoietic stem cells circulating in the peripheral blood is low and requires the use of mobilizing agents for successful apheresis. The HGFs granulocyte-macrophage colony-stimulating factor (sargramostim, Leukine) and granulocyte colony-stimulating factor (filgrastim, Neupogen; filgrastim-sndz, Zarxio) are used to mobilize stem cells from the bone marrow to the peripheral blood to collect an adequate number of PBPCs for transplantation. Filgrastim is the preferred agent as several studies have demonstrated superiority in PBPC mobilization and reduced toxicity compared with sargramostim. The use of pegylated granulocyte colony-stimulating factor (pegfilgrastim, Neulasta) for mobilization of PBPCs is more convenient due to less frequent dosing and is promising as a mobilization agent; however, further data are needed regarding graft composition, HSCT outcomes, and donor safety in allogeneic donations.[10]

The combination of chemotherapy with an HGF enhances PBPC mobilization relative to HGF alone.[1] In addition to treating the underlying malignancy, this approach lowers the risk of tumor cell contamination and the number of apheresis collections required, but there is a greater risk of thrombocytopenia, neutropenia, and hospitalization for neutropenic fever.[10] The HGF is initiated after completion of chemotherapy and is continued until apheresis is complete. Many centers monitor the number of cells that express the CD34 antigen (ie, CD34+ cells) to determine when to start apheresis. The CD34 antigen is expressed on almost all unipotent and multipotent colony-forming cells and on precursors of colony-forming cells, but not on mature peripheral blood cells. Apheresis is continued daily until the target number of PBPCs per kilogram of the recipient's weight is obtained. For adult recipients, the number of CD34+ cells correlates with time to engraftment. Lower yield of CD34+ cells is associated with administration of stem cell toxic drugs (eg, carmustine and melphalan) and intensive prior chemotherapy or radiotherapy, which should be avoided prior to transplant if possible.

LO 3

If patients are unable to obtain an adequate yield of CD34+ cells per kilogram after mobilization attempts fail, then allogeneic transplant may be considered as an alternative. Additionally, plerixafor (Mobozil) is approved by the Food and Drug Administration (FDA) for use in combination with granulocyte colony-stimulating factor to mobilize PBPCs for collection and

subsequent autologous transplantation in patients with NHL and MM. Plerixafor is an inhibitor of the CXCR4 chemokine receptor that results in more circulating PBPCs in the peripheral blood because of the inability of CXCR4 to assist in anchoring hematopoietic stem cells to the bone marrow matrix. Because administration of plerixafor with granulocyte colony-stimulating factor results in increased yield of CD34+ cells per kilogram compared to granulocyte colony-stimulating factor alone, this combination serves as an alternative mobilization strategy in patients deemed to be at risk for mobilization failure with conventional methods.[16]

Allogeneic Transplants The allogeneic donor first undergoes mobilization therapy with an HGF to increase the number of hematopoietic cells circulating in the peripheral blood. The most commonly used regimen to mobilize allogeneic donors is a 4- to 5-day course of filgrastim, 10 mcg/kg/day, administered subcutaneously followed by apheresis on the fourth or fifth days when peripheral blood levels of CD34+ cells peak. An adequate number of hematopoietic cells usually are obtained with one to two apheresis collections, with the optimal number of CD34+ collected being a minimum of 4–8 $\times$ 10^6 cells/kg of recipient body weight. Higher numbers of CD34+ cells are associated with more rapid neutrophil and platelet engraftment; patients who receive less than 2 $\times$ 10^6/kg CD34+ cells are at risk for delayed engraftment.[5] Hematopoietic stem cells obtained from the peripheral blood are processed like bone marrow–derived stem cells and may be infused immediately into the recipient or frozen for future use. Compared with bone marrow donation, allogeneic PBPC donation leads to a shorter time to neutrophil engraftment, shorter time to platelet engraftment and a decrease in platelet transfusions.[11] The donor may experience musculoskeletal pain, headache, and mild increases in hepatic enzyme or lactate dehydrogenase levels related to filgrastim administration. Hypocalcemia may also occur owing to citrate accumulation, which decreases ionized calcium concentrations during apheresis.

Allogeneic PBPC grafts contain approximately 10 times more T and B cells than bone marrow grafts. Historically, there has been significant concern that the greater T- and B-cell content of PBPCs could increase the risk of acute and/or chronic GVHD. No difference in acute GVHD or transplant-related mortality has been reported in patients receiving allogeneic PBPC transplants; however, in retrospective studies an increased risk of chronic GVHD has been observed.[17] In patients with a hematologic malignancy who have an HLA-matched sibling donor, a PBPC graft is optimal relative to bone marrow graft because the PBPC graft is associated with quicker neutrophil and platelet engraftment and potentially improved disease-free survival rates.[18] In patients receiving PBPC transplants from matched unrelated donors, an increased risk of chronic GVHD was reported; however, there was no difference in overall survival, relapse, acute GVHD, or mortality at 2 years. Numerous factors including risk of GVHD and relapse must be considered when selecting an optimal stem cell source for transplantation.[19]

T-Cell Depletion Immunocompetent T lymphocytes may be depleted from the donor bone marrow ex vivo before infusion (referred to as T-cell–depleted hematopoietic cells) into the recipient as a means of preventing GVHD. Depletion of T lymphocytes in donor hematopoietic cells is completed ex vivo using physical (eg, density-gradient fractionation) and/or immunologic (eg, antithymocyte globulin [ATG] antibodies) methods. Functional recovery of T cells in the recipient is delayed, and the risk of Epstein-Barr virus–associated lymphoproliferative disorders is higher with the use of T-cell–depleted bone marrow. The use of T-cell–depleted grafts reduces the incidence of GVHD, but graft failure and relapse are more common.[20] The use of donor lymphocyte infusion in patients who relapse after receiving a T-cell–depleted HSCT is being investigated.

LO 3

Engraftment After chemotherapy and radiation, pancytopenia lasts until the infused stem cells reestablish functional hematopoiesis. The median time to engraftment is a function of several factors, including the source of stem cells such as PBPCs, which can result in earlier engraftment than bone marrow. Myeloablative preparative regimens have significant regimen-related toxicity and morbidity and thus usually are limited to healthy, younger (ie, usually < 50 years) patients. Alternatively, nonmyeloablative transplants and reduced intensity preparative regimens are being used with the hope of curing more patients with cancer by increasing the availability of HSCT with less regimen-related toxicity and by using the graft-versus-tumor effect.[1]

A delicate balance exists between host and donor effector cells in the bone marrow environment. Residual host-versus-graft effects may lead to graft failure, which is also known as graft rejection. Graft failure is defined as the lack of functional hematopoiesis after HSCT and can occur early (ie, lack of initial hematopoietic recovery) or late (ie, in association with recurrence of the disease or reappearance of host cells after initial donor cell engraftment). Engraftment usually is evident within the first 30 days in patients undergoing an HSCT; however, rejection can occur after initial engraftment.

► *Graft-Versus-Tumor Effect*

A graft-versus-tumor effect caused by the donor lymphocytes occurs after transplant. This results in lower relapse rates in patients with GVHD relative to those who did not have GVHD; a higher rate of leukemia relapse after T-cell–depleted, autologous, or syngeneic HSCT; and the effectiveness of donor lymphocyte infusions in reinducing a remission in patients who relapsed after allogeneic HSCT. Rapid taper of immunosuppression in patients with residual disease may induce a graft-versus-tumor effect. In donor lymphocyte infusion, lymphocytes are collected from the peripheral blood of the donor and administered to the recipient. Eradication of the recurrent malignancy is caused by either specific targeting of the tumor antigens or GVHD, which may affect cancer cells preferentially. Patients with hematologic malignancies (eg, CML and acute myelogenous leukemia [AML]) and certain solid tumors (eg, renal cell carcinoma) appear to benefit from a graft-versus-tumor effect. These data gave rise to the use of nonmyeloablative preparative regimens.

Pharmacologic Therapy

► *Preparative Regimens for HSCT*

Examples of commonly used preparative regimens are included in Table 98–2.

Myeloablative Preparative Regimens Myeloablative conditioning refers to regimens of high-dose chemotherapy with or without radiation causing irreversible cytopenias that would lead to death without stem cell support.[4] In both autologous and allogeneic HSCT, infusion of stem cells circumvents this dose-limiting myelosuppression, maximizing the potential value of the steep dose–response curve to alkylating agents and radiation, suppressing the host immune system, and creating space in the marrow compartment to facilitate engraftment. The preparative

Table 98–2

Commonly Used Preparative Regimens for HSCT

Type of HSCT	Preparative Regimen	Dose and Schedule for Adults
Allogeneic	Myeloablative CY-TBI	CY 60 mg/kg/day IV on 2 consecutive days before TBI 10–16 Gy fractionated over 1–7 days (varies)
Allogeneic, autologous	Myeloablative BU-CY	Busulfan 1 mg/kg per dose po or 0.8 mg/kg per dose IV every 6 hours × 16 doses CY 60 mg/kg/day IV daily × 2 days after BU
Allogeneic	Myeloablative BU-FLU[a]	Busulfan 130 mg/m^2 IV daily × 4 days Fludarabine 40 mg/m^2 IV daily × 4 days
Autologous	Myeloablative BEAM (carmustine/etoposide/-cytarabine/melphalan)	Carmustine 300 mg/m^2 IV Etoposide 400–800 mg/m^2 IV given over 4 days Cytarabine 400–1600 mg/m^2 IV given over 4 days Melphalan 140 mg/m^2 IV
Allogeneic	Reduced intensity FLU-MEL	Fludarabine 25–30 mg/m^2 IV daily × 4–5 days Melphalan 100–180 mg/m^2 IV daily × 1 day
Allogeneic	Nonmyeloablative FLU-TBI	Fludarabine 25–30 mg/m^2/day IV daily × 3 days TBI 2 Gy × one dose

[a]Regimen may be considered myeloablative or reduced intensity dependent on busulfan AUC target.

BEAM, carmustine, etoposide, cytarabine, and melphalan; BU-CY, busulfan and cyclophosphamide; BU-FLU, busulfan and fludarabine; CY-TBI, cyclophosphamide–total-body irradiation; FLU-MEL, fludarabine and melphalan; IV, intravenous; po, oral; TBI, total-body irradiation.

Data from Gyurkocza B, Sandeaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014;124:344–353.

regimen is designed to eradicate immunologically active host tissues (lymphoid tissue and macrophages) and to prevent or minimize the development of host-versus-graft reactions. Most allogeneic preparative regimens for the treatment of hematologic malignancies contain cyclophosphamide, radiation, or both. The combination of cyclophosphamide and total-body irradiation (TBI) was one of the first preparative regimens developed and is still used widely today. This regimen is immunosuppressive and has inherent activity against hematologic malignancies (eg, leukemias and lymphomas). TBI has the added advantage of being devoid of active metabolites that might interfere with the activity of donor hematopoietic cells. In addition, TBI eradicates residual malignant cells at sanctuary sites such as the central nervous system. Modifications of the cyclophosphamide–TBI preparative regimen include replacing TBI with other agents (eg, busulfan) or adding other chemotherapeutic or monoclonal agents to the existing regimen in hopes of minimizing long-term toxicities. In the case of a mismatched allogeneic HSCT with a substantially increased chance of graft rejection, ATG also may be added to the preparative regimen to further immunosuppress the recipient through T-cell depletion.

The optimal myeloablative preparative regimen remains elusive as no clinical trial has definitively shown superiority of one regimen. Busulfan–cyclophosphamide (BU-CY) is a chemotherapy-only option used to avoid the toxicities associated with TBI. Busulfan is an alkylating agent with activity in numerous hematologic malignancies. Intravenous busulfan with pharmacokinetic monitoring may improve outcomes when utilized with BU-CY compared to CY-TBI in AML patients although preparative regimens should be tailored to the primary disease and to the degree of HLA compatibility.[21]

Reduced Intensity and Nonmyeloablative Preparative Regimens A reduced intensity preparative regimen is composed of less toxic agents, lower doses of chemotherapy, and radiation, in the hope of being able to offer the benefit of an allogeneic HSCT to more patients with less toxicity. These regimens rely on the concept of a graft-versus-tumor effect. Due to the severe regimen-related toxicity of a myeloablative preparative regimen, the use of HSCT traditionally was limited to younger patients with minimal comorbidities.[22] Most patients diagnosed with cancer are elderly; therefore, myeloablative HSCT could not be offered to a substantial portion of cancer patients. The concept of donor immune response having a graft-versus-tumor effect gave rise to the theory of a strongly immunosuppressive, but not completely myeloablative, preparative regimen (ie, transplant may result in a state of chimerism in which the recipient and donor are coexisting). Reduced intensity is an intermediate category of reduced dose chemotherapy that may be considered myeloablative or nonmyeloablative. Fludarabine, a purine analog, is commonly used due to potent immunosuppressive effects in combination with lower dose alkylating agents (eg, busulfan, melphalan) or TBI.

Nonmyeloablative regimens cause minimal cytopenias and do not require stem cell support.[4] These preparative regimens

Patient Encounter Part 1

A 44-year-old woman is diagnosed with acute myeloid leukemia with complex cytogenetics. The patient achieved complete remission with induction chemotherapy and is now being evaluated for an allogeneic stem cell transplant. She has two siblings that underwent HLA typing at her first clinic visit and the results of the test will be available today. Her transplant preparative regimen will consist of cyclophosphamide and busulfan.

What nonhematologic toxicities are associated with the preparative regimen?

What type of preparative regimen is this patient receiving? How does this differ from other types of preparative regimens?

What are the implications for this patient if neither of her sisters are an HLA match?

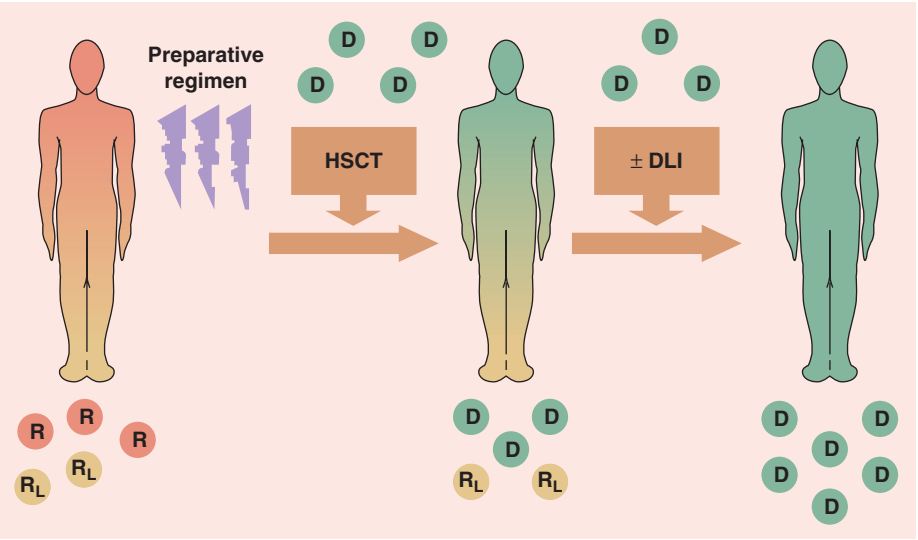

FIGURE 98–1. Schema for nonmyeloablative transplantation. Recipients (R) receive a nonmyeloablative preparative regimen and an allogeneic hematopoietic stem cell transplantation (HSCT). Initially, mixed chimerism is present with the coexistence of donor (D) cells and recipient-derived normal and leukemia or lymphoma (R_L) cells. Donor-derived T cells mediate a graft-versus-host hematopoietic effect that eradicates residual recipient-derived normal and malignant hematopoietic cells. Donor-lymphocyte infusions (DLIs) may be administered to enhance graft-versus-tumor effects. (Reprinted with permission from Champlin R, Khouri I, Anderlini P, et al. Nonmyeloablative preparative regimens for allogeneic hematopoietic transplantation. Blood Marrow Transplantation. 2001:27:S13–S22.)

allow for development of mixed chimerism (defined as 5%–95% peripheral donor T cells) between the host and recipient to allow for a graft-versus-tumor effect as the primary form of therapy (Figure 98–1). Chimerism is assessed within peripheral blood T cells and granulocytes and bone marrow using conventional (eg, using sex chromosomes for opposite-sex donors) and molecular (eg, variable number of tandem repeats) methods for same-sex donors.

The nonmyeloablative preparative regimen does not completely eliminate host normal and malignant cells. Donor cells eradicate residual host hematopoiesis, and the graft-versus-tumor effects generally occur after the development of full donor T-cell chimerism. After chimerism develops, donor-lymphocyte infusion can be administered safely in patients without GVHD to eradicate malignant cells. The risk of GVHD remains with nonmyeloablative transplant; the GVHD prophylaxis regimens are reviewed in the GVHD section below.

Reduced intensity preparative regimens have made HSCT available to patients who in the past were not healthy or young enough to receive a myeloablative preparative regimen.[22] The role of these regimens needs to be further defined, as although transplant-related mortality due to toxicity is reduced, relapse and GVHD are the major causes of treatment failure.

Toxicities and Management of Preparative Regimens Myelosuppression is a frequent dose-limiting toxicity for antineoplastics when administered in the conventional doses used to treat cancer. However, because myelosuppression is circumvented with hematopoietic rescue in the case of patients receiving HSCT, the dose-limiting toxicities of these myeloablative preparative regimens are nonhematologic and vary with the preparative regimen used. Most patients undergoing HSCT experience toxicities commonly associated with chemotherapy (eg, alopecia, mucositis, nausea and vomiting, and infertility), albeit these toxicities are magnified in the HSCT population.

LO 4

Busulfan Seizures Seizures have been reported in both adult and pediatric patients receiving high-dose busulfan for HSCT preparative regimens. Anticonvulsants are used to minimize the risk of seizures. Anticonvulsants are begun shortly before busulfan, with the loading dose completed at least 6 hours before the first busulfan dose. Oral loading and maintenance regimens generally are sufficient because target phenytoin concentrations of 10 to 20 mcg/mL (10–20 mg/L; 40–79 µmol/L) can be achieved by the peak time of seizure risk. Due to drug interactions and adverse effects, alternatives to phenytoin are being investigated. Benzodiazepines such as lorazepam or clonazepam and the second-generation antiepileptic drug levetiracetam have been used for seizure prophylaxis during high-dose busulfan therapy before HSCT.[23] Antiseizure medications usually are discontinued 24 to 48 hours after administration of the last dose of busulfan. Seizures still can occur despite the use of prophylactic anticonvulsants and usually do not result in permanent neurologic deficits.

Adaptive Dosing of Busulfan The considerable interpatient variability in the clearance of both oral and IV busulfan along with the identified concentration–effect relationships has led to the adaptive dosing of busulfan. Adjusting the oral busulfan dose to achieve a target concentration minimizes the toxicities of the BU-CY regimen, particularly hepatic sinusoidal obstruction syndrome (SOS; formerly referred to as veno-occlusive disease) while improving engraftment and relapse rates. Complete reviews of these relationships after oral busulfan administration are available elsewhere.[24] An IV busulfan product, Busulfex, was approved by the FDA in February 1999 in combination with cyclophosphamide as a preparative regimen before allogeneic HSCT for CML. In combination with either cyclophosphamide or fludarabine, the data available with busulfan suggest that therapeutic drug monitoring may be needed to optimize patient outcome with regards to efficacy and toxicity.[25]

LO 4 **Hemorrhagic Cystitis** High-dose cyclophosphamide causes moderate to severe hemorrhagic cystitis; acrolein, a metabolite of cyclophosphamide, is the putative bladder toxin. Preventive measures to lower the risk of hemorrhagic cystitis include vigorous hydration, continuous bladder irrigation, or concomitant use of the uroprotectant mesna. The American Society of Clinical Oncology (ASCO) Guidelines for the Use of Chemotherapy and Radiotherapy Protectants recommends the use of Mesna (2-mercaptoethane sulfonate) plus saline diuresis or forced saline diuresis to lower the incidence of urothelial toxicity with high-dose cyclophosphamide in the setting of HSCT.[26]

LO 4 **Chemotherapy-Induced Gastrointestinal Effects** Preparative regimens for myeloablative HSCT result in other end-organ toxicities such as renal failure and idiopathic pneumonia syndrome. In addition, recipients of myeloablative preparative regimens are at risk for severe gastrointestinal (GI) toxicity, specifically chemotherapy-induced nausea and vomiting (CINV), diarrhea, and mucositis. CINV can be caused by administration of highly emetogenic chemotherapy over several days, TBI, and poor control of CINV before HSCT. Thus, patients who are undergoing a myeloablative HSCT are at high risk for acute and delayed CINV in the peritransplant period, and the prevention and treatment of CINV should be addressed accordingly as per published clinical practice guidelines.[27]

Diarrhea is also an adverse effect experienced by a majority of patients undergoing HSCT. Chemotherapy-induced diarrhea occurs because of the effects of the preparative regimen, which results in inflammation and damage to the cells lining the GI tract. Diarrhea caused by the preparative regimen is usually apparent within the first week after the initiation of chemotherapy and/or radiation. Treatment strategies for chemotherapy-induced diarrhea include the administration of antidiarrheals after excluding infectious causes of diarrhea and the prevention of dehydration.

Virtually all patients receiving a myeloablative preparative regimen experience severe mucositis owing to its effects on rapidly dividing cells of the oral epithelium and subsequent inflammation of the oropharyngeal cavity. Routine oral care protocols are indicated to reduce the severity of mucositis, which may onset within the first week of HSCT and persist for up to approximately 2 weeks. Palifermin, a keratinocytic growth factor, may be considered for patients undergoing autologous HSCT with myeloablative TBI-based preparative regimens.[28] Patients may require parenteral opioid analgesics for pain relief owing to mucositis, and total parenteral nutrition may be necessary to prevent the development of nutritional deficiencies.

LO 4 **Sinusoidal Obstruction Syndrome** Hepatic SOS is a life-threatening complication that may occur secondary to preparative regimens or radiation. The pathogenesis of SOS is not understood completely, but several mechanisms have been proposed. The key event appears to be endothelial damage caused by the preparative regimen. The primary site of the toxic injury is the sinusoidal endothelial cells; the endothelial damage initiates the coagulation cascade, induces thrombosis of the hepatic venules, and eventually leads to fibrous obliteration of the affected venules.[29]

The clinical manifestations of SOS are hyperbilirubinemia, jaundice, fluid retention, weight gain, and right upper quadrant abdominal pain. To make a clinical diagnosis of SOS, these features must occur in the absence of other causes of posttransplant liver failure, including GVHD, viral hepatitis, fungal abscesses, or drug reactions. Most cases of SOS occur within 3 weeks of HSCT, and the clinical diagnosis can be confirmed histologically via liver biopsy.

Patients with mild SOS have an excellent prognosis, but those with more severe disease (ie, bilirubin > 20 mg/dL [342 μmol/L] or weight gain > 15%) have a high mortality rate. Pretransplant risk factors for SOS include a mismatched or unrelated graft, increased age, prior abdominal radiation or stem cell transplant, and increased transaminases before HSCT.[29] Interpatient variability in the metabolism and clearance of the chemotherapy (ie, busulfan and cyclophosphamide) used within the preparative regimen also may be associated with a poor outcome, although the relationships vary within the various preparative regimens. The association of SOS with busulfan concentrations is discussed in the section on adaptive dosing of busulfan. Use of ursodiol, unfractionated heparin, or low-molecular-weight heparin has been associated with a lower incidence of SOS in a limited number of small, randomized studies and may be recommended for SOS prophylaxis.[29]

The mainstay of treatment for established SOS is supportive care aimed at sodium restriction, increasing intravascular volume, decreasing extracellular fluid accumulation, and minimizing factors that contribute to or exacerbate hepatotoxicity and encephalopathy. Recombinant tissue plasminogen activator administered with or without heparin has been investigated for treatment of SOS, but the life-threatening risk of bleeding precludes any potential benefit.[29] Defibrotide, an oligonucleotide with antithrombotic, anti-ischemic, and anti-inflammatory activity, is FDA approved for the treatment of SOS in patients with renal or pulmonary dysfunction following HSCT, due to decreased mortality observed within this population in clinical trials.[29]

Myelosuppression and Hematopoietic Growth Factor Use HGFs may be administered to mobilize PBPCs before an HSCT, to hasten hematopoietic recovery during the period of aplasia after an autologous HSCT, and to stimulate hematopoietic recovery when the patient fails to engraft.[30]

Autologous HSCT is associated with profound aplasia owing to the myeloablative preparative regimen. Aplasia typically lasts 7 to 14 days after an autologous PBPC transplant. During this period of aplasia, patients are at high risk for complications such as bleeding and infection. HGFs exert their effects by stimulating the proliferation of committed progenitor cells and accelerating recovery on hematopoiesis. Once engraftment occurs, HGFs may be discontinued. The anatomic source of hematopoietic cells predicts the degree of benefit, with the greatest benefit reached when bone marrow is the graft source. With autologous PBPC transplant, the effect of HGF on neutrophil recovery is variable.

The use of HGF after allogeneic HSCT—whether from bone marrow or PBPC grafts—is controversial. The data with filgrastim after allogeneic HSCT have shown more rapid neutrophil but slower platelet engraftment in those receiving grafts from bone marrow or PBPCs.[30,31] The effects of post-HSCT filgrastim use on acute and chronic GVHD have been conflicting, with either no effect or increases in both the incidence of acute and chronic GVHD and treatment-related mortality.[31] Thus, there is little reason to treat allogeneic HSCT recipients with filgrastim as prophylaxis after HSCT and limited data exists with other HGFs in this setting.[30]

Graft Failure A delicate balance between host and donor effector cells in the bone marrow is necessary to ensure adequate engraftment because residual host-versus-graft effects may lead to graft rejection. The incidence of graft rejection is higher

Patient Encounter Part 2

The patient is excited to learn that her younger sister is an 8 of 8 HLA match and she will donate peripheral blood stem cells. Based on this information, her physician decides on a GVHD prophylaxis regimen consisting of tacrolimus and methotrexate. She has many questions on her risk of infection after HSCT, especially while on these immunosuppressive medications in the hospital setting.

What are the advantages and disadvantages of obtaining and infusing hematopoietic stem cells from a peripheral blood stem cell source as opposed to a bone marrow source?

When will this patient's calcineurin inhibitor start and why? What monitoring parameters are necessary for this medication to ensure safety and efficacy?

What infectious complications are of a concern for this patient during the early transplant period?

in patients with aplastic anemia and those undergoing HSCT with histoincompatible marrow or T-cell–depleted marrow.[1] Graft rejection is uncommon in leukemia patients receiving myeloablative preparative regimens with a histocompatible allogeneic donor.

Clinical Presentation and Diagnosis of Sinusoidal Obstructive Syndrome

General

- Sinusoidal obstructive syndrome (SOS) usually occurs within the first 3 weeks after HSCT.
- Busulfan, cyclophosphamide, pretransplant exposure to gemtuzumab, TBI-containing preparative regimens, and pretransplant abnormalities in liver function tests may increase the risk for SOS.

Symptoms

- Patients may complain of weight gain and abdominal pain.

Signs

- Fluid retention: Weight gain caused by ascites greater than 5% compared with pretransplant weight
- Hepatomegaly: May result in right upper quadrant pain
- Hepatic: Jaundice caused by hyperbilirubinemia defined as a bilirubin greater than 2 mg/dL (34.2 µmol/L)

Laboratory Tests

- Hepatic: Elevation of bilirubin, alkaline phosphatase, and γ-glutamyltransferase (GGT)
- Hematologic: Complete blood count with differential may reveal thrombocytopenia, elevated plasminogen activator-1 levels, decreased antithrombin III, protein C, and protein S

Other Diagnostic Tests

- Reversal of blood flow in portal and hepatic veins on Doppler ultrasonography
- Liver biopsy for pathologic review

Therapeutic options for the treatment of graft rejection or graft failure are limited. A second HSCT is the most definitive therapy, although the associated complications and toxicities may preclude its use. Graft rejection is best managed with immunosuppressants such as ATG. Primary graft failure occasionally can be treated successfully using HGFs, although patients who received purged autografts are less likely to respond.

▶ *Graft-Versus-Host Disease*

KEY CONCEPT GVHD is caused by the activation of donor lymphocytes, leading to immune damage to the skin, gut, and liver in the recipient. Immune-mediated destruction of tissues, a hallmark of GVHD, disrupts the integrity of protective mucosal barriers and thus provides an environment that favors the establishment of opportunistic infections. KEY CONCEPT An immunosuppressive regimen is administered to prevent GVHD in recipients of an allogeneic graft; this regimen is based on the type of preparative regimen and the source of the graft. The combination of GVHD and infectious complications are leading causes of mortality for allogeneic HSCT patients. GVHD is divided into two forms (ie, acute and chronic) based on clinical manifestations. Traditionally, the boundary between acute and chronic GVHD was set at 100 days after HSCT; however, more recent definitions hinge upon different clinical symptoms rather than the time of onset.[32,33]

Acute GVHD The degree of histocompatibility between donor and recipient is the most important factor associated with the development of acute GVHD. The pathophysiology for acute GVHD is a multistep phenomenon, including the development of an inflammatory milieu that results from host tissue damage induced by the preparative regimen; both recipient and donor antigen-presenting cells and inflammatory cytokines triggering activation of donor-derived T cells; and the activated donor T cells mediate cytotoxicity through a variety of mechanisms, which leads to tissue damage characteristic of acute GVHD.[33] LO 5

Despite prophylaxis, 20% to 80% of patients will develop acute GVHD.[34] Other factors that increase the risk of acute GVHD include increasing recipient or donor age (older than 20 years), female donor to a male recipient, and mismatches in minor histocompatibility antigens in HLA-matched transplants.[33] T-cell depletion or receipt of a UCB graft appears to lower the risk of acute GVHD.[1]

Clinical Presentation and Staging of Acute GVHD Acute GVHD targets the skin, liver, and GI tract; it must be distinguished accurately from other causes of skin, liver, or GI toxicity in HSCT patients. Other causes of toxicities affecting the skin, liver, or GI tract may include a drug reaction or an infectious process. A staging system based on clinical criteria is used to grade acute GVHD (Figure 98–2). The severity of organ involvement is scored on an ordinal scale from 0 (no symptoms) to IV (severe symptoms), and then an overall grade is established based on the number and extent of involved organs.

Immunosuppressive Prophylaxis of Acute GVHD GVHD is a leading cause of morbidity and mortality after allogeneic HSCT and thus, efforts have focused on preventing acute GVHD. The donor graft and preparative regimen influence the prophylactic regimen for acute GVHD, with two approaches having been taken by clinicians over time. One approach involves T-cell depletion, which was discussed more fully in the section on T-cell depletion earlier. The more common method is to use two-drug immunosuppressive therapy that typically consists of a calcineurin inhibitor (ie, cyclosporine or tacrolimus) with LO 6

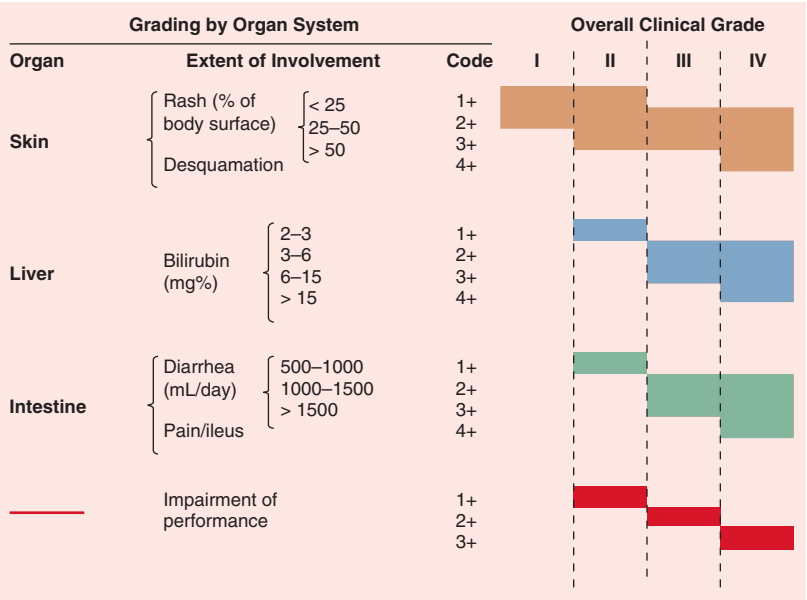

FIGURE 98–2. Staging system for graft-versus-host disease.

methotrexate after myeloablative HSCT. Prophylaxis of acute GVHD for preparative regimens may be varied based on regimen intensity and stem cell source; the role of additional agents such as cyclophosphamide, sirolimus, mycophenolate mofetil, and monoclonal antibodies is currently being studied in acute GVHD prophylaxis trials.[33]

The calcineurin inhibitors (ie, cyclosporine and tacrolimus) should be initiated before donor cell infusion (eg, day –1) when used for GVHD prophylaxis. This schedule is recommended because of the known mechanism of action of calcineurin inhibitors, which entails blocking the proliferation of cytotoxic T cells by inhibiting production of T helper cell–derived interleukin-2 (IL-2). Administering calcineurin inhibitors before the donor cell infusion allows inhibition of IL-2 secretion to occur before a rejection response has been initiated. Studies comparing cyclosporine and tacrolimus in combination with methotrexate have shown that tacrolimus administration is associated with a lower incidence of grade II to IV acute GVHD and a similar incidence of chronic GVHD but variable effects on overall survival.[35,36]

Adaptive Dosing of the Calcineurin Inhibitors Most HSCT centers have their own standardized approach to dose adjust the calcineurin inhibitors cyclosporine and tacrolimus to target concentration ranges. Cyclosporine and tacrolimus trough concentrations are associated with acute GVHD and nephrotoxicity. Cyclosporine trough concentrations usually are maintained between 150 and 400 ng/mL (125 and 333 nmol/L) in patients undergoing allogeneic HSCT. Tacrolimus trough concentrations are targeted to a range of 5 to 15 ng/mL (6.2–18.6 nmol/L).[33,37] Dosage adjustments to either calcineurin inhibitor also should be made for elevated serum creatinine regardless of their serum concentrations. Nephrotoxicity can occur despite low or normal concentrations of the calcineurin inhibitor cyclosporine and may be a consequence of other drug- or disease-related factors known to influence the development of nephrotoxicity (eg, genetic risk factors, concurrent use of other nephrotoxic agents, and sepsis). Careful monitoring for drug interactions via CYP 3A4 and P-glycoprotein is also warranted. The calcineurin inhibitor doses are adjusted based on serum drug levels and the calculated creatinine clearance. Common adverse effects to these agents include neurotoxicity, hypertension, hyperkalemia, hypomagnesemia, and/or nephrotoxicity (which may lead to an impaired clearance of methotrexate).

Clinical Presentation and Diagnosis of Acute Graft-Versus-Host Disease

General

- Patients may present with any or all of the following: Skin rash, GI complaints, or jaundice.
- Signs and symptoms present after engraftment when donor lymphoid elements begin to proliferate.

Symptoms

- Patients may complain of nausea, vomiting, bloody diarrhea, or itching from skin rash.

Signs

- Skin: Maculopapular skin rash on the face, truck, extremities, palms, soles, and ears which may progress to generalized total-body erythroderma, bullous formation, and skin desquamation
- GI: Ileus, malnutrition, dehydration and electrolyte abnormalities due to nausea, vomiting, and diarrhea
- Hepatic: Jaundice due to hyperbilirubinemia

Laboratory Tests

- Hepatic: Elevation of bilirubin, alkaline phosphatase, and hepatic transaminases
- GI: Send stool for bacterial, viral, and parasitic cultures to rule out infectious causes

Other Diagnostic Tests

- Biopsy of affected site for pathologic review

Tapering schedules for the calcineurin inhibitors after myeloablative HSCT vary widely. In patients without GVHD, the calcineurin inhibitor doses usually are stable for the first 3 months after HSCT and then are tapered slowly with the intent of discontinuing all immunosuppressive agents by 6 months after HSCT. By this time, immunologic tolerance has developed, and patients no longer require immunosuppressive therapy. There is a paucity of information regarding the optimal duration of GVHD prophylaxis after nonmyeloablative HSCT and immunosuppression taper schedules may be individualized based on GVHD and disease-specific factors.[33]

Treatment of Acute GVHD The most effective way to treat GVHD is to prevent its development. Corticosteroids, usually in combination with a calcineurin inhibitor, are the first-line therapy for treatment of established acute GVHD. Corticosteroids indirectly halt the progression of immune-mediated destruction of host tissues by blocking macrophage-derived IL-1 secretion. IL-1 is a primary stimulus for T helper cell–induced secretion of IL-2, which, in turn, is responsible for stimulating proliferation of cytotoxic T lymphocytes. The recommended dosage of methylprednisolone in this setting is 2 mg/kg/day; there is no advantage to higher corticosteroid doses (ie, 10 mg/kg/day).[34] A partial or complete response is seen in approximately 50% of patients treated with corticosteroids. Once a clinical improvement occurs, there is no consensus on the optimal method for tapering the corticosteroids. Patients with steroid-refractory acute GVHD have a poor prognosis, and a number of medications are being studied for salvage therapy.

Chronic GVHD Chronic GVHD is a major cause of nonrelapse mortality and morbidity in allogeneic HSCT recipients with up to 40% of patients requiring systemic therapy within 2 years of HSCT.[38] The clinical course of chronic GVHD is multifaceted, involving almost any organ in the body, and its symptoms resemble autoimmune and immunologic disorders (eg, scleroderma). Chronic GVHD symptoms usually present within 1 year after allogeneic HSCT and often are preceded by acute GVHD, although up to 10% of cases present later.[38] Traditionally, the boundary between acute and chronic GVHD was set at 100 days after HSCT; however, more recent definitions hinge on different clinical symptoms rather than the time of onset.[32] A consensus document regarding the diagnosis and scoring of chronic GVHD has been published that proposes a clinical scoring system to describe chronic GVHD as opposed to historical descriptions of chronic GVHD, which described the phenomenon as being "limited" versus "extensive" in nature.[32] The diagnosis of chronic GVHD requires distinction from acute GVHD; the presence of at least one diagnostic clinical sign of chronic GVHD or presence of at least one distinctive manifestation confirmed by pertinent biopsy or other relevant tests; and exclusion of other possible diagnoses.

Prevention and Treatment of Chronic GVHD Chronic GVHD is not a continuation of acute GVHD, and separate approaches are needed for its prevention and management. Prevention of chronic GVHD through prolonged use of immunosuppressive medications has been unsuccessful.[39] Thus, its prevention is focused on minimization of factors associated with higher rates of chronic GVHD. Several recipient, donor, and transplant factors are relevant. Recipient risk factors that are not modifiable include older age, certain diagnoses (eg, chronic myeloid leukemia), and lack of an HLA-matched donor. Modifiable factors that may lower the risk of chronic GVHD include selection of a younger donor, avoidance of a multiparous female donor, use of UCB or bone marrow grafts rather than PBPCs, and limitation of CD34+ and T-cell dose infused.[39] Development of acute GVHD is a major predictor for chronic GVHD, with 70% to 80% of those with grade II to IV acute GVHD developing chronic GVHD.[39]

Relative to no treatment, survival in those with chronic GVHD is improved by extended corticosteroid therapy; however, multiple long-term adverse effects are associated with corticosteroid use. The prednisone dosage is 1 mg/kg/day administered orally in divided doses for 30 days and then slowly converted to an alternate-day therapy. One to two months may pass before an improvement in clinical symptoms is noted, and therapy usually is continued for 9 to 12 months. Therapy can be tapered slowly after resolution of signs and symptoms of chronic GVHD. If a flare of chronic GVHD occurs during the tapering schedule or after therapy is discontinued, immunosuppressive therapy is restarted. Ibrutinib has been approved for treatment of chronic GVHD after failure of at least one treatment option. Other potential approaches for patients who are refractory to initial therapy include etanercept (Enbrel), infliximab (Remicade), mycophenolate mofetil (Cellcept), rituximab (Rituxan), extended use of calcineurin inhibitors, or extracorporeal photochemotherapy.[39] When immunosuppressive therapy is administered for long periods, the patient must be monitored closely for chronic toxicity. Cushingoid effects, aseptic necrosis of the joints, and diabetes can develop with long-term corticosteroid use. Other severe complications include a high incidence of infection with encapsulated organisms and atypical pathogens such as *Pneumocystis jiroveci*, cytomegalovirus (CMV), and varicella zoster virus (VZV).

▶ *Infectious Complications*

KEY CONCEPT Recipients of HSCT are at higher risk of bacterial, viral, and fungal infections and usually receive a prophylactic or preemptive regimen to minimize the morbidity and mortality associated with infectious complications. After myeloablative and nonmyeloablative HSCT, opportunistic infections are a major source of morbidity and mortality. There are three periods of infectious risks, preengraftment (from 15 days prior and to 45 days after HSCT), postengraftment (engraftment to day 100 post engraftment), and late (100 days after engraftment).

Patient Encounter Part 3

The patient is admitted for allogeneic HSCT with a preparative regimen consisting of busulfan and cyclophosphamide. Her hospital course was complicated for neutropenic fever and gastrointestinal toxicities. Neutrophil engraftment occurred on day +14 after HSCT, and the patient was discharged from the hospital on day +16 with minimal complaints. She presents to the transplant clinic on day +25 complaining of a skin rash covering 50% of her body surface including on her palms, arms, soles, and trunk. She also reports being persistently nauseous and having multiple stools throughout the day. After further evaluation, she is diagnosed with GVHD of the skin and intestinal tract.

What grade of GVHD is this patient likely experiencing and how should this be managed?

How should this patient be monitored for progression of GVHD?

From days 0 to 30 after HSCT, particularly for patients undergoing myeloablative HSCT, the primary pathogens are aerobic bacteria, *Candida* spp., and herpes simplex virus (HSV). Respiratory viruses such as respiratory syncytial virus (RSV), influenza, adenovirus, and parainfluenza virus are recognized increasingly as pathogens causing pneumonia, particularly during community outbreaks of infection with these organisms. Because of the need to administer chemotherapy, blood products, antibiotics, and other adjunctive medications, the placement of a semipermanent double- or triple-lumen central venous catheter is necessary before HSCT. However, the indwelling IV central catheters put HSCT recipients at increased risk for *Staphylococcus* infections.

The second period of infectious risk occurs after engraftment to posttransplant day 100. Bacterial infections are still of concern, but pathogens such as CMV, adenovirus, and *Aspergillus* spp. are common. A common manifestation of infection is interstitial pneumonitis (IP), which can be caused by CMV, adenovirus, *Aspergillus,* and *P. jiroveci*. Suppression of the immune system from acute GVHD and corticosteroids contributes to the risk of such infections during this period.[40]

During the late period (100 days after engraftment), the predominant organisms are the encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*), fungi, and VZV. The encapsulated organisms commonly cause sinopulmonary infections. The risk of infection during this late period is increased in patients with chronic GVHD as a result of prolonged immunosuppression.

Prevention and Treatment of Bacterial and Fungal Infections Between the time of administration of the preparative regimen and successful engraftment, allogeneic myeloablative HSCT patients undergo a period of pancytopenia that can last from 2 to 6 weeks. The risk of infection is also reduced by aggressive use of antibacterial, antifungal, and antiviral therapy both prophylactically and for the treatment of documented infection. The antibacterial prophylactic regimens vary substantially among HSCT centers. Some HSCT centers use a prophylactic fluoroquinolone (eg, levofloxacin) on admission for HSCT and then switch to a broad-spectrum IV antibiotic (eg, cefepime) when the patient experiences his or her first neutropenic fever. Although fluoroquinolones reduce the incidence of gram-negative bacteremia, they have not been shown to affect mortality; the possibility of developing clostridium difficile-associated diarrhea exists with fluoroquinolone use and infectious causes should be ruled out if diarrhea occurs. Concerns with fluoroquinolone use in the prophylactic setting during HSCT include the emergence of resistant organisms and an increased risk for streptococcal infection. Broad-spectrum IV antibiotics should be initiated immediately at the time of the first neutropenic fever under the treatment guidelines endorsed by the Infectious Disease Society of America for management of fever of unknown origin in the neutropenic host.[41]

Prevention of HSV and VZV Patients who are HSV antibody seropositive before HSCT are at high risk for reactivation of their HSV infection. Acyclovir is highly effective in preventing HSV reactivation, and thus, prophylactic acyclovir is used commonly in HSV-seropositive patients who are undergoing an allogeneic or autologous HSCT. In the setting of HSV prophylaxis, dosing regimens for prophylactic acyclovir vary widely.[40] Valacyclovir (Valtrex), a prodrug of acyclovir with improved bioavailability, may allow for adequate serum concentrations to prevent HSV in patients undergoing HSCT as well.

In those with a history of VZV infection, VZV disease occurs in 30% of allogeneic HSCT recipients.[42] The appropriate duration of VZV prophylaxis is controversial. Although VZV infections are reduced by prophylactic acyclovir administered from 1 to 2 months until 1 year after HSCT, the risk of VZV persists in those on continued immunosuppression.[40]

Prevention and Preemptive Therapy of CMV Disease After allogeneic HSCT, CMV disease is common and has high morbidity and mortality rates. Allogeneic patients are at greater risk than autologous recipients primarily because the latter more efficiently reconstitute their immune system after transplantation. Infection caused by CMV is usually asymptomatic and develops when CMV replication occurs. Replication occurs primarily in body fluids such as the blood (viremia), bronchoalveolar fluid, or urine (viruria). CMV disease is symptomatic and occurs when the virus invades an organ or tissue. Pneumonia and gastritis are the most common types of CMV disease after allogeneic HSCT. The presence of a CMV infection substantially increases the risk for developing invasive CMV disease. Strategies to prevent CMV infection have resulted in dramatic reductions in the incidence of CMV disease.

Primary CMV can be prevented with CMV seromatching, which includes transplanting PBPCs or bone marrow from CMV-seronegative donors and infusing CMV-negative blood products to CMV-negative recipients. Antivirals are important in those who are CMV seropositive or have a CMV-seropositive graft, with two available approaches to minimize the morbidity associated with CMV. The first is universal prophylaxis, in which ganciclovir is begun at the time of engraftment and is continued until approximately 100 days after engraftment. The second approach is called preemptive therapy, for which ganciclovir is selectively administered based on detection of CMV reactivation.

Preemptive therapy is the most commonly used strategy for preventing CMV disease after allogeneic HSCT because ganciclovir is used only in patients at highest risk for developing CMV disease. This approach minimizes administration of ganciclovir, thus lowering the risk of ganciclovir-induced neutropenia with its subsequent increased risk of invasive bacterial and fungal infections. Preemptive strategies typically use an induction course of ganciclovir for 7 to 14 days followed by a maintenance course until 2 or 3 weeks after the last positive antigenemia result or until 100 days after HSCT.[40] Oral valganciclovir (Valcyte) is an orally bioavailable prodrug of ganciclovir that is converted to ganciclovir in vivo after intestinal absorption and has been used for preemptive therapy. Foscarnet may be given as an alternative to ganciclovir to prevent CMV disease, although its use is complicated by nephrotoxicity and electrolyte wasting.

Fungal Infections

▶ *Prevention of Fungal Infections*

The widespread use of fluconazole prophylaxis since the early 1990s has led to a significant decline in the morbidity and mortality associated with invasive candidiasis in HSCT recipients. However, invasive aspergillosis (IA); zygomycetes; and fluconazole-resistant *Candida* spp., such as *Candida krusei* and *Candida glabrata,* have increased markedly in incidence.[43] Itraconazole, another azole antifungal agent, has better in vitro activity against fluconazole-resistant fungi (eg, *Aspergillus* and some *Candida* spp.) and is more effective than fluconazole for long-term prophylaxis of invasive fungal infections after allogeneic HSCT; however, itraconazole is used less often because of frequent GI side effects

and concern for potential drug interactions.[44] Posaconazole (Noxafil) is a triazole antifungal that has been approved by the FDA for prophylaxis against IA in HSCT patients with GVHD and is now the recommended prophylactic agent for this subset of HSCT patients on immunosuppression. Posaconazole oral suspension should be given with food for adequate absorption. The posaconazole tablet can be administered without regard to food. Micafungin (Mycamine), an agent of the newer class of antifungals known as the echinocandins, has been FDA approved for prophylaxis of *Candida* infections in patients undergoing HSCT.

▶ Risk Factors for Invasive Mold Infections

Invasive mold infections (eg, *Aspergillus* spp., *Fusarium* spp., *Zygomycetes*, and *Scedosporium* spp.) are an increasing cause of morbidity and death after allogeneic and autologous HSCT. It has been estimated that up to one-third of febrile neutropenic patients who do not respond to antibiotic therapy after 1 week are harboring a fungal infection.[41] In HSCT recipients, risk factors for invasive fungal infections include previous history of IA; recipient factors, including older age, CMV seropositivity, and type of stem cell transplant; treatment factors (eg, a fludarabine-based preparative regimen); transplant complications (eg, prolonged neutropenia, graft failure, and higher grade GVHD); and host factors (eg, diabetes, iron overload).[45] Infections with *Aspergillus* spp. remain the most common mold infections diagnosed in the HSCT population and optimal treatment must be promptly initiated if indicated.

▶ Treatment of Invasive Aspergillosis

Early diagnosis and initiation of appropriate therapy may reduce the high mortality rate of IA. Outcomes also depend on recovery of the recipient's immune system and reduction of immunosuppression. Diagnosis is difficult with the use of computed tomography scans and cultures. Research is ongoing to evaluate the benefit of using nonculture-based methods, such as galactomannan and (1,3)-β-D-glucan antigen detection, which are components of the fungal cell wall that can be detected by commercially available assays.

Practice guidelines are available for the treatment of invasive *Aspergillus* infections in immunocompromised patients.[46] Available mold-active agents include triazole antifungals (itraconazole, voriconazole, posaconazole, and isavuconazole), echinocandins (caspofungin, micafungin, and anidulafungin), and amphotericin B formulations.

The optimal duration of appropriate antifungal therapy for treating IA is individualized to the reconstitution of the patient's immune system and his or her response to antifungal treatment. Most clinicians continue aggressive antifungal therapy until the infection has stabilized radiographically and may continue with less aggressive "maintenance" therapy (eg, oral voriconazole) until immunosuppression is lessened or completed. In general, it is common to require several months of antifungal therapy to treat IA.

▶ Pneumocystis jiroveci

After allogeneic HSCT, prophylaxis for *P. jiroveci* (formerly *P. carinii*) pneumonia (PJP) is used because *Pneumocystis* is a serious infection with a high mortality rate if left untreated. Most centers use sulfamethoxazole/trimethoprim for 6 to 12 months after HSCT;[40] aerosolized or IV pentamidine and oral dapsone are alternatives for patients who are allergic to sulfa drugs or who do not tolerate sulfamethoxazole/trimethoprim. Because PJP most often occurs after engraftment, sulfamethoxazole/trimethoprim usually is begun after neutrophil recovery because of its myelosuppressive effects. Patients receiving prophylactic sulfamethoxazole/trimethoprim should be monitored closely for rash and unexplained neutropenia or thrombocytopenia. Sulfamethoxazole/trimethoprim usually is avoided on days of methotrexate administration because the sulfonamides can displace methotrexate from plasma binding sites and decrease renal methotrexate clearance, resulting in higher methotrexate concentrations. Autologous HSCT patients do not receive posttransplant immunosuppression, and thus, their risk of developing PJP is lower.[40] PJP prophylaxis is used often after autologous HSCT in patients with a hematologic malignancy.

▶ Issues of Survivorship After HSCT

The number of long-term HSCT survivors is increasing as 5-year disease-free survival rates improve. HSCT recipients—with either an autologous or an allogeneic graft—have a higher mortality rate than the general population.[47] KEY CONCEPT Long-term survivors of HSCT should be monitored closely, particularly for infections and secondary malignant neoplasms.

LO 8

Survivors of HSCT are at higher risk for secondary malignant neoplasms.[47] Long-term impairment of end-organ function, including the kidneys, liver, and lungs, may be caused by the preparative regimen, infectious complications, and/or posttransplant immunosuppression. Many HSCT recipients experience endocrine dysfunction, such as hypothyroidism from TBI, adrenal insufficiency from long-term corticosteroids to treat GVHD, and infertility from radiation and/or high doses of alkylating agents in myeloablative preparative regimens. Osteopenia has been found in more than half of HSCT recipients, most likely from gonadal dysfunction and/or corticosteroid administration.

Close monitoring of HSCT recipients for infections is necessary because recovery of immune function is slow, sometimes requiring more than 2 years, even in the absence of immunosuppressants.[47] Fevers should be assessed and treated rapidly to minimize the likelihood of a fatal infection. HSCT recipients—both autologous and allogeneic—lose protective antibodies to vaccine-preventable diseases; international guidelines have been published regarding recommendations for reimmunization of HSCT recipients.[40]

Survivors of HSCT should be monitored routinely for signs of relapse and, if an allogeneic graft was used, chronic GVHD. They should be advised regarding revaccination and obtaining prompt medical care for fevers or signs of infection. Routine evaluations of organ function (ie, renal, hepatic, thyroid, and ovarian) and osteopenia should occur and the appropriate management strategies initiated if necessary.

OUTCOME EVALUATION

Monitor for symptoms and signs of the disease that is being treated by HSCT to assess the effectiveness of the HSCT. For example, the monitoring plan for a patient with CML would be to monitor disease response by PCR of the *BCR-ABL* transcript. The actual clinical outcome monitored, along with the frequency of monitoring, is based on the underlying disease.

Monitor for nonhematologic toxicity of the preparative regimen during its administration. Monitor these symptoms at least daily, with more frequent monitoring if the patient is experiencing these nonhematologic effects. The goal is to prevent or minimize these adverse effects.

Patient Care Process

Collect Information:

- Obtain a current medication list and medication use history for prescription and nonprescription medications, herbal products, and dietary supplements. Review and update allergies and intolerances to medications and other substances.
- Review past medical history and/or interim medical history, physical assessment findings, and laboratory values.
- Interview patient to identify and discuss lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication access and/or adherence.

Assess the Information:

- Assess efficacy, safety, drug interactions, adherence, and access to current pharmacotherapy including any barriers to adherence.
- Analyze physical assessment and review of systems findings to determine if patient is exhibiting signs or symptoms of disease progression, infection, or noninfectious HSCT complications, including graft-versus-host disease where applicable.
- Evaluate clinical findings and assess need for medication adjustments to antimicrobials, immunosuppression, supportive care medications, immunizations, or home medications.
- Trend laboratory values (eg, renal function, hepatic function, electrolytes, hemogram with differential, lipid panel, drug levels) and compare with previous values to determine if medication adjustments are warranted.
- Review microbiology data (eg, cultures, fungal serologies, and viral surveillance studies), radiology findings, and other diagnostic tests to assess whether pharmacotherapeutic intervention is appropriate.

Develop a Care Plan:

- If patient is exhibiting a complication related to HSCT or medication therapy, determine if pharmacotherapeutic intervention is indicated.
- Select effective pharmacotherapeutic agents while minimizing drug interactions and overlapping adverse effects with current medication therapy.
- Adjust doses of medications according to prescribed guidelines for organ function, drug interactions, and adverse effects where applicable.

Implement the Care Plan:

- Determine whether the patient's insurance plan will require a prior authorization or if prescribed medication is on institution's formulary.
- Create a new medication list and educate patient on changes to current medications, administration, and how to manage and report adverse effects should they occur.
- Emphasize the importance of medication adherence post-HSCT and address any patient concerns to adherence.

Follow-up: Monitor and Evaluate:

- In the immediate post-HSCT period, follow up at least daily until engraftment and then at frequent intervals (eg, at least weekly) through first 3 months post-HSCT.
- Review medication adherence, vital signs, physical examination findings, laboratory data, monitorable drug levels, microbiology results, radiology data, and other tests related to organ function and disease assessment at each visit.
- Review post-HSCT timeline and make drug therapy modifications in consultation with health care team based on immune reconstitution, drug interactions, and adverse effects.

Abbreviations Introduced in This Chapter

AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ATG	Antithymocyte globulin
BMT	Bone marrow transplantation
BU-CY	Busulfan–cyclophosphamide
CINV	Chemotherapy-induced nausea and vomiting
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
CY-TBI	Cyclophosphamide–total-body irradiation
GVHD	Graft-versus-host disease
HGF	Hematopoietic growth factors
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplant
IA	Invasive aspergillosis
IL-2	Interleukin-2
MHC	Minor histocompatibility
MM	Multiple myeloma
NHL	Non-Hodgkin lymphoma
NK	Natural killer
PBPC	Peripheral blood progenitor cells
PJP	Pneumocystis pneumonia
SOS	Sinusoidal obstruction syndrome
SCr	Serum creatinine
TBI	Total-body irradiation
UCB	Umbilical cord blood
VZV	Varicella zoster virus

REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006;354:1813–1826.
2. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015;21:1863–1869.
3. D'Souza A, Zhu X. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2016. Available from: http://www.cibmtr.org. Accessed August 29, 2017.
4. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15:1628–1633.

5. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. Registry. N Engl J Med. 2014;371:339–348.
6. Ballen KK, Koreth J, Chen YB, et al. Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. Blood. 2012;119:1972–1980.
7. Kekre N, Antin JH. Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match does not exist. Blood. 2014;124(3):334–343.
8. Morishima Y, Kashiwase K, Matsuo, et al. Biological significance of HLA locus matching in unrelated donor bone marrow transplantation. Blood. 2015;125:1189–1197.
9. Petersdorf EW, Hansen JA, Martin PJ, et al. Major-histocompatibility-complex class I alleles and antigens in hematopoietic-cell trans-plantation. N Engl J Med. 2001;345: 1794–1800.
10. Duong HK, Savani BN, Copelan E, et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2014;20:1262–1273.
11. Schmitz N, Dreger P. Peripheral blood hematopoietic cells for allogeneic transplantation. In: Forman SJ, Negrin RS, Antin JH, Appelbaum FR, eds. Thomas' Hematopoietic Cell Transplantation, 5th ed. Oxford, UK: Wiley-Blackwell; 2015:460–471.
12. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. Blood. 2013;122:491–498.
13. Barker JN, Cyam CE, Kernan NA, et al. Availability of cord blood extends allogeneic hematopoietic stem cell transplant access to racial and ethnic minorities. Biol Blood Marrow Transplant. 2010;16(11):1541–1548.
14. Ballen KK, Koreth J, Chen YB, et al. Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. Blood. 2012;119(9):1972–1980.
15. Wingard J, Gastineau D, Leather H, Synder E, Szczepiorkowski Z, eds. Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians, 2nd ed. Bethesda, MD: American Association of Blood Banks (AABB); 2015.
16. Körbling M, Freireich EJ. Twenty-five years of peripheral blood stem cell transplantation. Blood. 2011;117:6411–6416.
17. Holtick U, Albrecht M, Chemnitz JM, et al. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. Cochrane Database Syst Rev. 2014:CD010189.
18. Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. J Clin Oncol. 2005;23:5074–5087.
19. Anasetti C, Logan BR, Lee SJ, et al.; Blood and Marrow Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med 2012;367:1487–1496.
20. Soiffer R. T-cell depletion to prevent graft-versus-host disease. In: Forman SJ, Negrin RS, Antin JH, Appelbaum FR, eds. Thomas' Hematopoietic Cell Transplantation, 5th ed. Oxford, UK: Wiley-Blackwell; 2015:1004–1014.
21. Copelan EA, Hamilton BK, Avalos B, et al. Better leukemia-free and overall survival in AML in first remission following cyclophosphamide in combination with busulfan compared with TBI. Blood. 2013;122:3863–3870.
22. Pingali SR, Champlin RE. Pushing the envelope-nonmyeloablative and reduced intensity preparative regimens for allogeneic hematopoietic transplantation. Bone Marrow Transplant. 2015;50:1157–1167.
23. Eberly AL, Anderson GD, Bubalo JS, et al. Optimal prevention of seizures induced by high-dose busulfan. Pharmacotherapy. 2008;28:1502–1510.
24. McCune JS, Gibbs JP, Slattery JT. Plasma concentration monitoring of busulfan: does it improve clinical outcome? Clin Pharmacokinet. 2000;39:155–165.
25. Grochow LB. Parenteral busulfan: is therapeutic monitoring still warranted? Biol Blood Marrow Transplant. 2002;8:465–467.
26. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2008;27(1):127–145.
27. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017;35(28):3240–3261.
28. Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120:1453–1461.
29. Dalle JH, Giralt SA. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: risk factors and stratification, prophylaxis, and treatment. Biol Blood Marrow Transplant. 2016;22:400–409.
30. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33:3199–3212.
31. Ringden O, Labopin M, Gorin NC, et al. Treatment with granulocyte colony-stimulating factor after allogeneic bone marrow transplantation for acute leukemia increases the risk of graft-versus-host disease and death: a study from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2004;22:416–423.
32. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 diagnosis and staging working group report. Biol Blood Marrow Transplant. 2015;21:389–401.
33. Ram R, Storb R. Pharmacologic prophylaxis regimens for acute GVHD—past, present, and future. Leuk Lymphoma. 2013;54:1591–1601.
34. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2012;18:1150–1163.
35. Ratanatharathorn V, Nash RA, Przepiorka D, et al. Phase III study comparing methotrexate and tacrolimus (prograf, FK506) with methotrexate and cyclosporine for graft-versus-host disease prophylaxis after HLA-identical sibling bone marrow transplantation. Blood. 1998;92:2303–2314.
36. Nash RA, Antin JH, Karanes C, et al. Phase 3 study comparing methotrexate and tacrolimus with methotrexate and cyclosporine for prophylaxis of acute graft-versus-host disease after marrow transplantation from unrelated donors. Blood. 2000;96:2062–2068.
37. McCune JS, Bember MJ. Pharmacokinetics, pharmacodynamics, and pharmacogenomics of immunosuppressants in allogeneic hematopoietic cell transplantation: part I. Clin Pharmacokinet. 2016;55:525–550.
38. Flowers ME, Martin PJ. How we treat chronic graft-versus-host disease. Blood. 2015;125:606–615.
39. Lee SJ. New approaches for preventing and treating chronic graft-versus-host disease. Blood. 2005;105:4200–4206.

40. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143–1238.
41. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):56–93.
42. Boeckh M, Kim HW, Flowers ME, et al. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation—a randomized double-blind placebo-controlled study. Blood. 2006;107:1800–1805.
43. Vazquez JA, Miceli MH, Alangaden G. Invasive fungal infections in transplant recipients. Ther Adv Infect Dis. 2013;1:85–105.
44. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. Ann Intern Med. 2003;138:705–713.
45. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. Clin Infect Dis. 2008;47:1041–1050.
46. Patterson TF, Thompson GR, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1–e60.
47. Battiwalla M, Tichelli A, Majhail NS. Long-term survivorship after Hematopoietic cell transplantation: roadmap for research and care. Biol Blood Marrow Transplant. 2017;23:184–192.

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99 Supportive Care in Oncology

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LEARNING OBJECTIVES

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

1. Describe the impact of various supportive care interventions on the prognosis of patients with cancer.
2. Discuss the scientific basis for providing various supportive care interventions in the oncology patient population.
3. Identify patient-related and disease-related risk factors in defining a population for whom supportive care interventions would be of benefit.
4. Recognize typical presenting signs and symptoms of common complications and emergencies that require supportive care interventions.
5. Outline appropriate prevention and management strategies for various supportive care interventions.
6. Prepare a monitoring plan to evaluate the efficacy and toxicity of pharmacotherapy interventions for supportive care problems.

INTRODUCTION

Patients with cancer are at risk for serious adverse events that result from their treatment, the cancer, or both. The management of these complications is generally referred to as supportive care (or symptom management). Examples of treatment-related complications include chemotherapy-induced nausea and vomiting (CINV), myelosuppression, febrile neutropenia (FN), hemorrhagic cystitis, mucositis, and tumor lysis syndrome (TLS). Tumor or cancer-related complications include superior vena cava (SVC) obstruction, spinal cord compression, hypercalcemia, and brain metastases. In some cases, these events can be life threatening. SVC obstruction, spinal cord compression, TLS, and hypercalcemia have traditionally been defined as oncologic emergencies. Treatment- and disease-related complications in the oncology population require rapid assessment and supportive care interventions. The onset of oncologic emergencies may herald the onset of an undiagnosed malignancy or progression or relapse of a preexisting malignancy. Optimal management of patients with various oncologic emergencies and complications requiring supportive care interventions can significantly decrease morbidity and mortality in patients with cancer. This chapter provides an overview of these issues. First, an overview of the management of common side effects of treatment is given. Later, a summary of common oncologic emergencies is presented.

CHEMOTHERAPY-INDUCED TOXICITIES: NAUSEA/VOMITING

Nausea and vomiting are among the most commonly feared toxicities by patients undergoing chemotherapy.[1] KEY CONCEPT The optimal method of managing CINV is to provide adequate pharmacologic prophylaxis given a patient's risk level for emesis. Insufficient control during the first cycle of chemotherapy leads to more difficulty in controlling emesis for subsequent cycles.[2]

EPIDEMIOLOGY AND ETIOLOGY

Although it is widely known that chemotherapy causes nausea and vomiting, the rate of emesis varies depending on individual patient risk factors and drug therapy regimen. Therefore, cancer treatments are stratified into varying risk levels: high, moderate, low, and minimal. Agents with a "high" emetic risk cause emesis in more than 90% of cases if not given any prophylaxis. The rates of emesis for "moderate," "low," and "minimal" are 30% to 90%, 10% to 30%, and less than 10%, respectively. Table 99–1 lists the individual agents and their risk category.[3]

PATHOPHYSIOLOGY

LO 2

The pathophysiology of nausea and vomiting is described in Chapter 20. Specific to CINV, the key receptors include serotonin ($5\text{-}HT_3$) receptors (located in the chemoreceptor trigger zone, emetic center of the medulla, and gastrointestinal [GI] tract) and neurokinin-1 (NK1) receptors (located in the emetic center of the medulla). Serotonin plays an important role in the genesis of acute vomiting, occurring within the first 24 hours of chemotherapy, because some cancer drug therapies can stimulate a release of serotonin from enterochromaffin cells in the GI tract. Serotonin then activates the emetic response by binding to $5HT_3$ receptors in the emetic center. This short-lived release of serotonin likely explains why serotonin antagonists are more beneficial for preventing acute versus delayed vomiting.[4] Other sites that are targeted by antiemetics include dopamine, muscarinic (acetylcholine), histamine, and cannabinoid receptors.[5]

CLINICAL PRESENTATION AND DIAGNOSIS

CINV, although frequently discussed as one syndrome, includes two distinct clinical entities, including both nausea and vomiting. Nauseous patients may present with general GI upset and reflux and may report a sensation or desire to vomit without being able

Table 99–1

Emetogenic Potential of Selected Chemotherapy

Risk	Agent	Risk	Agent
High emetic risk (> 90% of patients will vomit without appropriate antiemetics)	AC combination (doxorubicin or epirubicin and cyclophosphamide) Carmustine > 250 mg/m^2 Carboplatin AUC ≥ 4 Cisplatin Crizotinib (oral) Cyclophosphamide > 1500 mg/m^2 Dacarbazine Doxorubicin ≥ 60 mg/m^2 Epirubicin > 90 mg/m^2 Etoposide (oral) Ifosfamide ≥ 2 g/m^2 Temozolomide >75 mg/m^2/day (oral)	Low emetic risk (10%–30%)	Ado-trastuzumab emtansine Afatinib (oral) Amifostine < 300 mg/m^2 Bexarotene Brentuximab Cabazitaxel Carfilzomib Capecitabine (oral) Dasatinib (oral) Docetaxel Doxorubicin (liposomal) Eribulin Erlotinib (oral) Etoposide 5-Fluorouracil Gemcitabine Ixabepilone Methotrexate > 50 mg/m^2 and < 250 mg/m^2 Mitomycin Mitoxantrone Paclitaxel Palbociclib (oral) Pemetrexed Sunitinib (oral) Topotecan Vorinostat
Moderate emetic risk (30%–90%)	Amifostine > 300 mg/m^2 Arsenic trioxide Azacitidine Bendamustine Busulfan > 4 mg/m^2 Carboplatin AUC < 4 Carmustine ≤ 250 mg/m^2 Cyclophosphamide ≤ 1500 mg/m^2 Cytarabine > 200 mg/m^2 Daunorubicin Doxorubicin < 60 mg/m^2 Epirubicin < 90 mg/m^2 Idarubicin Ifosfamide < 2 g/m^2 Irinotecan Methotrexate > 250 mg/m^2 Oxaliplatin	Minimal risk (< 10%)	Most other agents

Data from National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemetic v.2.2017.

to do so.[5] In all cases, it is important that other etiologies of nausea and vomiting are ruled out before diagnosing chemotherapy as the cause.[6] Other causes of nausea and vomiting may include bowel obstruction, opioid intolerance, electrolyte imbalances, brain metastases, and vestibular dysfunction.[6]

TREATMENT

Desired Outcomes

The desired outcome is to completely prevent or minimize the severity of nausea, vomiting, and the use of breakthrough antiemetic medications. In clinical trials, a common end point is "complete response," defined as having no emesis and no breakthrough medication use within a defined period of time.[5] If patients experience nausea or emesis, the goal is to quickly relieve the episode and prevent future nausea or vomiting, whether in the next few days or for the next cycle of chemotherapy.[6]

General Approach to Treatment

Treatment-related factors and patient-related factors can help define a patient population at risk for developing CINV.[2] Treatment-related factors include those chemotherapy agents with high and moderate levels of emetogenicity, dose, and schedule (see Table 99–1 for a complete listing).[3] CINV is typically a cyclical occurrence. Although this section focuses on CINV, it can be helpful for practitioners to remember that patients undergoing concomitant radiation therapy and chemotherapy are at risk for more severe nausea and vomiting. Radiation (particularly total-body irradiation as part of a conditioning regimen for stem cell transplant) can cause a more cumulative (versus cyclical) nausea/vomiting phenomenon.[3]

LO 3

Specific patient-related factors such as female gender, age less than 50, history of motion sickness, pregnancy-induced nausea or vomiting, and poor emetic control in previous chemotherapy cycles increase the risk of emesis.[2] Interestingly, patients with a history of alcohol abuse have a reported decreased risk of emesis.[5] It is important to design an antiemetic regimen with consideration of these patient-specific risk factors.[6]A well-designed regimen includes a prophylactic regimen targeting the various phases of nausea/vomiting and a breakthrough antiemetic drug "as needed." Although many drugs are recommended as "breakthrough" drugs, choose a drug with a different mechanism of action compared with the drugs used for prophylaxis.[6]

▶ *Nonpharmacologic Therapy*

Nonpharmacologic therapy for nausea and vomiting can be useful adjuncts to drug therapy, particularly in the setting of anticipatory nausea and vomiting. Behavior therapies such as relaxation, guided imagery, and music therapy as well as acupuncture or acupressure may be useful in this setting.[6] Other general measures that can be taken include ensuring adequate

Clinical Presentation and Diagnosis of CINV

Acute Nausea/Vomiting

- Occurs within the first 24 hours after chemotherapy administration

Delayed Nausea/Vomiting

- Occurs between 24 hours and 5 days after chemotherapy administration

Anticipatory Nausea/Vomiting

- A learned, conditioned reflex response to a stimulus (sight, sound, smell) often associated with poor emetic control in a previous cycle of chemotherapy

Breakthrough Nausea/Vomiting

- Occurs despite prophylaxis with an appropriate antiemetic regimen

Differential Diagnosis

- Surgery, radiation
- Brain metastases
- Gastric outlet or bowel obstruction, constipation
- Hypercalcemia, hyperglycemia, hyponatremia, uremia
- Food poisoning or intolerance
- Other drugs (opioids)

Table 99–2

Recommended Therapy by Emetic Risk

Emetic Risk Category (Incidence of Emesis Without Antiemetics)	Antiemetic Regimens and Schedules
High (> 90%)	5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: days 1–4 Aprepitant: days 1–3 or fosaprepitant IV day 1 only Olanzapine: days 1–4
Moderate (30%–90%)	5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: day 1 *Or* 5-HT_3 serotonin receptor antagonist: day 1 Dexamethasone: days 1–3 for regimens with drugs known to cause delayed nausea/vomiting
Low (10%–30%)	Dexamethasone: day 1 *Or* 5-HT_3 serotonin receptor antagonist: day 1
Minimal (< 10%)	No routine prophylaxis. 5-HT3 receptor antagonists, others as needed

Data from American Society of Clinical Oncology. Antiemetics: Clinical Practice Guideline Update, 2017 and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemetics v.2.2017.

sleep before treatment, eating smaller meals, and avoiding spicy and greasy foods and foods with strong odors.[6]

▶ *Pharmacologic Therapy*

Nonprescription medications such as antacids, histamine-2 receptor blockers, and proton pump inhibitors can be helpful in reducing gastroesophageal reflux associated with some cancer treatments that may trigger or exacerbate CINV.[6] Nonprescription antihistamines marketed for nausea associated with motion sickness are not usually helpful in managing CINV.

LO 5

Four drug classes are highly effective in preventing CINV: corticosteroids (dexamethasone), serotonin receptor antagonists, NK1 receptor antagonists (aprepitant or fosaprepitant), and the thienobenzodiazepine, olanzapine.[3] Drugs with differing mechanisms of action are combined, depending on the emetic risk level of the chemotherapy regimen (Table 99–2).

Intravenous (IV) antiemetics are usually administered 30 minutes before chemotherapy, and oral antiemetics are administered 60 minutes before chemotherapy. Dexamethasone is the preferred agent to prevent CINV in the delayed setting (days 2–4 after chemotherapy administration) and is given at dose of 8 mg once daily for 3 to 4 days.[3,6] Recently, experts have modified recommendations and advise limiting the use of multi-day dexamethasone to only highly emetogenic risk chemotherapy and only for those moderately emetogenic regimens known to cause delayed nausea and vomiting (such as cyclophosphamide, doxorubicin, and oxaliplatin) due to concerns for toxicities related to dexamethasone.[3] In some cases, the serotonin antagonists may also be continued orally for 2 to 3 days after chemotherapy or be used in place of dexamethasone, though practice guidelines differ in their recommendations.[3,6] When oral aprepitant is used prechemotherapy, the aprepitant is continued as 80 mg orally once daily on days 2 and 3 of the chemotherapy cycle. No oral aprepitant is necessary when fosaprepitant 150 mg IV is given on day 1. Olanzapine is now a standard component of the antiemetic regimens for high emetic-risk chemotherapy at 10 mg by mouth once daily (5 mg by mouth once daily for elderly patients) for 4 days starting the day of chemotherapy, and an option to add to the antiemetic regimen for moderately emetogenic chemotherapy.[3,6] Concerns of QT prolongation have resulted in the IV formulation of dolasetron to be removed from the market and dosing of ondansetron has been reduced to 16 mg IV as the 32 mg IV was reported to extend the QT interval.[7]

The other classes of antiemetics are usually prescribed "as needed" for breakthrough nausea or vomiting. The dopamine antagonists prochlorperazine and metoclopramide are usually recommended because they antagonize a different receptor than the drugs already given for prophylaxis. Other medications, including serotonin receptor antagonists, cannabinoids, dexamethasone, scopolamine, or olanzapine, may be used as alternatives to dopamine antagonists for breakthrough nausea and vomiting.[3,6] Breakthrough medications should have different mechanisms of action than the medications a patient is taking to prevent nausea and vomiting. For those in any risk group who experience anticipatory nausea and vomiting, the addition of lorazepam for prophylaxis and breakthrough is recommended for its antiemetic and antianxiety properties, but not as a single-agent to prevent CINV.[3] Table 99–3 lists the doses of the antiemetic agents for prophylaxis and breakthrough use.

LO 5

A prophylactic antiemetic regimen for high emetic risk levels of IV chemotherapy should be with a four-drug combination using dexamethasone, (fos)aprepitant IV (or aprepitant, an oral agent), olanzapine, and 5-HT_3 antagonist to prevent both acute and delayed emesis.[3,6] Dexamethasone and olanzapine should be continued until day 4, and aprepitant is also administered on days 2

Table 99–3

Antiemetic Dosing

Antiemetic	Single Dose Administered Before Chemotherapy	Daily Schedule
5-HT$_3$ Serotonin Receptor Antagonists		
Dolasetron	By mouth: 100 mg	100 mg by mouth daily
Granisetron	By mouth: 2 mg IV: 1 mg or 0.01 mg/kg Topical: 34.3-mg patch (apply 24–48 hours before chemotherapy, leave on for 7 days)	1–2 mg by mouth daily or 1 mg by mouth two times a day
Ondansetron	By mouth: 16–24 mg IV: 8–16 mg	8 mg by mouth two times a day or 16 mg by mouth daily
Palonosetron	IV: 0.25 mg	
Others		
Aprepitant	By mouth: 125 mg	80 mg by mouth days 2 and 3
Fosaprepitant	IV: 150 mg × 1	None
Dexamethasone	By mouth or IV: 12 mg	8 mg by mouth days 2–4
Olanzapine	10 mg by mouth daily	10 mg by mouth daily

Data from American Society of Clinical Oncology. Antiemetics: Clinical Practice Guideline Update, 2017 and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemetics v.2.2017.

and 3 if the oral formulation is used.[3,6] A phase 3 trial of 241 patients comparing aprepitant, palonosetron, and dexamethasone to olanzapine with a palonosetron and dexamethasone for patients treated with highly emetogenic chemotherapy had similar rates of CINV control (87%–97% prevention of acute CINV, 73%–77% prevention of delayed CINV), though nausea was better controlled by the olanzapine-based regimen (69% overall vs 38% overall).[8]

LO 5

For moderately emetogenic regimens, acute emesis is still of major concern, but the incidence of delayed emesis is less. Therefore, dexamethasone plus a 5-HT$_3$ antagonist should be given on day 1. On days 2 to 3, choose to continue either the dexamethasone or the 5-HT$_3$ antagonist (dexamethasone preferred for regimens known to cause delayed CINV),[3,6] though one exception is when palonosetron is given as the 5-HT$_3$ antagonist on day 1. Because its half-life is long, no redosing is necessary on subsequent days. Aprepitant and fosaprepitant

Patient Encounter 1: CINV

A 73-year-old man with non–small cell lung cancer (NSCLC) presents today for initiation of chemotherapy with carboplatin AUC 5 and paclitaxel 175 mg/m^2.

What category of emetic risk should this dose regimen fall under?

What do you recommend for preventing nausea and vomiting in this patient?

150 mg IV are also approved by the Food and Drug Administration (FDA) for the prevention of CINV in the moderate setting. While an NK1 receptor antagonist is not routinely used for moderately emetogenic chemotherapy, if patients have clinical risk factors or if they experienced uncontrolled emesis with previous chemotherapy cycles, follow the suggest guidelines for "high-" emetogenic risk level.[6]

LO 5

For low emetic risk IV chemotherapy regimens, single-agent antiemetic prophylaxis with either dexamethasone or 5HT$_3$ antagonist is recommended 30 minutes before chemotherapy.[3,6] For minimal emetic risk groups, guidelines do not recommend routine prophylaxis with antiemetics; instead, patients should be provided with a drug to take as needed for nausea and vomiting.[3,6] Table 99–2 summarizes regimens for antiemetic prophylaxis for the different risk levels of IV chemotherapy.

Many oral anticancer agents are now available and are typically administered daily. For highly and moderately emetogenic oral anticancer therapy, an oral 5HT$_3$-antagonist is administered 60 minutes before each chemotherapy dose.[6] For low–minimal risk oral anticancer agents an "as needed" antiemetic agent may be given for any breakthrough nausea/vomiting.[6]

OUTCOME EVALUATION

It is often difficult to evaluate nausea and vomiting when chemotherapy is given as an outpatient. After drug administration, patients return home and may or may not report inadequate control of nausea or emesis. Subsequent chemotherapy cycles may also be poorly controlled, especially if patients do not state their experience with the previous cycle. To ameliorate this problem, patients' experiences with CINV should be assessed, particularly after the first and second cycles of chemotherapy. Patients should be asked about their previous emesis control with subsequent cycles of chemotherapy, and a prophylactic regimen may need to be adjusted. Patients should also be encouraged to self-report poor control of emesis while at home. Side effects of the antiemetic regimen should also be assessed and reported.

MUCOSITIS

Mucositis is the inflammation of the mucosal lining in the oral cavity and GI tract caused by damage from radiation or cytotoxic chemotherapy, often leading to ulcers.[9] Stomatitis is a related term that is specific to inflammation in the oral cavity and associated with targeted anticancer agents.[9] Both mucositis and stomatitis are common supportive care issues that deserve attention and are associated with many negative health consequences, including pain, inadequate nutritional intake, and risk for infection. Diagnosis is based on symptoms of pain, vomiting, diarrhea, and impact on appetite, all of which are surrogates for the inflammation and damage to the mucosal lining due to the impractical nature of a definitive diagnosis by invasive endoscopic biopsy.[10] Biomarkers are currently under investigation to better standardize the severity of mucosistis.[10] Patients with mucositis often require parenteral analgesics, nutrition supplementation, and anti-infectives to treat concomitant bacterial, fungal, or viral infections. Furthermore, mucositis is associated with economic consequences, primarily increased length of hospital stay, nutrition support, and infection management.[11,12] The use of evidence-based practice for prevention and treatment of mucositis can help improve patient outcomes.

LO 1

EPIDEMIOLOGY AND ETIOLOGY

The incidence of chemotherapy or radiation-induced mucositis depends mostly on the type of chemotherapy, the type and area of radiation, and the specific cancer. Studies have reported an incidence of about 85% in head and neck cancer patients receiving chemoradiation.[9] The World Health Organization estimates that approximately 75% of patients who are treated with high-dose chemotherapy for stem cell transplantation developed oral mucositis.[9] Specific chemotherapy agents associated with moderate–severe mucositis include taxanes, anthracyclines, platinum analogues, methotrexate, and the fluoropyrimidines.

PATHOPHYSIOLOGY

The classical concept of mucositis pathophysiology asserts that direct cytotoxicity from chemotherapy or radiation to basal epithelial cells results in ulcerative lesions caused by a lack of regeneration. These lesions are further complicated by trauma or microorganism growth. However, the most recent theory of mucositis pathophysiology is more detailed and involves a multistage, dynamic process that builds upon the historical model.[12] According to this theory, there are five stages of mucositis: initiation, primary damage response, signal amplification, ulceration, and healing. It is important to note that these stages do not occur sequentially and may be influenced by both the oral and gut microbiome as well as genetic polymorphisms in individual patients.[13] Prevention of mucositis or treatment in early stages results in the best outcomes for patients.

CLINICAL PRESENTATION AND DIAGNOSIS

LO 1 LO 4

Patients with mucositis may present along a continuum of mild, painless, erythematous ulcers to those that are painful and/or bleeding that may interfere with eating and swallowing or that may require treatment with hydration, antibiotics, and/or parenteral nutrition or opioid therapy in its most severe forms.[9,12] The severity of mucositis can be assessed with validated scales such as the Oral Mucositis Assessment Scale (OMAS)[14] or the Patient-Reported Oral Mucositis Symptom (PROMS) scale.[15]

Clinical Presentation and Diagnosis of Mucositis

- Painful, erythematous ulcers develop on the lips, cheeks, soft palate, floor of mouth, and throughout the entire gastrointestinal (GI) tract.
- Assess mucositis using validated scales, either oral mucositis assessment scale (OMAS) or Patient-Reported Oral Mucositis Symptom (PROMS) Scale.
- Symptoms appear within 5 to 7 days after chemotherapy and resolve in 2 to 3 weeks.
- Pain may affect ability to swallow and eat.
- The patient may have concomitant localized or systemic infection.
- Diarrhea is a symptom of mucositis in the lower GI tract; can lead to electrolyte imbalances.

TREATMENT

Nonpharmacologic Treatment

The goal of nonpharmacologic measures to prevent mucositis is to reduce the bacterial load. KEY CONCEPT The fundamental approach to lessen the severity of mucositis begins with basic, good oral hygiene (brushing with a soft-bristled toothbrush at least twice daily, flossing, bland rinses, and saliva substitutes) and maintaining optimal nutritional support.[9,12] Cryotherapy with ice chips is also helpful for patients at risk for mucositis who are receiving 5-FU–based chemotherapy.[9,12] Low-level laser therapy (in centers that have the resources to offer it) is also helpful to prevent mucositis in the hematopoietic cell transplant (HCT) setting.[9,12]

Pharmacologic Treatment

LO 5

In the setting of radiation therapy, amifostine, a free radical scavenger, at doses equal to or greater than 340 mg/m^2 intrarectal before each dose of radiation therapy for rectal cancer may be considered to prevent GI mucositis.[9,12] Gelclair, Caphasol, and Biotene are gels that provide a protective barrier between damaged oral mucosa and the environment, lessening pain and irritation and are also sometimes used as part of the overall treatment of patients with mucositis.[10]

While benzydamine mouthwash is recommended by practice guidelines, antimicrobial mouth washes and lozenges, sucralfate and chlorhexidine rinses, and "magic-mouthwash" compounded rinses are not generally recommended by clinical practice guidelines for mucositis prevention even though they are sometimes used in practice.[9,12] Ranitidine or omeprazole orally are recommended to prevent pain associated with mucositis and reflux following offending chemotherapy.[9,12] Additionally, octreotide at a dose of at least 100 mcg subcutaneously twice daily is recommended to treat mucositis-related diarrhea associated with high-dose stem cell transplantation if loperamide is ineffective.[9,12]

Unfortunately, little evidence is available to recommend specific treatments for mucositis. Pain assessment and appropriate management are important.[9,12] Pain management may be achieved with oral or intravenous opioids, topical anesthetic products, and compounded rinses that incorporate lidocaine.[9,12] In more severe cases in which infection of the oral mucosa is suspected, appropriate antimicrobial therapy is necessary to prevent systemic infection.[9,12]

Palifermin is FDA-approved for the prevention and treatment of mucositis in patients receiving high-dose chemotherapy as part of stem cell transplant or induction regimens for leukemia. Palifermin is administered as an IV bolus injection at a dosage of 60 mcg/kg/day for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of six doses. Administering palifermin within 24 hours of chemotherapy can result in an increased sensitivity of rapidly dividing epithelial cells to the cytotoxic agent. For this reason, palifermin should not be administered for 24 hours before, 24 hours after, or during the infusion of myelotoxic chemotherapy to avoid increasing the severity and the duration of oral mucositis.[9,12]

OUTCOME EVALUATION

The goal of therapy is to prevent or decrease the severity and duration of mucositis. Outcomes measured in clinical trials often assess the incidence, duration, and severity of mucositis with a given intervention intended to prevent or treat mucositis. Agents that are intended to palliate the symptoms of mucositis are usually assessed by measures in pain scales and the ability to eat or drink.

HEMATOLOGIC COMPLICATIONS: FEBRILE NEUTROPENIA (FN)

INTRODUCTION

LO 1

FN is a common adverse effect after administration of cytotoxic chemotherapy. The mortality rate in neutropenic patients caused by infectious complications currently remains between 5% and 10%; therefore, FN is considered a true oncologic emergency. Patients frequently require hospitalization for prompt administration of broad-spectrum antibiotics that are critical to avoid morbidity and mortality.

EPIDEMIOLOGY AND ETIOLOGY

The microorganisms responsible for infections in neutropenic patients have changed significantly in the last 50 years. From the 1960s through the mid-1980s, gram-negative organisms were the most common bacteria isolated. This pattern shifted to the gram-positive organisms in the late 1980s, which remain the most common isolates. Recent data indicate that gram-positive organisms account for up to 75% to 80% of all bloodstream infections in cancer patients while gram-negative species are more prevalent in nonbloodstream infections and particularly if there is deep tissue involvement.[16] The causes of this change are attributed to the widespread use of central venous catheters and more aggressive chemotherapy regimens as well as the use of prophylactic antibiotics with relatively poor gram-positive coverage (quinolones). Commonly isolated pathogens are shown in Table 99–4. Although gram-negative infections are less common, they cause the majority of infections in sites other than the blood and are particularly virulent.[16] It should be noted that isolates vary considerably among institutions; thus, attention to institutional isolation patterns is prudent.

Fungal infections caused by *Candida* spp. (especially *Candida albicans*) have emerged as significant pathogens, especially in patients with hematologic malignancies and those undergoing bone marrow transplantation (BMT).[16] In addition, *Aspergillus* spp. are important pathogens in patients with prolonged and severe neutropenia.[16]

Table 99–4

Commonly Isolated Pathogens in Patients with FN

Type of Organism	Comments
Bacteria	
Gram-positive organisms	Most common isolates in FN
Coagulase-negative *staphylococci* (ie, *Staphylococcus epidermidis)*	Between 70% and 90% resistant to methicillin; indolent course with low mortality
Staphylococcus aureus	Some centers report > 50% resistance to methicillin
Enterococcus spp.	Resistance to vancomycin ≥ 30%
Viridans streptococci	Increasing resistance to penicillin; result of fluoroquinolone prophylaxis; associated with mucositis
Gram-negative organisms	Infections rapidly fatal
Pseudomonas aeruginosa	High mortality rate; increasing resistance to quinolones
Escherichia coli	Increased incidence of β-lactamase–producing strains
Klebsiella spp	
Enterobacter spp.	Increased incidence of β-lactamase–producing strains
Fungi	Occur primarily after prolonged neutropenia (> 1 week)
Yeasts	
Candida albicans	Increasing incidence (~10%); high mortality rate
Non-*albicans Candida* (*Candida krusei, Candida glabrata*)	Resistant to fluconazole; high mortality rate
Molds	Resistant to fluconazole; high mortality
Aspergillus spp.	Pulmonary infection common
Fusarium spp.	Emerging pathogen
Scedosporium spp.	Emerging pathogen

FN, febrile neutropenia.

PATHOPHYSIOLOGY

The neutrophils are the primary defense mechanism against bacterial and fungal infection. Most infections in neutropenic patients are a result of organisms contained in endogenous flora, both on the skin and within the GI tract. These organisms are provided access to the bloodstream through breakdowns in host defense barriers (**mucositis**, use of central venous catheters).

Neutropenia is defined as an absolute neutrophil count (ANC) less than 500/μL (0.50×10^9/L) cells or an ANC less than 1000/μL (1.00×10^9/L) cells with a predicted decrease to less than 500/μL (0.50×10^9/L) cells over the next 48 hours. The ANC is calculated by multiplying the total WBC by the percentage of neutrophils (segmented neutrophils plus "bands"). Fever is defined as a single oral temperature greater than or equal to 38.3°C (101°F) or a temperature greater than or equal to 38.0°C (100.4°F) for at least 1 hour. The combination of these two factors defines FN.[17–19] The risk of infection during the period of neutropenia depends primarily on two factors:

- The duration of the neutropenia (time period of ANC < 500/μL [0.50×10^9/L] cells)
- The severity of the neutropenia (lowest ANC level reached [nadir])

LO 3

A multitude of other risk factors for FN have been identified[20] (Table 99–5). Many of these are also risk factors for poor outcome in patients who experience FN. Cancer drug therapy regimens are also categorized as being high risk (> 20% incidence of FN reported in clinical trials) or intermediate risk (10%–20% risk of FN reported in clinical trials). Similar to the approach to the

Patient Encounter 2: FN

A 63-year-old woman receiving treatment for metastatic breast cancer presents today, 8 days after chemotherapy, for follow-up and laboratory check. Relevant laboratory study results include WBC count, 0.7×10^3/mL (0.7×10^9/L); HgB 9.0 g/dL (90 g/L; 5.59 mmol/L)); HCT 26.6% (0.266); PLT, 6×10^3/mL (6×10^9/L); serum chemistries within normal limits except; SCr, 1.3 mg/dL (115 μmol/L); and estimated GFR 54 mL/min/1.73m^2. Vitals: T 98.2°F (36.8°C); P 71 beats/min; RR 18 breaths/min; BP 116/64 mm Hg. The patient has no known drug allergies.

What risk factors for FN does this patient have?

How would you approach this patient?

Table 99–5

Risk Factors for FN

Patient Related	Therapy Related
Age ≥ 60 years	History of extensive chemotherapy
Poor performance status	Planned full dose intensity of chemotherapy
Bone marrow involvement by tumor	High-dose chemotherapy (ie, stem cell transplant)
Poor nutritional status	> 20% incidence of FN reported in clinical trials with treatment regimen
Hematologic malignancy	10%–20% incidence of FN reported in clinical trials with treatment regimen plus presence of patient-specific risk factors
Elevated LDH	
Decreased hemoglobin level	
Baseline or first-cycle low neutrophil counts	
History of previous FN	
Renal or hepatic insufficiency	
Uncontrolled or advanced stage cancer	
MASCC Risk Index Score < 21	

FN, febrile neutropenia; LDH, lactate dehydrogenase; MASCC, Multinational Association for Supportive Care in Cancer.

Data from The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections. V.2.2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed August 29, 2017.

Table 99–6

MASCC Risk-Index for Identifying Low-Risk Patients with FN[a]

Characteristic	Score
Burden of illness[b]	
No symptoms	5
Mild symptoms	5
Moderate symptoms	3
No hypotension	5
No COPD	4
Solid tumor or hematologic malignancy without fungal infection	4
No dehydration	3
Outpatient onset of fever	3
Age < 60 years[c]	2

[a]Note: A risk-index score of ≥ 21 indicates that the patient is likely to be at low risk for complications and morbidity.

[b]Choose one symptom assessment.

[c]Does not apply to patients aged ≤ 16 years.

COPD, chronic obstructive pulmonary disease; FN, febrile neutropenia; MASCC, Multinational Association for Supportive Care in Cancer.

From Klastersky J, Paesmans M. The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer. 2013;21(5):1487–1495.

prevention of CINV, it is important to consider both the regimen and patient-specific risk factors when determining whether a patient should receive prophylactic therapy for FN.

It is clear that patients with FN represent a heterogenous group. Some patients are at lower risk and could potentially be treated as outpatients, thereby avoiding the risk and cost of hospitalization. LO 3 The Multinational Association for Supportive Care in Cancer (MASCC) has validated a risk assessment tool that assigns a risk score to patients presenting with FN (Table 99–6).[20] Patients with a risk-index score greater than or equal to 21 are identified as low risk and are candidates for outpatient therapy (discussed under section Treatment).

PREVENTION

LO 5 Three primary modalities for preventing infection in patients who are expected to become neutropenic have been utilized, the first of which is the least expensive and simplest:

- Vigilant hand hygiene
- Prophylactic antibiotics
- Colony-stimulating factors (CSFs)

The advantages and disadvantages of these strategies are discussed individually in the following sections.

Hand Hygiene

As previously discussed, most infections in neutropenic patients are a result of endogenous flora; however, prevention of further acquisition of environmental pathogens is also important. Patients who are or will become neutropenic should practice careful handwashing and avoid contact with people who neglect hand hygiene. Although practice guidelines do not advocate for a "neutropenic diet" (ingestion of certain fresh fruits and vegetables as well as unprocessed dairy products) due to a lack of strong evidence that following such a diet will reduce the risk of infection-related morbidity and mortality, this is a common clinical advice given to patients.[18] Practitioners should also engage in vigilant hand hygiene after each patient encounter to limit the spread of infections between patients.[19]

Clinical Presentation and Diagnosis of FN[17–19]

General

- Only 50% of patients with FN have a clinically documented infection.
- Only 25% of patients with FN have a microbiologically documented infection.

Signs and Symptoms

- Fever is typically the only sign of infection, although septic patients may have chills.
- Infected catheter sites may be erythematous and tender to the touch.

Laboratory Tests

- CBC with differential
- Two blood cultures from each access site (peripheral and central), urinalysis, urine culture, chest x-ray, sputum cultures

Other Diagnostic Tests

- Detailed physical examination of the oral mucosa, sinuses, skin, catheter access sites, perineal area (no rectal examination because of the risk of bacteremia)

Prophylactic Antibiotics

Routine antibacterial prophylaxis is controversial and has been attempted primarily with sulfamethoxazole–trimethoprim (SMZ-TMP) and quinolones. SMZ-TMP offers improved prophylaxis against gram-positive organisms compared with quinolones; quinolones are more effective prophylaxis against gram-negative infections. The Infectious Diseases Society of America (IDSA), American Society of Clinical Oncology, and National Comprehensive Cancer Network guidelines recommend fluoroquinolone prophylaxis in patients who are at high risk for "prolonged and profound" neutropenia.[17–19] None of these expert groups recommend routine antibiotic prophylaxis for low-risk patients because of the lack of a clear benefit on mortality rates and concerns regarding increasing antibiotic resistance. One exception is that SMZ-TMP is recommended for prophylaxis of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonitis (PCP) in all at-risk patients (ie, hematopoietic cell transplant recipients, AIDS), regardless of the presence of neutropenia.[17–19]

A recent systematic review of 109 trials involving over 13,000 patients demonstrated a significant reduction in the rates of fever, infection, and infection-related and all-cause-mortality when afebrile neutropenic chemotherapy patients were given fluoroquinolone or TMP-SMZ prophylaxis compared to placebo or no prophylaxis.[21] However, most of these studies were conducted in patients with hematologic malignancies (an inherently high-risk group). Although two additional randomized trials in patients with both solid tumors and hematologic malignancies demonstrated lower rates of FN, infection, and hospitalization with oral prophylactic levofloxacin compared with placebo,[22–23] both were significantly criticized for methodological concerns and theoretical concerns about drug resistance and effectiveness of early treatment in low-risk patients. NCCN, ASCO, and IDSA only recommend prophylactic levofloxacin for patients with expected duration of neutropenia (defined as an ANC < 1000/μL [1.00×10^9/L]) for more than 7 days because of the:

- Unknown long-term consequences on the development of resistant organisms
- Emergence of *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA) from fluoroquinolone overuse
- Ability to treat lower-risk patients on an outpatient basis, reducing the need for prophylactic antibiotics[17–19]

Therefore, the use of prophylactic quinolones in patients who are at high risk for infection (ie, hematologic malignancies receiving high-dose chemotherapy for allogeneic stem cell transplant) is reasonable; however, use should not be routine for low-risk patients. If prophylactic quinolone use is adopted, changes in local patterns of resistance should be closely monitored.

Colony-Stimulating Factors

The CSFs stimulate the maturation and differentiation of neutrophil precursors. Four agents are currently approved for use in the United States (Table 99–7). The prophylactic use of these agents decreases days of hospitalization and use of empiric antibiotics by shortening the duration of severe neutropenia (defined as ANC < 500/μL [0.50×10^9/L]). There is little to no effect on the depth of neutrophil nadir. A meta-analysis found that the use of prophylactic granulocyte CSF (either filgrastim or pegfilgrastim) results in a 46% risk reduction of FN and a 48% risk reduction in infectious mortality, although absolute differences are small (3.3% vs 1.7%).[24] A more recent meta-analysis also found that a small (7%) but statistically significant reduction in the relative risk of all-cause mortality was found for patients treated with G-CSF prophylactically, with the benefit (11%) greater for patients receiving dose-dense regimens.[25] It is critical to note that patients who receive these agents may still experience FN despite the risk reduction. The primary limitation of the use of these agents is cost and in fact, ASCO recently identified inappropriate G-CSF use as one of the "Top 5" interventions clinicians can make to reduce cancer care costs without compromising patient care.[26] CSFs are recommended beginning with the first cycle (primary prophylaxis) of chemotherapy when the risk of FN is greater than or equal to 20%, regardless of whether the goal of therapy is curative or palliative.[27] This is the point where the use of CSFs is cost effective when balanced against the cost of hospitalization and antimicrobials.

Table 99–7

Overview of CSF

Agent	Effector Cell(s)	Dosage	Common Adverse Effects	Comments[a]
Filgrastim (G-CSF, Neupogen; filgrastim-sndz, Zarzio; tbo-filgrastim, Granix)	Neutrophil	5 mcg/kg/day SC or IV or round to 300- *or* 480-mcg vial size	Bone pain (~25%)	Begin 1–3 days after chemotherapy
Pegfilgrastim (Neulasta; Neulasta On-body Injector)	Neutrophil	6 mg SC once *or* Apply 1 device once	Bone pain (~25%)	Self-mediated clearance via neutrophils Once per cycle dosing Administer 1–3 days after chemotherapy
Sargramostim (Leukine GM-CSF)	Neutrophil, eosinophil, macrophage	250 mcg/m^2/day SC or IV or round to 250- *or* 500-mcg vial size	First dose effect (hypotension, flushing) Low-grade fever Bone pain Injection site skin reaction	Indicated for use after induction chemotherapy in older patients with AML Limited experience and lack of FDA approval for prevention of FN

[a]No renal or hepatic dose adjustments are required for any product listed in this table.

AML, acute myeloid leukemia; FDA, Food and Drug Administration; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; SC, subcutaneous.

Secondary prophylaxis refers to the subsequent prophylactic use of a CSF after a patient has had an episode of FN. This strategy should be used especially when the chemotherapy is being given in patients with the intention of cure (ie, Hodgkin lymphoma, early breast cancer). In this circumstance, administration of full doses of chemotherapy on time without delays has been shown to improve patient outcomes.[24,25]

Although generally well tolerated, CSFs may cause bone pain in around 25% of patients. This may be managed with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), although attention to the platelet count is warranted with the use of NSAIDs. Sargramostim in particular may result in low-grade fever and myalgias, perhaps as a result of its wider pattern of effector cell stimulation.[27]

TREATMENT

Desired Outcomes

Because rapid death may occur with certain infections in neutropenic patients, prompt and emergent treatment is indicated. The primary goal is to prevent morbidity and mortality during the neutropenic period. This is accomplished by effectively treating subclinical or established infections.

General Approach to Treatment

KEY CONCEPT A risk assessment should be performed at presentation of FN to identify low-risk patients for potential outpatient treatment (see Table 99–6). Patients who do not meet low-risk criteria should be hospitalized for parenteral administration of broad-spectrum antibacterials. The IDSA has published evidence-based guidelines for the management of FN (Figure 99–1).[17] The choice of initial antimicrobial agent(s) depends on the following factors:

- Presence of a central venous catheter
- Drug allergies
- Concurrent renal dysfunction or use of nephrotoxic agents
- Use of prophylactic antibiotics
- Institutional and/or community susceptibility patterns
- Cost

KEY CONCEPT The administration of empiric therapy should begin immediately after cultures are taken. Therapy should not be withheld until after culture results are obtained.

As illustrated in Figure 99–1, specific criteria exist for the addition of vancomycin for coverage of resistant gram-positive organisms or agents for coverage of fungal infections. Additional agents are necessary in the setting of continued fever or declining clinical status in neutropenic patients. In general, all empiric therapy is continued until recovery of the ANC to levels above 500 cells/μL (0.500×10^9/L) in patients with negative culture results. If a specific etiology is identified, appropriate therapy should generally be continued until 7 days after neutropenia resolves. Specific regimens with recommended dosages are summarized in Table 99–8.

▶ *Nonpharmacologic Therapy*

Prevention of infection is key. Handwashing is critical in the prevention of disease transmission.[17–19] It is also important to ensure that patients receive annual influenza vaccines and have had a pneumonia and meningococcal vaccine, and neutropenic patients should avoid individuals with active respiratory infections.[17–19] Indwelling catheters are often sources of infection; however, the IDSA acknowledges that catheters do not always need to be removed.[17] Catheters should be removed in the following circumstances: established tunnel infection (subcutaneous tunnel or periport infection, septic emboli, hypotension associated with catheter use, or a nonpatent catheter), recurrent infection, or no response to antibiotics within 2 or 3 days.[17] Wound debridement should also be performed upon catheter removal. In the setting of peripheral blood stem cell or bone marrow transplant, the Centers for Disease Control and Prevention recommends the use of high-efficiency particulate air (HEPA) filtration systems in patient rooms, and the NCCN suggests that HEPA filters are reasonable to be considered for other patients who experience prolonged neutropenia.[17] HEPA filters are likely to be most useful in preventing mold infections. Although several small studies have attempted to evaluate the effectiveness of isolation of neutropenic patients as a mechanism for infection prevention, no clear data are available to support this practice, nor are neutropenic diets, footwear exchange, and other dietary interventions.[18–19]

▶ *Pharmacologic Therapy*

There are two primary choices for the initial management of high-risk FN: monotherapy and dual therapy (see Figure 99–1). Both regimens have been shown to be equivalent in randomized studies and meta-analyses. Monotherapy avoids the nephrotoxicity of the aminoglycosides and is potentially less expensive but lacks significant gram-positive coverage and may increase selection of resistant organisms. Dual therapy provides synergistic activity, decreased resistance, and dual coverage of *Pseudomonas aeruginosa* but also lacks gram-positive coverage and requires therapeutic monitoring for aminoglycosides. The choice between monotherapy and dual therapy is usually provider and institution preference, although dual therapy may be preferred in an acutely symptomatic patient (eg, hypotensive).

Vancomycin adds broad-spectrum gram-positive coverage; however, the increasing emergence of vancomycin-resistant organisms (ie, *Enterococcus* spp.) prompts conservative use of this medication. Vancomycin should only be included as part of the initial therapy if the following are present:

- Severe mucositis
- Soft tissue infection
- Quinolone or TMP-SMX prophylaxis
- Hypotension or septic shock
- Colonization with resistant gram-positive organisms (ie, MRSA)
- Evidence of central venous catheter infection[17]

Vancomycin may be added to the empiric regimen after 3 to 5 days in persistently febrile patients or if cultures reveal gram-positive organisms. Vancomycin should be changed if the gram-positive organism is susceptible to other antibacterials or discontinued in patients with persistent fever after 3 days with negative culture results. Linezolid, quinupristin–dalfopristin, tigecycline, and daptomycin may be used in cases of vancomycin-resistant organisms or if vancomycin is not an option because of drug allergy or intolerance.[17]

Empiric antifungal agents are typically added in persistently febrile patients after 5 to 7 days, especially if continued neutropenia is expected. Amphotericin B has historically been the drug of choice because of its broad-spectrum activity against both yeast (*Candida* spp.) and mold (*Aspergillus* spp.) infections. Because frequent toxicity (nephrotoxicity, infusion reactions) limits the use of amphotericin B, less toxic alternatives have been studied. Lipid formulations of amphotericin provide decreased toxicity,

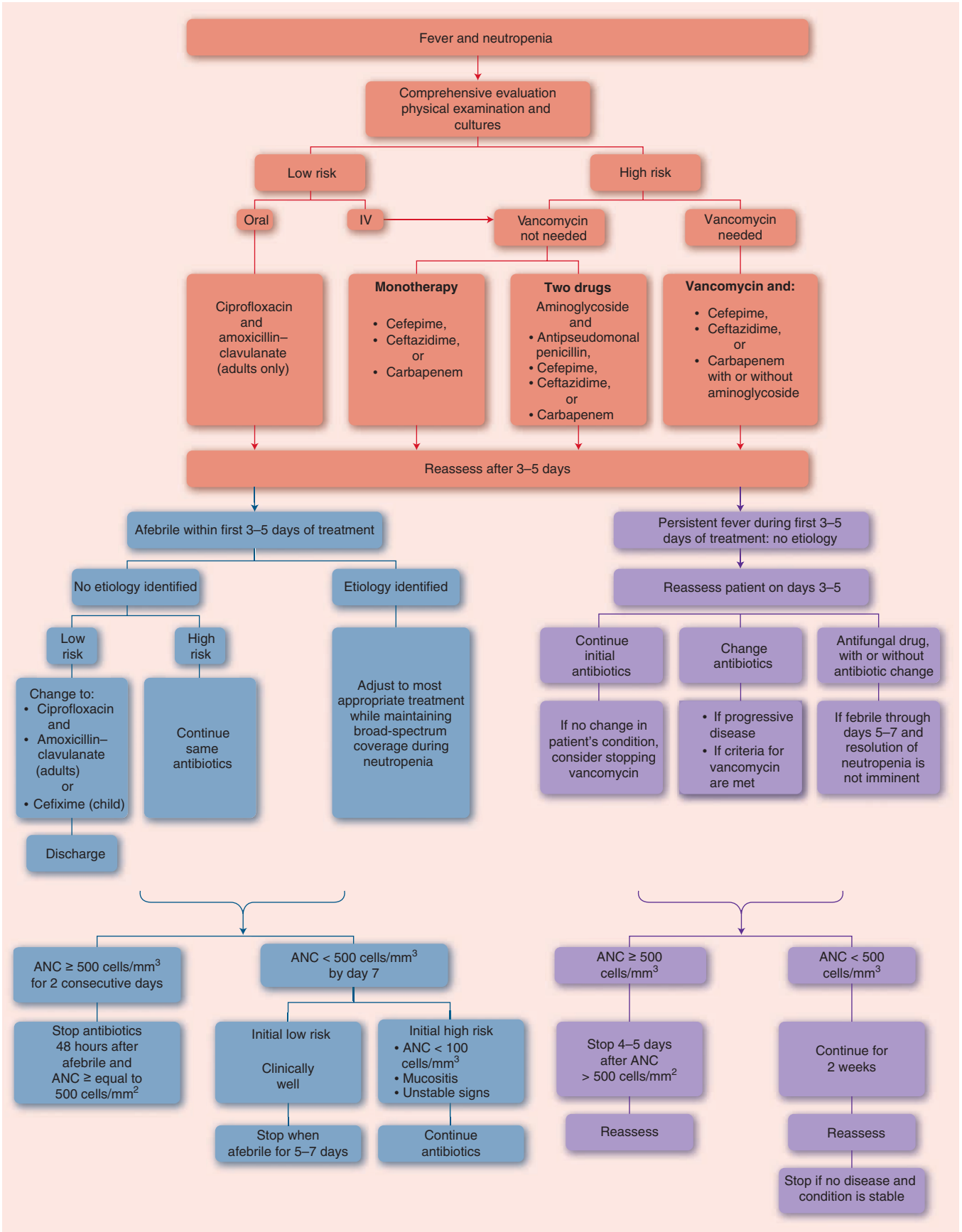

FIGURE 99–1. Management of febrile episodes in neutropenic cancer patients. (ANC, absolute neutrophil count.)

Table 99–8

Dosing Guidelines for Empiric Antimicrobial Agents in FN

Regimen Type	Agents and Dosing[a]	Comments
Antibacterial		
β-Lactam monotherapy	Cefepime 2 g IV every 8 hours Ceftazidime 2 g IV every 8 hours Imipenem 500 mg IV every 6 hours Meropenem 1 g IV every 8 hours Piperacillin–tazobactam 4.5 g IV every 6 hours	Although piperacillin–tazobactam is not recommended in the IDSA guidelines, recent data demonstrate equivalence to other monotherapy and dual therapy regimens. All these agents require renal dose adjustment, and none requires adjustment in hepatic dysfunction. All except meropenem require adjustment during dialysis.
Dual therapy with antipseudomonal β-lactam plus aminoglycoside	Cefepime, ceftazidime, imipenem, meropenem, piperacillin–tazobactam (above dosages), ticarcillin–clavulanic acid 3.1 g IV every 6 hours and gentamicin or tobramycin	Gentamicin or tobramycin 2 mg/kg loading dose followed by doses adjusted by serum concentrations; once-daily dosing of aminoglycosides may be used. Both gentamicin and tobramycin require renal dose adjustment but are dosed based on serum levels. Neither gentamicin nor tobramycin requires hepatic dose adjustment.
Empiric regimens containing vancomycin	Cefepime, ceftazidime, imipenem, meropenem (above dosages) and vancomycin 0.5–1 g every 6–12 hours with or without aminoglycoside	Vancomycin dosages may be adjusted based on serum levels and are adjusted for renal disease and dialysis. No dose adjustment is recommended for hepatic dysfunction.
Dual therapy containing fluoroquinolone	Ciprofloxacin 400 mg IV every 8 hours and piperacillin–tazobactam or ceftazidime (above dosages)	Cannot be used in patients who receive fluoroquinolone prophylaxis. Dose adjusted in renal disease and dialysis but not for hepatic dysfunction.
Low-risk po regimen	Ciprofloxacin 750 mg po every 12 hours and amoxicillin–clavulanate 500–875 mg po every 12 hours	For patients with MASCC scores ≥ 21 not receiving fluoroquinolone prophylaxis. Amoxicillin–clavulanate is adjusted in renal disease and dialysis but not hepatic dysfunction.
Antifungal		
Amphotericin B deoxycholate	0.5–1 mg/kg IV daily	Premedication with acetaminophen and diphenhydramine; 500 mL normal saline boluses before and after. No dose adjustments are recommended for renal or hepatic dysfunction or during dialysis.
Liposomal amphotericin B	3 mg/kg IV daily	Lower incidence of nephrotoxicity and infusion reactions; more expensive. No dose adjustments are recommended for renal or hepatic dysfunction or during dialysis.
Caspofungin	70 mg/kg IV loading dose on day 1 followed by 50 mg/kg IV daily	Dosage adjustment in hepatic dysfunction but not for renal disease or dialysis.
Voriconazole	6 mg/kg IV loading dose every 12 hours on day 1 followed by 4 mg/kg po or IV every 12 hours	Dosage adjustment in hepatic dysfunction; IV formulation contraindicated if creatinine clearance < 50 mL/min (0.83 mL/s); multiple drug interactions.
Posaconazole	Prophylactic: 200 mg po three times a day with food 300 mg IV twice a day on day 1, then 300 mg IV daily Salvage: 200 mg po four times a day with food; then 400 mg po two times a day when stable	Not FDA-approved for primary or salvage therapy for invasive fungal infections but used clinically; no dose adjustments required for renal or hepatic dysfunction or during dialysis.

[a]Dosing for adult patients; adjust doses for renal dysfunction.

AML, acute myeloid leukemia; FDA, Food and Drug Administration; IDSA, Infectious Diseases Society of America; IV, intravenous; MDS; myelodysplastic syndrome; NCCN, National Comprehensive Cancer Network; po, oral.

and liposomal amphotericin B (AmBisome) has been shown to be equivalent to conventional amphotericin B as empiric therapy but is significantly more expensive. Caspofungin is equivalent with less toxicity compared with liposomal amphotericin B in a randomized trial and is FDA-approved for this indication.[17,19] Voriconazole is equivalent to liposomal amphotericin in mortality, but response was improved in those receiving liposomal amphotericin. Voriconazole does not have an indication, but it is sometimes used. Itraconazole has also been used in some institutions, but its use is complicated by poor bioavailability of oral preparations and numerous drug interactions. Posaconazole is FDA-approved for the prevention of invasive *Aspergillus* and *Candida* infections in patients at high-risk due to being severely immunocompromised (ie, prolonged neutropenia; hematopoietic stem cell transplant patients with graft-versus-host-disease). The oral suspension of posaconazole is also approved for the treatment of local oropharyngeal Candidiasis. It is not FDA-approved as primary or salvage therapy for the treatment of invasive fungal infections but it is approved by the European Union for invasive aspergillosis and other fungal infections that are refractory to standard antifungal agents.

As stated earlier, low-risk patients fulfilling the MASCC criteria (see Table 99–6) may be treated empirically as an outpatient with a regimen combining amoxicillin–clavulanic acid

and ciprofloxacin. Ciprofloxacin and clindamycin are reasonable alternatives for penicillin-allergic patients.

The CSFs should not routinely be used for treatment of FN in conjunction with antimicrobial therapy.[17,19] However, the use of CSFs in certain high-risk patients with hypotension, documented fungal infection, pneumonia, or sepsis is reasonable. A meta-analysis demonstrated that hospitalization and neutrophil recovery are shortened and infection-related mortality is marginally improved with CSF prophylaxis in high-risk patients.[24] As with prophylactic use of these agents, cost considerations limit their use to high-risk patients.

OUTCOME EVALUATION

The success of the treatment of FN depends on the adequate recovery of the ANC and either optimal antimicrobial coverage of identified organisms or empiric coverage of unidentified organisms. Monitor the complete blood count (CBC) with differential and T_{max} (maximum temperature during previous 24 hours) daily. Assess renal and hepatic function at least twice weekly, especially in patients receiving nephrotoxic agents. Vital signs should be taken every 4 hours. Follow up on blood and urine culture results daily because many cultures do not become positive for several days. Assess the patient daily for pain that may indicate an infectious source. Conduct daily physical examination of common sites of infection. Repeat cultures and chest x-ray in persistently febrile patients and culture developing sources of infection (ie, stool cultures for diarrhea).

CARDIOVASCULAR COMPLICATIONS: SUPERIOR VENA CAVA SYNDROME (SVCS)

INTRODUCTION

Superior vena cava syndrome (SVCS) is a relatively rare complication that may occur in patients with cancer. SVCS is rarely immediately life threatening except in patients with airway compromise and/or laryngeal or cerebral edema. However, rapid recognition of typical presenting symptoms facilitates referral for tissue diagnosis (if unknown) and treatment.

EPIDEMIOLOGY AND ETIOLOGY

SVCS occurs in around 15,000 patients per year, 90% of which are caused by malignancy. Specific cancers most commonly associated with SVCS are listed in Table 99–9. Lung cancer is the most frequent cause, of which small cell lung cancer (SCLC) is the most frequent subtype associated with SVCS. This is thought to be because of its predilection for the central and perihilar areas of the lung. Interestingly, right-sided lung cancers are four times more likely than left-sided lesions to cause SVCS. Mediastinal masses from lymphomas are the second most common cause.

The most common nonmalignant etiology of SVCS is catheter-related thrombosis, primarily caused by the increasing use of central access devices. Other causes include benign teratoma, tuberculosis, silicosis, and sarcoidosis.

Table 99–9

Tumors Most Commonly Associated with SVCS

Cause	Frequency (%)
Non–small cell lung cancer	50
Small cell lung cancer	22
Lymphoma	12
Metastatic cancer (especially breast)	9
Germ cell tumor	3
Thymoma	2
Mesothelioma	1

Data from Wilson LD, Detterbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. N Engl J Med. 2007;356(8):1862–1869.

Clinical Presentation and Diagnosis of SVCS[28]

General

- Presentation depends on the degree of SVCS obstruction.
- Almost complete obstruction is necessary to demonstrate symptoms.

Signs and Symptoms

- Most common: swelling of face, neck, and upper extremity edema; dyspnea; cough; dilated upper extremity veins; orthopnea
- Less common: hoarseness, dysphagia, dizziness, headache, lethargy, chest pain
- Patients with elevated ICP may have mental status changes
- Patients with airway obstruction may have shortness of breath

Diagnostic Tests

- Tissue biopsy to determine underlying malignancy (if unknown), chest x-ray, CT scan, bronchoscopy, mediastinoscopy

PATHOPHYSIOLOGY

The SVC is the primary drainage vein for blood return from the head, neck, and upper extremities. It is a relatively thin-walled vein that is particularly vulnerable to obstruction from adjacent tumor invasion or thrombosis. The obstruction leads to elevated venous pressure, although collateral veins partially compensate. This is one reason for the relatively slow onset of the classic symptoms of SVCS. In fact, 75% of patients have signs and symptoms for more than 1 week before seeking medical attention.[28]

CLINICAL PRESENTATION AND DIAGNOSIS TREATMENT

Desired Outcomes

KEY CONCEPT The primary goal of treatment of SVCS is to relieve the obstruction of the SVC by treating the underlying malignancy. In the case of SVCS caused by thrombosis, the goal is to eliminate the thrombus and prevent further clot formation. Resolution of the obstruction will rapidly relieve symptoms and restore normal SVC function. The final goal of therapy is to avoid potentially fatal complications of SVCS such as cerebral edema from rapid increases in intracranial pressure (ICP) and intracranial thrombosis or bleeding.

General Approach to Treatment

Because the majority of SVCS is not immediately life threatening, a tissue diagnosis (if malignancy is unknown) to specifically identify the cancer origin is critical because treatment approaches vary considerably according to tumor histology. Thus, therapy can typically be withheld until a definitive tissue diagnosis is established. While biopsy results are pending, supportive measures such as head elevation, diuretics, corticosteroids, and supplemental oxygen may be used.

▶ *Nonpharmacologic Therapy*

Radiation therapy is the treatment of choice for chemotherapy-resistant tumors such as non–small cell lung cancer (NSCLC) or in chemotherapy-refractory patients with SVCS. Between 70% and 90% of patients experience relief of symptoms. Radiation therapy may also be combined with chemotherapy for chemotherapy-sensitive tumors such as SCLC and lymphoma. In the rare emergency situations of airway obstruction or elevated ICP, empiric radiotherapy before tissue diagnosis should be used. In most patients, symptoms resolve within 1 to 3 weeks.

Surgical options for the management of SVCS include stent placement and surgical bypass. SVC stenting may provide longer-term relief of symptoms than radiotherapy, so it is often used in the palliative care setting when chemotherapy has failed.[28] One disadvantage of SVC stenting is the need for anticoagulation, especially in patients at high risk for thrombosis. The role of surgical bypass is limited to patients with complete SVC obstruction or patients who are refractory to chemotherapy and radiotherapy; thus, it is rarely indicated.

▶ *Pharmacologic Therapy*

LO 5 Cytotoxic chemotherapy is the treatment of choice for chemotherapy-sensitive tumors such as SCLC and lymphoma. As indicated earlier, chemotherapy may also be combined with radiotherapy, especially in patients with lymphoma who have bulky mediastinal lymphadenopathy.

Corticosteroids play a key role in the management of SVCS, particularly in cases of lymphoma, because these tumors inherently respond to corticosteroid therapy. They are also helpful in the setting of respiratory compromise. Corticosteroids benefit patients who are receiving radiation therapy by reduction of local radiation-induced inflammation and patients with increased ICP. Dexamethasone 4 mg IV or by mouth every 6 hours is a frequently used regimen. The dosage should be tapered upon completion of radiation therapy or resolution of symptoms.

The role of diuretics in the management of SVCS is controversial. Although patients may derive symptomatic relief from edema, complications such as dehydration and reduced venous blood flow may exacerbate the condition. If diuretics are used, furosemide is most frequently used with diligent monitoring of the patient's fluid status and blood pressure.

In the case of thrombosis-related SVCS, anticoagulation is controversial because there is a lack of survival benefit. However, thrombolytics (ie, alteplase) and anticoagulation with heparin and warfarin may be beneficial in patients with thrombosis caused by indwelling catheters if used within 7 days of onset of symptoms, although catheter removal may be required.[28]

OUTCOME EVALUATION

The major measure of outcome of treatment of SVCS is the relief of symptoms, regardless of the therapy used.

NEUROLOGIC COMPLICATIONS: SPINAL CORD COMPRESSION

INTRODUCTION

Although not typically life threatening, spinal cord compression is a true oncologic emergency because delays in treatment by mere hours may lead to permanent neurologic dysfunction. Practitioners must quickly recognize the signs and symptoms of this condition to facilitate rapid management strategies.

EPIDEMIOLOGY AND ETIOLOGY

LO 1 Around 20,000 cancer patients experience spinal cord compression in the United States every year, most of which involves the thoracic spine (~70%). Cancers that inherently metastasize to the bone (ie, breast, prostate, and lung) are the most frequent underlying malignancies associated with this complication. Most spinal cord compression occurs in patients with a known malignancy; however, 20% to 25% of cases occur as the initial presentation of cancer, especially in patients with non-Hodgkin lymphoma, multiple myeloma, and lung cancer.[29] Recently, predictive models have been developed to predict survival from SCC from myeloma and NSCLC.[30,31]

PATHOPHYSIOLOGY

The spinal cord emerges from the brain stem at the base of the skull and terminates at the second lumbar vertebra. The thoracic spine is most vulnerable to cord compression because of natural kyphosis and because the width of the thoracic spinal canal is the smallest

Clinical Presentation and Diagnosis of Spinal Cord Compression

General

- Once neurologic deficits appear, progression to irreversible paralysis may occur within hours to days.
- Around 30% to 50% of patients present with multiple sites of spinal involvement.

Signs and Symptoms

- Back pain is present in more than 90% of patients.
- Initially localized and increases in intensity over several weeks
- Aggravated by movement, supine positioning, coughing, sneezing, neck flexion, straight leg raise, Valsalva maneuver, palpation of spine
- Sensory deficit
- Cervical spine compression: quadriplegia
- Thoracic spine compression: paraplegia
- Upper lumbar spine compression: bowel and bladder dysfunction (constipation and urinary retention) and abnormal extensor plantar reflexes
- Weakness

Diagnostic Tests

- MRI with gadolinium enhancement is the gold standard.
- X-rays may be helpful to identify bone abnormalities.

among the vertebrae. Most spinal cord compression is caused by adjacent vertebral metastases that compress the spinal cord or from pathologic compression fracture of the vertebra. This results in significant edema and inflammation in the affected area.

Patients with spinal cord compression are in acute, severe back and/or neck pain and may present to the emergency department for evaluation. Diagnosis is made based on symptoms and imaging studies that show fractured vertebrae.

TREATMENT

Desired Outcomes

KEY CONCEPT Because patients with cancer and spinal metastases are generally incurable, the primary goal of treatment of spinal cord compression is palliation. The most important prognostic factor for patients presenting with spinal cord compression is the degree of underlying neurologic dysfunction. Only around 10% of patients who present with paralysis are able to ambulate after treatment.[29] Therefore, the goals of treatment are recovery of normal neurologic function, local tumor control, pain control, and stabilization of the spine. Therapeutic options depend primarily on the following factors:

- Underlying malignancy
- Prior therapies
- Stability of the spine at presentation
- Overall patient prognosis

▶ *Nonpharmacologic Therapy*

Radiation therapy at 20 Gy in five daily fractions or 30 Gy in 10 daily fractions is generally considered to be the treatment of choice for most patients. Exceptions to this include patients with prior radiation to the treatment site and patients with inherently radio-resistant tumors (ie, melanoma, renal cell carcinoma). The radiation field should include two vertebral bodies above and below the involved area.

Surgery for spinal cord compression typically involves either laminectomy for posterior lesions or decompression with fixation. Surgery is the treatment of choice for the following patients: (a) patients with unstable spine requiring stabilization, (b) immediately impending sphincter dysfunction requiring rapid spinal decompression, (c) patients who do not respond to or have received their maximum dose of radiotherapy, and (d) direct compression of the spinal cord caused by spinal bony fragments.[29] Surgery followed by radiation therapy may be superior to radiotherapy alone in terms of increased ambulation time after treatment, maintenance of continence, and rates of nonambulatory patients becoming ambulatory.[32] Surgery is also useful for establishing a tissue diagnosis in cases of unknown malignancy. Overall, the risks and benefits of surgery must be weighed against the expected prognosis of the patient in light of the significant rehabilitation required after surgery.

▶ *Pharmacologic Therapy*

LO 5 Corticosteroids play a vital role in the management of spinal cord compression. Dexamethasone is most frequently used to reduce edema, inhibit inflammation, and delay the onset of neurologic complications. Dexamethasone has been shown to improve ambulation in combination with radiation compared with radiation alone.[29] Significant controversy exists regarding the optimal dosing of dexamethasone though both the UK and Canadian guidelines recommend 16 mg orally or IV immediately, followed by a short course of 8 mg by mouth or intravenously twice daily. Higher doses may be used in cases of rapidly progressing symptoms, but adverse effects, including GI bleeding and psychosis, are more severe. Steroids should be continued during radiation therapy and then tapered appropriately.

LO 5 Pain management is also of critical importance in patients with spinal cord compression. Although dexamethasone will provide some benefit, opioid analgesics should also be used and titrated rapidly to achieve adequate pain control.

Clinical Presentation and Diagnosis of Brain Metastasis

General

- Almost all patients with brain metastases are symptomatic.
- New cerebral neurologic symptoms in a cancer patient should initiate evaluation for brain metastases.
- Other causes of brain lesions, including hemorrhage, infection, and infarct, should be ruled out.

Signs and Symptoms

- Mental status changes (most common): loss of consciousness, irritability, confusion
- Hemiparesis, aphasia, papilledema, weakness, seizure, nausea, and vomiting
- Headache: may be of gradual onset or sudden in the case of hemorrhage

Diagnostic Tests

- MRI with contrast enhancement is the gold standard.
- CT scans may be used in patients with pacemakers, but may miss small metastases.

OUTCOME EVALUATION

Patients who receive definitive treatment with radiation and/or surgery generally derive benefit within days.

COMPLICATIONS OF BRAIN METASTASES

INTRODUCTION

Brain metastases are among the most feared complications of cancer and generally carry a poor prognosis. One serious consequence of brain metastases is elevated ICP, which can rapidly lead to fatal intracranial herniation and death. Rapid identification of the signs and symptoms of brain metastases is critical to improve long-term outcome and avoid mortality. The signs and symptoms of brain metastasis can be confused with common psychological distress or other neurologic problems (eg, headaches) that may go unrecognized. It is important that patients who are suspected to have brain metastasis are quickly referred for appropriate management.[33]

EPIDEMIOLOGY AND ETIOLOGY

Brain metastasis is the most common neurologic complication seen in patients with cancer. Approximately 170,000 patients develop brain metastases in the United States each year.[33] Many malignancies are frequently associated with brain metastases (Table 99–10). Although melanoma is the tumor type most likely

Table 99–10

Cancers Most Frequently Associated with Brain Metastases

Type of Cancer	Frequency (%)
Lung cancer	18–64
Breast cancer	2–21
Melanoma	4–16
Colorectal cancer	2–11
Hematologic malignancies (ie, leukemia)	~10 (primarily caused by leptomeningeal spread)

Data from Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol. 2015;33(30):3475–3484.

to metastasize to the brain, brain metastases caused by lung and breast cancer are seen more often because they are among the most common cancers. In addition, brain metastases may be diagnosed at the same time as the primary malignancy in around 20% of cases.[33] Around 80% of brain metastases occur in the cerebral hemispheres, 15% in the cerebellum, and 5% in the brain stem.

PATHOPHYSIOLOGY

A delicate balance of normal pressure is maintained in the brain and spinal cord by brain, blood, and cerebrospinal fluid. Because the brain is contained within a confined space (skull), any foreign mass contained within that space causes adverse sequelae. This results in either destruction or displacement of normal brain tissue with associated edema. Most brain metastases occur through hematogenous spread of the primary tumor and around 80% of patients have multiple sites of metastases within the brain.

TREATMENT

Desired Outcomes

Therapeutic modalities used for the management of brain metastases may be divided into symptomatic management and definitive management. KEY CONCEPT The goals of treatment of brain metastases are to manage symptoms by reducing cerebral edema, treat the underlying malignancy both locally and systemically, and improve survival.

General Approach to Treatment

Patients with brain metastases have a poor prognosis. Untreated patients generally have a median survival of 1 month. Recent advances in drug therapy and radiation/stereotactic radiosurgery now yield median survival times as long as 13.5 months in some patients with solitary brain lesions and good performance status.[33] The choice of treatment depends primarily on the status of the patient's underlying malignancy and the number and sites of brain metastases. The primary definitive treatments for brain metastases are surgery and radiation therapy. Pharmacologic modalities such as corticosteroids and antiepileptics are primarily used to control symptoms, although cytotoxic chemotherapy plays a limited role in the management. Monoclonal antibodies have a large molecular size and therefore would not be expected to cross the blood-brain-barrier (BBB); however, BBB permeability may be enhanced due to physical disruption from the brain metastasis itself and some of the targeted oral therapies have better BBB penetration.[33]

LO 5

▶ *Nonpharmacologic Therapy*

LO 5

Radiation therapy is the treatment of choice for most patients with brain metastases. Most patients receive whole-brain radiation (WBRT) because the majority of brain metastases are multifocal. Another method known as stereotactic radiosurgery provides intense focal radiation, typically using a **linear accelerator** or **gamma knife**, in patients who cannot tolerate surgery or have lesions that are surgically inaccessible (ie, brain stem). Stereotactic radiosurgery is also often used for selected patients with up to three lesions that are each less than 4 cm.[33] WBRT can cause long-term problems with memory and cognitive function but this risk is less than that seen with declines due to brain disease and thus the benefits of WBRT outweigh the risks in appropriate patients.[33] Because brain metastases can occur in up to 50% of patients with small cell lung cancer, prophylactic cranial irradiation (PCI) is recommended in patients with limited stage disease with good performance status who at least partially respond to chemotherapy to both prevent the development of brain metastases and to prolong survival; there is conflicting evidence on the role of PCI in extensive stage SCLC though generally many patients will be offered treatment.[34] Although other cancers can metastasize to the brain, the benefits of routine prophylactic cranial irradiation have only been demonstrated in studies conducted in patients with small cell lung cancer.[34] In fact, a recent meta-analysis reported that prophylactic cranial irradiation may reduce overall survival when used in NSCLC patients even though it reduced brain metastases in these patients.[35]

LO 5

Surgery plays a key role in the management of patients with brain metastases, particularly in patients whose systemic disease is well controlled and in patients with solitary lesions. Surgery may also benefit patients with multiple metastatic sites who have a single dominant lesion with current or impending neurologic sequelae.

▶ *Pharmacologic Therapy*

LO 5

Corticosteroids are a mainstay in the management of brain metastases. They reduce edema that typically surrounds sites of metastases thereby reducing ICP. A loading dose of dexamethasone 10 mg to 24 mg IV followed by 4 mg by mouth or IV every 6 hours or 8 mg by mouth twice daily is typically used. Symptom relief may occur shortly after the loading dose, although the maximum benefit may not be seen for several days (after definitive therapy).[36]

LO 5

Mannitol is an agent that may be used in patients with impending cerebral herniation. Mannitol is an osmotic diuretic that shifts brain osmolarity from the brain to the blood. Doses of 100 g (1–2 g/kg) as an IV bolus should be used. Repeated doses are typically not recommended because mannitol may diffuse into brain tissue, leading to rebound increased ICP.[36]

Around 20% patients with brain metastases may present with seizures and require anticonvulsant therapy. Phenytoin is the most frequently used agent with a loading dose of 15 mg/kg followed by 300 mg by mouth daily (titrated to therapeutic levels between 10 and 20 mcg/mL [40 and 79 μmol/L]). Diazepam 5 mg IV may be used for rapid control of persistent seizures. Prophylactic anticonvulsants have frequently been used; however, a systematic review did not support their use.[37] Thus, because adverse effects and drug interactions are common, the routine use of prophylactic anticonvulsants is not recommended.

OUTCOME EVALUATION

The success of therapy is based on the ability to decrease symptoms, treat the underlying sites of disease within the brain, and prolong survival.

UROLOGIC COMPLICATIONS: HEMORRHAGIC CYSTITIS

INTRODUCTION

LO 1

Hemorrhagic cystitis is defined as acute or insidious bleeding from the lining of the bladder. Although therapy with certain medications is the most common cause, it is also the most preventable. Once it occurs, hemorrhagic cystitis causes significant morbidity and mortality rates between 2% and 4%. This section focuses on preventive strategies for chemotherapeutic causes of hemorrhagic cystitis.

EPIDEMIOLOGY AND ETIOLOGY

Numerous etiologies have been linked to hemorrhagic cystitis (Table 99–11).[38] Of these, the oxazaphosphorine alkylating agents (cyclophosphamide and ifosfamide) are most frequently implicated. Hemorrhagic cystitis is the dose-limiting toxicity of ifosfamide and predisposes patients with bladder cancer. Incidence rates vary considerably but generally range between 20% and 25% with high-dose (300 mg/m^2 or more) cyclophosphamide in the absence of prophylactic measures and even more commonly with ifosfamide.[38] Chronic, low-dose oral cyclophosphamide as typically used in autoimmune disorders and chronic lymphocytic leukemia is infrequently associated with hemorrhagic cystitis. Cystitis occurs in 80% of patients treated with intravesicle bacillus Calmette-Guerin (BCG) for bladder cancer, with 20% also experiencing hematuria.[38]

Around 20% patients receiving pelvic irradiation may experience hemorrhagic cystitis, especially with concurrent cyclophosphamide. Notably, this toxicity can present acutely or long after treatment with radiation has ended (up to 15 years).[38] Viral infections commonly associated with this condition most frequently occur in bone marrow transplant recipients who may also receive cyclophosphamide.

PATHOPHYSIOLOGY

Cyclophosphamide- or ifosfamide-induced damage to the bladder wall is primarily caused by their shared metabolite known as acrolein. Acrolein causes sloughing and inflammation of the bladder lining, leading to bleeding and hemorrhage. This is most common when urine output is low because higher concentrations of acrolein come into contact with the bladder urothelium for longer periods of time. Radiation treatment directly damages the protective glycosaminoglycan layer of the bladder epithelium.[38]

Table 99–11

Primary Causes of Hemorrhagic Cystitis

Pharmacologic	Nonpharmacologic
Cyclophosphamide	Pelvic irradiation
Chronic low doses	Viral infection
High doses used in BMT	CMV
Ifosfamide	Papovavirus
Intravesicular thiotepa	Herpes simplex virus
Chronic oral busulfan	Adenovirus
Anabolic steroids	

BMT, bone marrow transplantation; CMV, cytomegalovirus.

Data from Payne H, Adamson A, Bahl A, et al. Chemical- and radiation-induced hemorrhagic cystitis: current treatments and challenges. BJU Int. 2013;112(7):885–897.

Clinical Presentation and Diagnosis of Hemorrhagic Cystitis

General

- Presentation may be mild (microscopic hematuria) or severe (massive hemorrhage) and develops during or shortly after chemotherapy infusion.
- Presentation may be delayed when associated with pelvic radiation.

Signs and Symptoms

- Suprapubic pain and cramping, urinary urgency and frequency, dysuria and burning, hematuria
- Urinary retention leading to hydronephrosis and renal failure may occur if large blood clots obstruct the ureters or bladder outlet.

Laboratory Tests

- Urine dipsticks for blood
- Urinalysis reveals more than three RBCs per high-power field: microscopic hematuria
- CBC with differential, prothrombin time or international normalized ratio, activated partial thromboplastin time, blood urea nitrogen, creatinine

PREVENTION

KEY CONCEPT The use of effective prevention strategies can decrease the incidence of hemorrhagic cystitis to fewer than 5% in patients receiving cyclophosphamide or ifosfamide. Three methods are used to reduce the risk: administration of Mesna (2-mercaptoethane sulfonate), hyperhydration, and bladder irrigation with catheterization. Mesna is the primary method used with ifosfamide; all three strategies are used with cyclophosphamide.

LO 3

Mesna is a thiol compound that is rapidly oxidized in the bloodstream after administration to dimesna, which is inactive. However, after being filtered through the kidneys, dimesna is reduced back to Mesna, which binds to acrolein, leading to its inactivation and excretion. ASCO has published evidence-based guidelines for the dosing and administration of Mesna (Table 99–12).[39] The dose of oral Mesna must be double the IV dose because of its oral bioavailability between 40% and 50%. Because the half-life of Mesna (~1.2 hours) is much shorter than that of ifosfamide or cyclophosphamide, prolonged administration of Mesna beyond the end of the chemotherapy infusion is critical (Figure 99–2). Patients should receive at least 2 L of IV fluids beginning 12 to 24 hours before and ending 24 to 48 hours after the last dose of chemotherapy.[38,39]

Hyperhydration with normal saline at 3 L/m^2/day with IV furosemide to maintain urine output greater than 100 mL/hour has also been used with cyclophosphamide. Continuous bladder

Table 99–12

ASCO Guidelines for the Use of Mesna with Ifosfamide and High-Dose Cyclophosphamide

Chemotherapy Schedule	Dosing Schedule for Mesna	Comments
Low-dose ifosfamide < 2 g/m²/day	Oral: 100% of total daily dose of ifosfamide given 20% IV: 15 minutes before and 40% po 2 and 6 hours after start of ifosfamide	Available in 400-mg tablets Peak urinary thiol concentrations with oral Mesna is at 3 hours If patient vomits within 2 hours of administration, repeat dose po or IV
Standard-dose ifosfamide equal to 2.5 g/m²/day	Bolus: 60% of total daily dose of ifosfamide given IV in 20% increments 15 minutes before and 4 and 8 hours after start of ifosfamide Infusion: 60% of total daily dose of ifosfamide given 20% IV 15 minutes before and 40% by continuous infusion during and for 12–24 hours after end of ifosfamide	Peak urinary thiol concentrations with IV Mesna is at 1 hour Compatible with ifosfamide and cyclophosphamide by Y-site administration or when admixed in the same bag
High-dose ifosfamide > 2.5 g/m²/day	Lack of evidence for dosing, but higher doses for longer duration recommended based on longer half-life of ifosfamide at high doses	
Standard-dose cyclophosphamide	Use of Mesna is not routinely necessary	
High-dose cyclophosphamide (BMT)	Bolus: 40% of cyclophosphamide dose given IV at hours 0, 3, 6, and 9 after cyclophosphamide Infusion: 100% of cyclophosphamide dose given by continuous infusion until 24 hours after cyclophosphamide	Should be combined with saline diuresis (1.5 L/m²/day of normal saline)

ASCO, American Society of Clinical Oncology; BMT, bone marrow transplantation; IV, intravenous; Mesna, 2-mercaptoethane sulfonate; po, oral.

Data from Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009;27(1):127–145.

irrigation by catheterization uses normal saline at 250 to 1000 mL/hour to flush acrolein from the bladder. Mesna is equivalent to both strategies in patients receiving high-dose cyclophosphamide and avoids the discomfort and infection risk with catheterization and the intensity of hyperhydration. Thus, mesna is the preventive method of choice.[38,39]

TREATMENT

Desired Outcomes

If hemorrhagic cystitis occurs, the goals of treatment are to decrease exposure to the offending etiology, establish and maintain urine outflow, avoid obstruction and renal compromise,

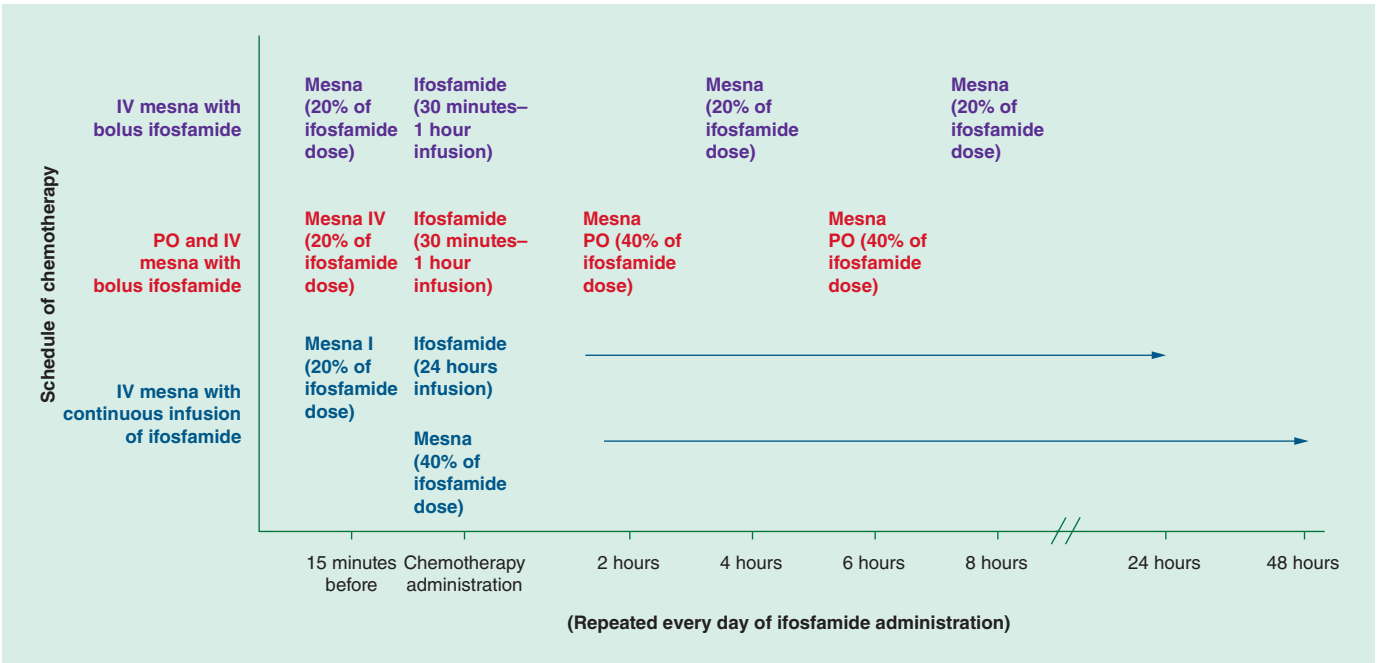

FIGURE 99–2. Examples of mesna (2-mercaptoethane sulfonate) administration with ifosfamide. (IV, intravenous; po, oral.)

and maintain blood and plasma volume. Restoration of normal bladder function is the ultimate goal following acute treatment.

General Approach to Treatment

The treatment of hemorrhagic cystitis first involves discontinuation of the offending agent. Agents such as anticoagulants and inhibitors of platelet function should also be discontinued. IV fluids should be aggressively administered to irrigate the bladder. Blood and platelet transfusions may be necessary to maintain normal hematologic values. Pain should be managed with opioid analgesics. Local intravesicular therapies may be necessary if hematuria does not resolve[38] (Figure 99–3).

▶ *Nonpharmacologic Therapy*

A large-diameter, multihole urethral catheter should be inserted to facilitate saline lavage and evacuation of blood clots. Surgical removal of blood clots under anesthesia may be required if saline lavage is ineffective. Active bleeding from isolated areas may be cauterized with an electrode or laser. In severe cases that are unresponsive to local or systemic pharmacologic intervention, urinary diversion with percutaneous nephrostomy or surgical removal of the bladder may be required.[38]

▶ *Pharmacologic Therapy*

LOS

A number of local or systemic agents are used in the treatment of hemorrhagic cystitis.[38] Local (direct instillation into the bladder), one-time administration of hemostatic agents such as alum, prostaglandins, silver nitrate, and formalin may be used; however, general anesthesia is required, especially with formalin, because of pain. Aluminum toxicity has been noted with alum irrigation, particularly in children. Systemic agents, including estrogens, vasopressin, aminocaproic acid, and hyperbaric oxygen (HBO), may be used in patients who are refractory to local therapy, although they introduce the risk of systemic side effects. HBO is particularly useful for radiation- and cyclophosphamide-induced cystitis. These agents should be continued until bleeding stops.

Antispasmodic agents such as oxybutynin 5 mg by mouth two to three times daily may be used for bladder spasms. In patients with refractory pain, opioid analgesics should be titrated to adequate pain control.[38] In very severe cases refractory to medical therapy, surgical procedures may be warranted.[38]

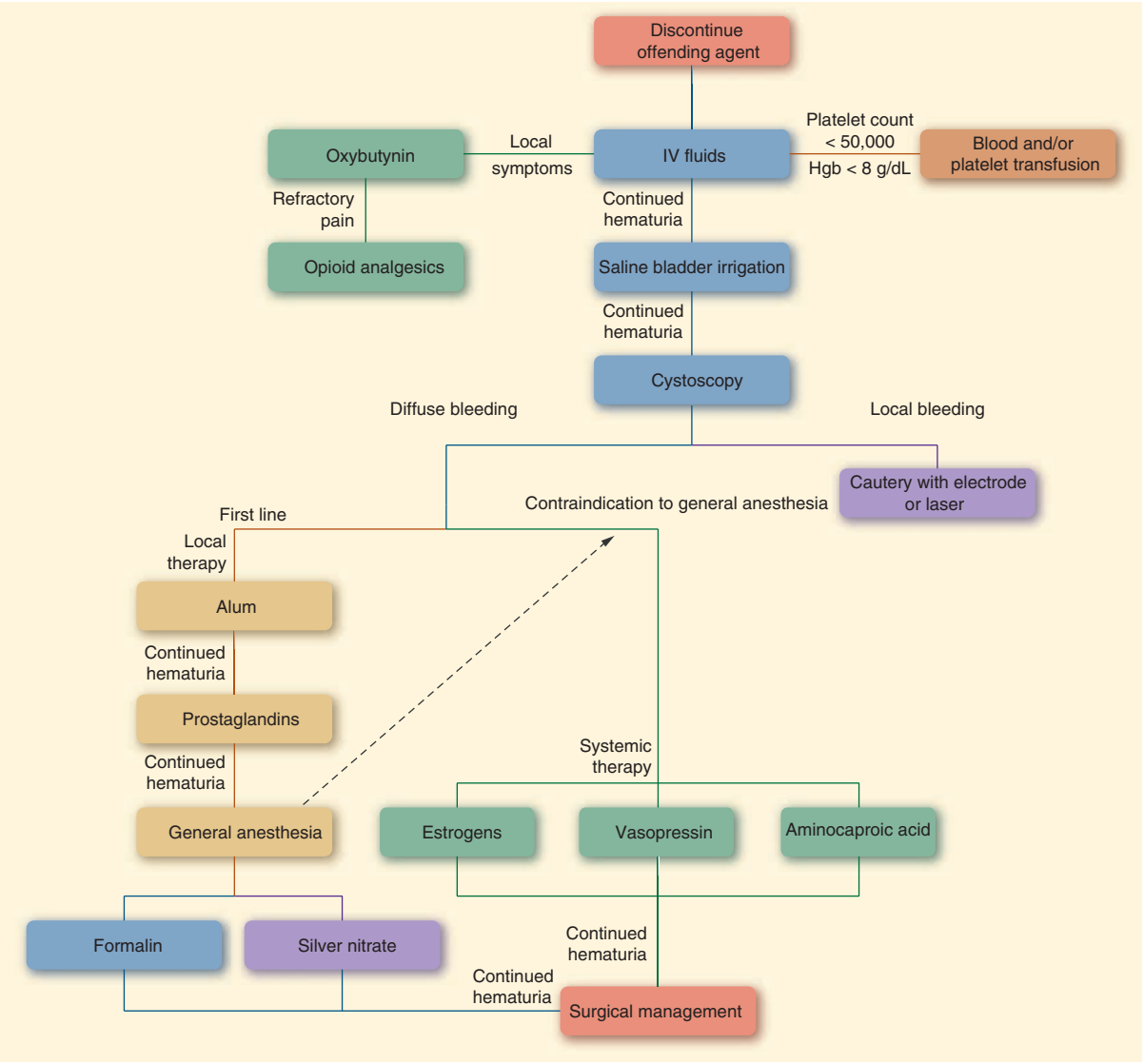

FIGURE 99–3. Treatment of hemorrhagic cystitis.

OUTCOME EVALUATION

The goal of treatment is resolution of bladder symptoms and appropriate pain management.

Monitor the patient for resolution of hematuria after each successive therapeutic intervention. The frequency of monitoring is based on the severity of hemorrhaging. Monitor urinary output and serum chemistries (including sodium, potassium, chloride, blood urea nitrogen [BUN], and serum creatinine) daily for renal dysfunction. Check the CBC at least daily to monitor hemoglobin and platelet count.

METABOLIC COMPLICATIONS: HYPERCALCEMIA OF MALIGNANCY

INTRODUCTION

Hypercalcemia is the most common metabolic abnormality experienced by patients with cancer. A small percentage of undiagnosed patients present with hypercalcemia. Once hypercalcemia occurs, it is associated with a very poor prognosis because of the frequent association with advanced or metastatic disease.[40]

EPIDEMIOLOGY AND ETIOLOGY

LO 3

Hypercalcemia occurs in 10% to 30% of patients with cancer during the course of their disease. The most common tumor types associated with hypercalcemia are breast cancer; squamous cell carcinomas of the head, neck, and lung; and renal cancer. Hematologic malignancies such as multiple myeloma and, rarely, lymphomas are other underlying malignancies associated with hypercalcemia.

PATHOPHYSIOLOGY

Around 99% of calcium is contained in the bones; the other 1% resides in the extracellular fluid. Of this extracellular calcium, approximately 40% is bound to albumin, and the remainder is in the ionized, physiologically active form. Normal calcium levels are maintained by three primary factors: parathyroid hormone (PTH), 1,25-dihydroxyvitamin D, and calcitonin. PTH increases renal tubular calcium resorption and promotes bone resorption. The active form of vitamin D, 1,25-dihydroxyvitamin D, regulates absorption of calcium from the GI t ract. Calcitonin serves as an inhibitory factor by suppressing osteoclast activity and stimulating calcium deposition into the bones.[40]

The delicate balance maintained by these factors is altered in patients with cancer by two principal mechanisms: tumor production of humoral factors that alter calcium metabolism in the absence of bone metastasis (humoral hypercalcemia) and by local osteolytic activity from bone metastases.[40] Humoral hypercalcemia causes around 80% of all hypercalcemia cases and is primarily mediated by systemic secretion of PTH-related protein (PTHrP). This protein mimics the action of endogenous PTH on bones. Local osteolytic activity causes 20% to 30% of hypercalcemia cases, although local osteolytic activity may also have a humoral component. Local production of various factors such as PTHrP, transforming growth factor-β, interleukin-1, and interleukin-6, and tumor necrosis factor-α promote RANK ligand expression on osteoblasts. RANK ligand signaling to the RANK receptor on osteoclasts causes osteoclast maturation and activation, leading to bone resorption.[40] Thus, these metastatic tumors perpetuate their own growth through this mechanism. Calcium is also released by the osteolytic activity, resulting in hypercalcemia.[40] Of note, multiple myeloma, breast, and lung cancer patients tend to develop osteolytic lesions and are at increased risk for hypercalcemia, whereas prostate cancer patients tend to develop osteoblastic lesions and are more at risk for hypocalcemia. A third and less common mechanism is production of 1,25-dihydroxyvitamin D by tumor cells (usually lymphoma), which increases GI absorption of calcium and enhances osteoclastic bone resorption.

TREATMENT

Desired Outcomes

KEY CONCEPT The primary goal of treatment for hypercalcemia is to control the underlying malignancy. Therapies directed at lowering the calcium level are temporary measures that are useful until anticancer therapy begins to work. The goals of calcium-lowering

Clinical Presentation and Diagnosis of Hypercalcemia[40]

General

- Presence of symptoms depends not only on the calcium level but the rapidity of onset.
- Normal calcium level is 8.5 to 10.5 mg/dL (2.13–2.63 mmol/L) (varies by laboratory).
- Serum calcium level *must* be corrected for albumin level using the following formula:

Corrected calcium (mg/dL) = Serum calcium + 0.8 (4 – Serum albumin) for serum calcium expressed in mg/dL and albumin in g/dL.

or

Corrected calcium (mmol/L) = Serum calcium + 0.02 (40 – serum albumin) for serum calcium expressed in mmol/L and albumin in g/L.

Signs and Symptoms

- Five primary organ systems may be affected:
  - GI: lack of appetite, nausea, vomiting, constipation
  - Musculoskeletal: weakness, bone pain, fatigue, ataxia
  - CNS: confusion, headache, lethargy, seizures, coma
  - Genitourinary: polydipsia, polyuria, renal failure
  - Cardiac: Bradycardia, ECG abnormalities, arrhythmias

Laboratory Tests

- Elevated corrected serum calcium level (≥ 10.5 mg/dL [2.63 mmol/L]), low serum albumin, low to normal serum phosphate
- Patient may have elevated blood urea nitrogen and serum creatinine.
- Elevated alkaline phosphatase may indicate bone destruction.
- ECG may indicate prolonged PR interval, shortened QT interval, widened T wave.

Other Diagnostic Tests

- Rule out other causes of hypercalcemia, including primary hyperparathyroidism, hyperthyroidism, vitamin D intoxication, chronic renal failure.

therapy are to (a) lower the corrected calcium to normal levels, (b) regain fluid and electrolyte balance, (c) relieve symptoms, and (d) prevent life-threatening complications.[40] Hypercalcemia is often indicative of a progressing cancer, with survival rates ranging from 2 months to 4.5 months.[40]

General Approach to Treatment

Therapeutic options for the treatment of hypercalcemia should be directed toward the level of corrected serum calcium and the presence of symptoms (Figure 99–4). Hypercalcemia may be classified as mild (corrected calcium equal to 10.5–11.9 mg/dL [2.63–2.98 mmol/L]), moderate (12–13.9 mg/dL [3.00–3.49 mmol/L]), and severe (> 14 mg/dL [3.50 mmol/L] or more).[40] Adequate treatment of mild or asymptomatic hypercalcemia may be achieved on an outpatient basis with nonpharmacologic measures. Moderate to severe or symptomatic hypercalcemia almost always requires pharmacologic intervention. Ultimately, effective treatment of the patient's underlying malignancy is the most important factor for the long-term prevention and management of hypercalcemia.[40]

▶ *Nonpharmacologic Therapy*

LOS

Calciuric therapy in the form of hydration is a key component in the treatment of hypercalcemia, regardless of severity or presence of symptoms.[40] Mild or asymptomatic patients may be encouraged to increase their oral fluid intake (3–4 L/day). Patients with moderate to severe or symptomatic hypercalcemia should receive normal saline at 200 to 500 mL/hour according to their dehydration and cardiovascular status. Patients should be encouraged to ambulate as much as possible because immobility enhances bone resorption. Although calcium should be discontinued from parenteral feeding solutions, oral calcium supplementation minimally contributes to hypercalcemia unless it is mediated by vitamin D. In these cases, oral calcium should be discontinued. Finally, agents that may contribute to hypercalcemia (thiazide diuretics, vitamin D, lithium) or decrease renal function (NSAIDs) should be discontinued. Dialysis may be used in refractory cases or patients who cannot tolerate aggressive saline hydration.[40]

Patient Encounter 3: Hypercalcemia of Malignancy

A 79-year-old man with stage IV moderately differentiated adenocarcinoma with features suggestive of a combined hepatocellular cholangiocarcinoma. The patient feels well but is fatigued and has a headache. He presents today to discuss treatment options for his disease. Relevant laboratory test results today are: calcium, 11.1 mg/dL (2.78 mmol/L) and albumin, 3.2 g/dL (32 g/L).

What is this patient's corrected calcium level?

How would you approach this patient's hypercalcemia?

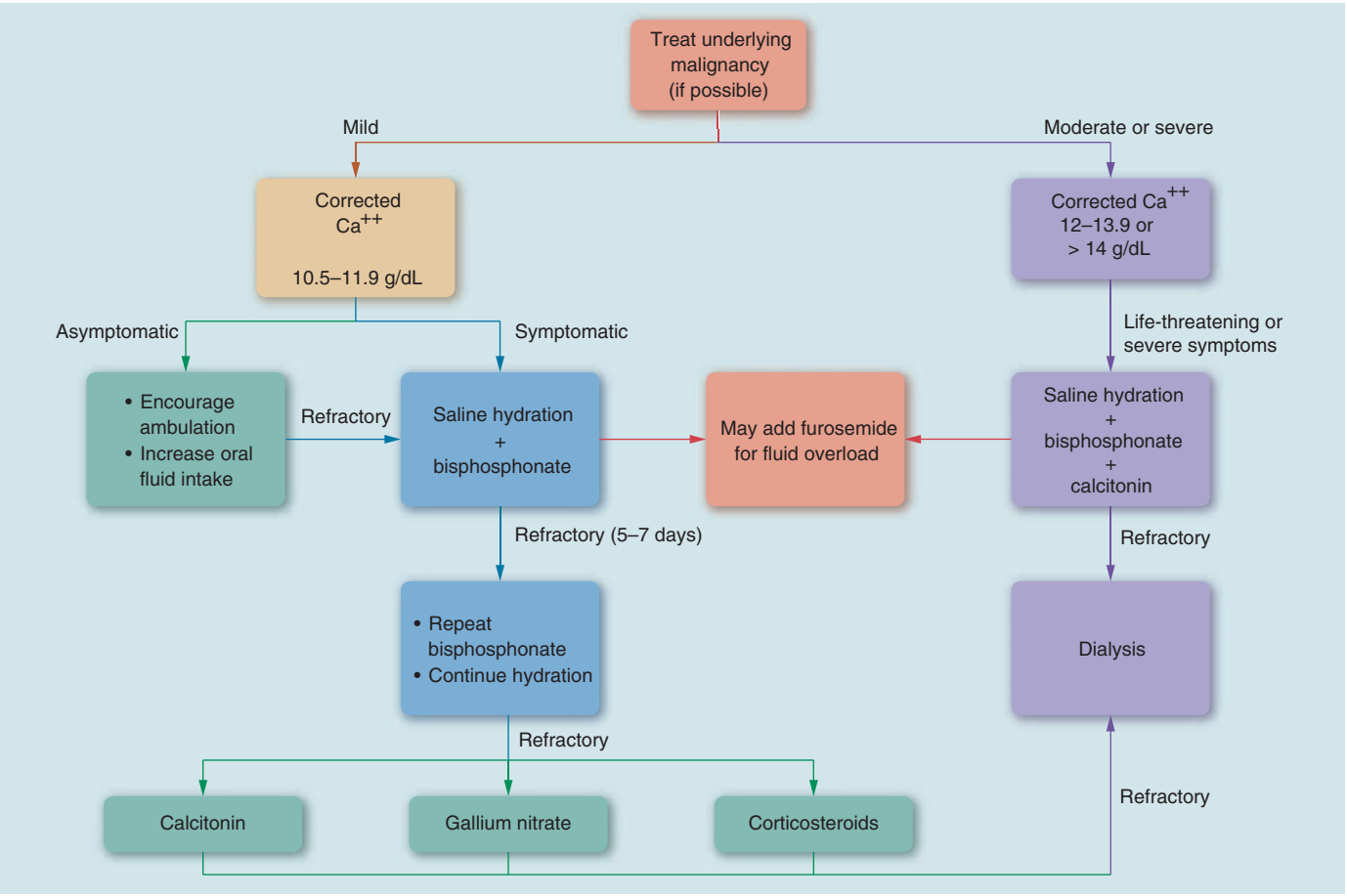

FIGURE 99–4. Treatment algorithm for the hypercalcemia of malignancy.

Table 99–13

Treatment Options for Hypercalcemia of Malignancy

	Agent	Dosage	Onset	Duration of Action	Reduction in Serum Calcium Concentration	Comments
Calciuric therapy	IV normal saline furosemide	200–500 mL/hour 20–40 mg IV	24–48 hours 4 hours	2–3 days 2–3 days	0.5–2 mg/dL (0.13–0.50 mmol/L)	Avoid fluid overload, monitor electrolytes Monitor for hypokalemia, dehydration
Antiresorptive therapy	Pamidronate	60–90 mg IV over 2–24 hours[a]	24–72 hours	3–4 weeks	> 1 mg/dL (0.25 mmol/L)	Nadir not seen until after 4–7 days; may cause fever, renal dysfunction
	Zoledronic acid	4 mg IV over 15 minutes	24–48 hours	4+ weeks	> 1 mg/dL (0.25 mmol/L)	
	Corticosteroids	Prednisone (or equivalent) 50–100 mg/day	5–7 days	3–4 days	0.5–3 mg/dL (0.13–0.75 mmol/L)	Monitor for hyperglycemia, insomnia, immunosuppression
	Calcitonin	4–8 IU/kg SC or IM every 6–12 hours	2–4 hours	1–3 days	2–3 mg/dL (0.50–0.75 mmol/L)	Salmon-derived formulation preferred; 1-unit test dose recommended; can be given in renal failure; may cause flushing, nausea
	Gallium nitrate	100–200 mg/m^2 CIV daily for 5 days	24–48 hours			Do not administer if creatinine > 2.5 mg/dL (221 µmol/L); may cause renal failure
	Denosumab	120 mg SQ days 1, 8, 15, and 29 the first month, then day 1 only every 4 weeks	48–96 hours	4+ weeks	> 1 mg/dL (0.25 mmol/L)	Not renally cleared, may be used in patients with renal dysfunction, but reduce dose as increased risk of hypocalcemia in renally impaired

[a]60 mg of pamidronate may be used in smaller patients or in patients with mild hypercalcemia or renal dysfunction. May use longer infusion time in patients with renal dysfunction.

CIV, continuous intravenous infusion; IM, intramuscular; IV, intravenous; SC, subcutaneous.

Data from Body JJ, Niepal D, Tonini G. Hypercalcemia and hypocalcemia: finding the balance. Support Care Cancer. 2017;25(95):1639–1649.

▶ *Pharmacologic Therapy*

Multiple pharmacologic interventions are available for the treatment of hypercalcemia (Table 99–13). Furosemide 20 to 40 mg/day may be added to hydration after rehydration has been achieved to avoid fluid overload and enhance renal excretion of calcium. Although effective in relieving symptoms, hydration and diuretics are temporary measures that are useful until the onset of antiresorptive therapy; thus, hydration and antiresorptive therapy should be initiated simultaneously.[40]

LOS

The antiresorptive therapy of choice for hypercalcemia of malignancy is a bisphosphonate. Because of poor oral bioavailability, only IV agents should be used. Pamidronate and zoledronic acid are most commonly used and are potent inhibitors of osteoclast activity.[39] The bisphosphonates should be administered at diagnosis of hypercalcemia because of their delayed onset of action.

Calcitonin is the drug of choice in cases of emergent hypercalcemia (patients with life-threatening electrocardiographic [ECG] changes, arrhythmias, or central nervous system [CNS] effects) because of its rapid onset of action. Calcitonin inhibits osteoclast activity and decreases renal tubular calcium resorption. However, calcitonin does not yield sustained effects and bisphosphonates are usually necessary as well. Corticosteroids are useful in patients with steroid-responsive malignancies, such as lymphomas or multiple myeloma, and may delay tachyphylaxis to calcitonin. Gallium nitrate is another treatment option, although the 5-day administration regimen and risk of nephrotoxicity limit its use. Denosumab, a RANKL inhibitor, is FDA-approved for hypercalcemia refractory to bisphosphonates at 120 mg subcutaneously days 1, 8, 15, and 29 then monthly thereafter.

OUTCOME EVALUATION

The long-term success of therapy for hypercalcemia is determined primarily by the success of treatment of the underlying malignancy. The goal of treatment is to reduce serum calcium levels to normal range and to relieve patient symptoms and life-threatening complications if present.

METABOLIC COMPLICATIONS: TLS

INTRODUCTION

Although not as common as hypercalcemia, TLS may cause significant morbidity and mortality if adequate prophylaxis and treatment are not instituted. TLS is the result of rapid destruction of malignant cells with subsequent release of intracellular contents into the circulation.

Table 99–14

Risk Factors for TLS

Disease Related
High risk
Acute lymphoblastic leukemia
High-grade non-Hodgkin lymphoma (ie, Burkitt lymphoma)
Intermediate risk
Chronic lymphocytic leukemia (especially bulky lymphadenopathy)
Acute myeloid leukemia (especially WBC count > 50,000 × 10^3/μL [50 × 10^9/L])
Multiple myeloma
Low risk
Low- and intermediate-grade non-Hodgkin lymphoma
Hodgkin disease
Chronic myeloid leukemia (blast crisis)
Rare
Breast cancer
Small cell lung cancer
Testicular cancer
Patient Related
Decreased urinary output, dehydration, or renal failure
Previous or current nephrotoxin exposure
Preexisting hyperuricemia
Acidic urine
WBC count > 50,000 10^3/μL (50 × 10^9/L)
LDH levels > 1500 IU/L (25.0 μkat/L)
High tumor sensitivity to treatment modalities

LDH, lactate dehydrogenase; WBC, white blood cell.

EPIDEMIOLOGY AND ETIOLOGY

LO 3

The overall incidence of TLS is unknown but has been linked to a number of patient- and tumor-related risk factors (Table 99–14).[41] TLS typically occurs in malignancies with high tumor burden or high proliferative rates. Because of this, children are most frequently affected because they frequently have aggressive malignancies. TLS is typically induced by cancer treatment modalities, including chemotherapy, hormonal therapy, radiation, biologic therapy, or corticosteroids, although some patients may present spontaneously before treatment.[41]

PATHOPHYSIOLOGY

Patients with TLS experience a wide range of metabolic abnormalities. The massive cell lysis that occurs leads to the release of intracellular electrolytes, resulting in hyperuricemia, hyperkalemia, and hyperphosphatemia. High concentrations of phosphate bind to calcium, leading to hypocalcemia and calcium phosphate precipitation in the renal tubule. Purine nucleic acids are also released, which are subsequently metabolized to uric acid through multiple enzyme-mediated steps (Figure 99–5). Uric acid is poorly soluble at urinary acidic pH, leading to crystallization in the renal tubule. The precipitation of uric acid and calcium phosphate leads to metabolic acidosis, facilitating further uric acid crystallization. Acute renal failure may be the end result.[41]

TREATMENT

Desired Outcomes

KEY CONCEPT The primary goals of management of TLS are (a) prevention of renal failure and (b) prevention of electrolyte imbalances. Thus, the best treatment for TLS is prophylaxis to enable delivery of cytotoxic therapy for the underlying malignancy. For patients who present with or develop TLS despite prophylaxis, treatment goals include (a) decreasing uric acid levels, (b) correcting electrolyte imbalances, and (c) preventing compromised renal function. These goals should be achieved in a cost-effective manner.

General Approach to Treatment

LO 5

Prevention of TLS is generally achieved by increasing the urine output and preventing accumulation of uric acid. Prophylactic strategies should begin immediately upon presentation, preferably 48 hours prior to cytotoxic therapy. Treatment modalities for established TLS primarily increase uric acid solubility, maintain electrolyte balance, and support renal output.[41]

▶ *Nonpharmacologic Therapy*

LO 5

Vigorous IV hydration with dextrose 5% in water with half normal saline at 3 L/m^2/day to maintain a urine output greater than or equal to 100 mL/m^2/hour is necessary unless the patient presents with acute renal dysfunction. Alkalinization

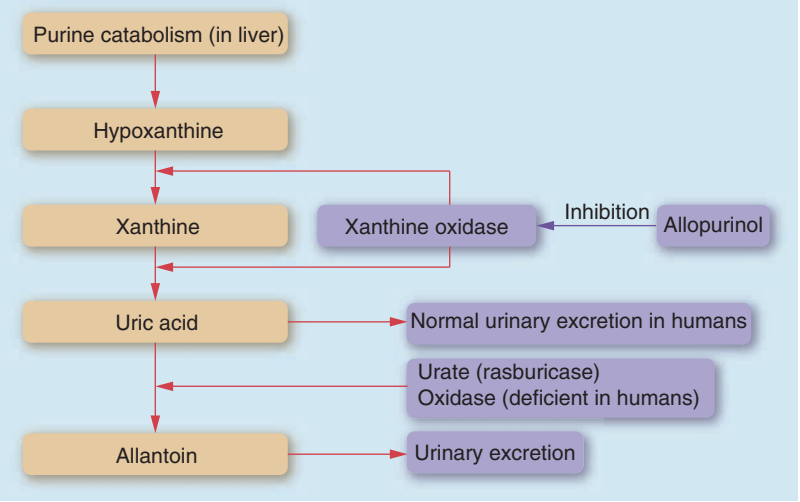

FIGURE 99–5. The role of allopurinol and rasburicase in the enzymatic degradation of purine nucleic acids.

Clinical Presentation and Diagnosis of TLS[41]

General

- Patients present primarily with laboratory abnormalities.
- Normal uric acid is equal to 2 to 8 mg/dL (119–476 µmol/L).
- Most often occurs within 12 to 72 hours of initiation of cytotoxic therapy

Signs and Symptoms

- Most patients are asymptomatic.
- Patients may develop edema, fluid overload, and oliguria, which may progress to anuria with acute renal failure.
- Some patients with hyperuricemia may have nausea, vomiting, and lethargy.
- Hyperkalemia: lethargy, muscle weakness, paresthesia, ECG changes, bradycardia
- Hypocalcemia: muscle cramps, tetany, irritability, paresthesias, arrhythmias

Laboratory Tests (Adults)

- Serum uric acid level greater than 8 mg/dL (476 µmol/L)
- Serum potassium greater than 6 mEq/L (6 mmol/L)
- Serum phosphorus greater than 4.5 mg/dL (1.45 mmol/L)
- Serum calcium less than 7 mg/dL (1.75 mmol/L)
- Elevated blood urea nitrogen and creatinine once renal dysfunction develops

or

- A change of greater than 25% from baseline in the above laboratory values

of the urine to a pH greater than or equal to 7.0 with 50 to 100 mEq/L (50–100 mmol/L) of sodium bicarbonate has been used to promote uric acid solubility for excretion. This measure is controversial because xanthine and hypoxanthine are less soluble at alkaline pH, potentially leading to crystallization, especially during and after allopurinol therapy (see Figure 99–5).[41] Medications that increase serum potassium (angiotensin-converting enzyme inhibitors, spironolactone) or block tubular resorption of uric acid (probenecid, thiazides) should be discontinued. Nephrotoxic agents such as amphotericin B or aminoglycosides should also be avoided. Hemodialysis may be required in patients who develop anuria or uncontrolled hyperkalemia, hyperphosphatemia, hypocalcemia, acidosis, or volume overload.[41]

▶ *Pharmacologic Therapy*

LO 2

Allopurinol is an xanthine oxidase inhibitor that is used for prevention only because it has no effect on preexisting elevated uric acid. Rasburicase is a recombinant form of urate oxidase that is useful for both prevention and treatment, but is expensive (Figure 99–6, Table 99–15). Although the approved dose is 0.2 mg/kg/day for 5 days, recent studies using abbreviated courses (1–3 days) and/or lower doses (0.05–0.1 mg/kg/day) may be equally efficacious with significantly reduced cost.[39] Because uric acid levels generally fall within 4 hours of the first dose, one dose may be administered with frequent, serial monitoring of the uric acid level for repeat dosing if necessary (see Figure 99–6). Of note, rasburicase continues to break down uric acid in blood samples drawn

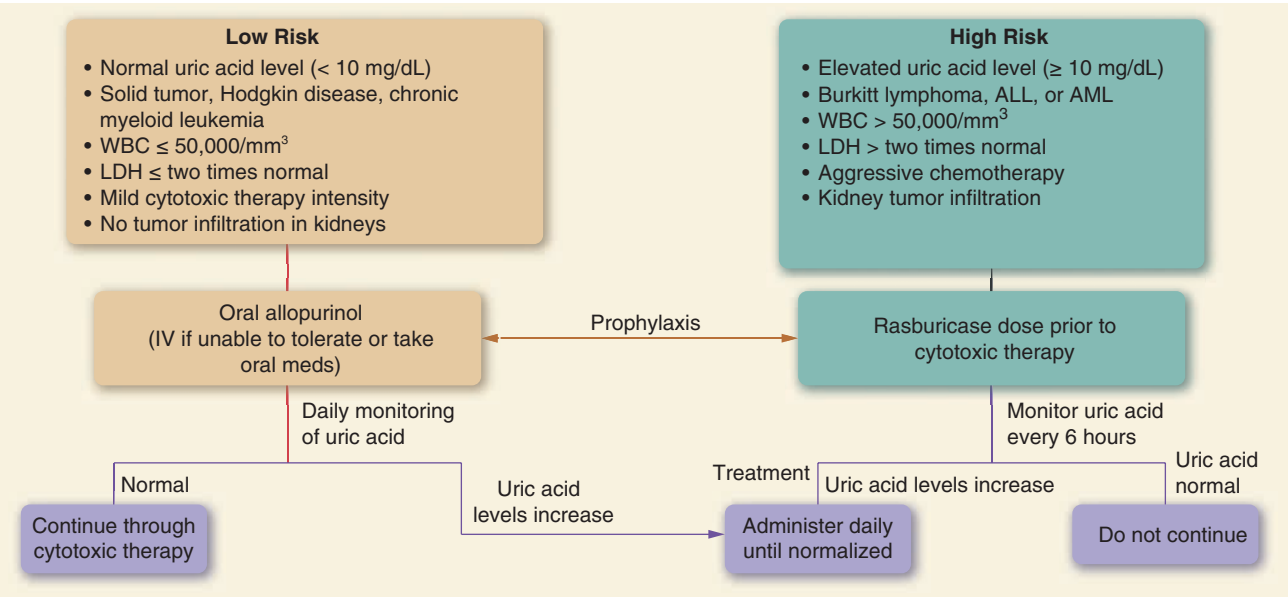

FIGURE 99–6. Prophylaxis and treatment of hyperuricemia associated with tumor lysis syndrome. (ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; IV, intravenous; LDH, lactate dehydrogenase; WBC, white blood cell.)

Table 99–15

Comparison of Allopurinol and Rasburicase in TLS

Drug	Dosing	AWP	Comments
Oral allopurinol (Zyloprim)	Adult: 600–800 mg/day in two to three divided doses Pediatric: 10 mg/kg/day or 200–300 mg/m^2/day	$1.80/day	Adjust dose for renal impairment Avoid drug interactions (mercaptopurine) Monitor for skin rash
IV allopurinol (Aloprim)	Adult: 200–400 mg/m^2/day Pediatric: 200 mg/m^2/day	$4680/day	As above Reserve for patients who cannot tolerate or take oral medications Maximum dose = 600 mg/day
Rasburicase (Elitek)	0.2 mg/kg/day for up to 5 days	$2809/day	Lower doses and abbreviated schedules may be used to decrease cost (0.05–0.1 mg/kg/day) May rarely cause nausea and vomiting Contraindicated in patients with G6PD deficiency → hemolytic anemia Rare cases of hypersensitivity and antibody formation

[a]Normalized for 70-kg patient or body surface area = 1.73 m^2; all costs are estimated and may vary.

AWP, average wholesale price; G6PD, glucose-6-phosphate dehydrogenase; po, oral.

From Wilson FP, Berns JS. Tumor lysis syndrome: new challenges and recent advances. Adv Chronic Kidney Dis. 2014;21(1):18–26. Accessed from RedBook Online ®, Truven Health Analytics/Micromedex. Subscription required for access. Accessed August 30, 2017.

from patients. This can be avoided by immediately placing the sample in an ice bath for processing to avoid falsely lowered uric acid levels.[41]

Electrolyte disturbances that develop in patients with TLS should be aggressively managed to avoid renal failure and cardiac sequelae. One exception pertains to the use of IV calcium for hypocalcemia. Adding calcium may cause further calcium phosphate precipitation in the presence of hyperphosphatemia and should be used cautiously.

OUTCOME EVALUATION

The most successful outcome in TLS is prevention. If the condition is not able to be prevented, the goal of treating established TLS is to avoid renal failure and quickly return electrolytes to normal.

Patient Care Process

Collect Information:

- Review patient history of chemotherapy regimens and concurrent medications.
  - Determine patient allergies, especially to antibiotics, antifungals, and antivirals.
- Evaluate risk of chemotherapy complications using appropriate NCCN practice guideline if available.
- Evaluate patient-specific risk factors.
- Review laboratory values, including WBC, electrolytes, hepatic and renal function, performance status, and vital signs.

Assess the Information:

- Determine complications (nausea, vomiting, febrile neutropenia, etc) to previous cycles of chemotherapy and risk with current cycle.
- Assess individual and treatment-related risk factors for chemotherapy complications.
  - Determine insurance coverage for supportive care interventions, availability of appropriate storage conditions.

Develop a Care Plan:

- Communicate treatment goals of symptomatic management to the patient.
- Provide patient with education regarding appropriate use of supportive therapies and potential adverse effects.
- Educate patient about nonpharmacologic interventions to manage chemotherapy complications.

Counsel patients regarding risk factors, symptoms to call their health care providers, and symptoms requiring a visit to the emergency room.

Implement the Care Plan:

- Initiate patient-specific supportive care therapy for managing chemotherapy complications.
- Coordinate follow-up with interprofessional team.

LO 6

Follow-up: Monitor and Evaluate:

- Review laboratory values, including WBC, electrolytes, hepatic and renal function, performance status, and vital signs.
  - Determine efficacy and adverse effects of supportive cancer intervention and determine if modifications in the treatment plan are required.
- Assess the patient for any new signs or symptoms of chemotherapy complications. Evaluate the patient for adverse drug reactions, drug allergies, and interactions. Have all medications been dose adjusted for renal or hepatic dysfunction?

Abbreviations Introduced in This Chapter

ANC	Absolute neutrophil count
AWP	Average wholesale price
BMT	Bone marrow transplantation
BUN	Blood urea nitrogen
CIV	Continuous intravenous infusion
CSF	Colony-stimulating factor
G6PD	Glucose-6-phosphate dehydrogenase
ICP	Intracranial pressure
IV	Intravenous
LDH	Lactate dehydrogenase
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non–small cell lung cancer
PCP	*Pneumocystis jiroveci* pneumonitis (formerly *Pneumocystis carinii*)
PTHrP	Parathyroid hormone–related protein
SCLC	Small cell lung cancer
SVCS	Superior vena cava syndrome

REFERENCES

1. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. Support Care Cancer. 2005;13(4):219–227.
2. Dranitsans G, Molassiotis A, Clemons M, et al. The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting. Ann Oncol. 2017;28(6):1260–1267.
3. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2017;35(28):3240–3261.
4. van der Vorst MJ, Neefjies EC, Konings IR, Verheul HM. Prophylactic treatment for delayed chemotherapy-induced nausea and vomiting after non-AC based moderately emetogenic chemotherapy; a systematic review of randomized controlled trials. Support Care Cancer. 2015;23(8):2499–2506.
5. Janelsins MC, tejani MA, Kamen C, et al. Current pharmacotherapy for chemotherapy-induced nausea and vomiting in cancer patients. Expert Opin Pharmacother. 2013;14(6):757–766.
6. Clinical practice guidelines in oncology: Antiemesis. version v.2.2017. National Comprehensive Cancer Network. Available from: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed August 28, 2017.
7. FDA Drug Safety Communication: new information regarding QT prolongation with ondansetron (Zofran). United States Food and Drug Administration. Available from: www.fda.gov/Drugs/DrugSafety/ucm310190.htm. Accessed August 28, 2017.
8. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol. 2011;9(5):188–195.
9. Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO clinical practice recommendations. Ann Oncol. 2911;22(suppl 6):vi78–vi84.
10. Kuiken NSS, Rings EHHM, Blijlevens NMA, Tissing WJE. Biomarkers and non-invasive tests for gastrointestinal mucositis. Support Care Cancer. 2017;25(9):2933–2941.
11. Carlotto A, Hogsett VL, Maiorini EM, Razulis JG, Sonis ST. The economic burden of toxicities associated with cancer treatment: review of the literature and analysis of nausea and vomiting, diarrhoea, oral mucositis, and fatigue. Pharmacoeconomics. 2013;31(9):753–766.
12. Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120(10):1453–1461.
13. Al-Dasooqi N, Sonis ST, Bowen JM, et al. Emerging evidence on the pathophysiology of mucositis. Support Care Cancer. 2013;21(11):3233–3241.
14. Sonis ST, Eiters JP, Epstein JB, et al. Validation of a new scoring system for the assessment of clinical trial research; oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. Cancer. 1999;85:2103–2113.
15. Kushner JA, Lawrence HP, Shoval I, et al. Development and validation of a patient-reported oral mucositis symptom (PROMS) scale. J Can Dent Assoc. 2008;74(1):59.
16. Nesher L, Rolston KV. The current spectrum of infection in cancer patients with chemotherapy related neutropenia. Infection. 2014;42(1):5–13.
17. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Disease Society of America. Clin Infect Dis. 2011;52(4): e56–e93.
18. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clincial Oncology clinical practice guideline. J Clin Oncol. 2013;31(6):794–810.
19. Clinical practice guidelines in oncology: Prevention and treatment of cancer-related infections. V.2.2017. National Comprehensive Cancer Network. Available from: http://www.nccn.org/professionals/physician_gls/PDF/infections.pdf. Accessed August 29, 2017.
20. Klastersky J, Paesmans M. The Multinational Association for Supportive Care in Cancer (MASCC) risk index score: 10 years of use for identifying low-risk febrile neutropenic cancer patients. Support Care Cancer. 2013;21(5):1487–1495.
21. Gafler-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev. 2012;1:CDC004386.
22. Bucavene G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med. 2005;353(10):977–987.
23. Cullen M, Steven N, Billingham L, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med. 2005;353(10):988–998.
24. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol. 2007;25(21):3158–3167.
25. Lyman GH, Dale DC, Culakova E, et al. The impact of granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol. 2013;24(10):2475–2484.
26. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol. 2012;30(14):1715–1724.
27. Clinical practice guidelines in oncology: myeloid growth factors. V.1.2017. National Comprehensive Cancer Network. Available from: http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf. Accessed August 29, 2017.
28. Wilson LD, Detterbeck FC, Yahalom J. Superior vena cava syndrome with malignant causes. N Engl J Med. 2007;356(8): 1862–1869.
29. Al-Qurainy R, Collis E. Metastatic spinal cord compression: diagnosis and management. BMJ 2016;353:i2539.

30. Douglas S, Schild SE, Rades D. A new score predicting the survival of patients with spinal cord compression from myeloma. BMC Cancer. 2012;12:425.
31. Rades D, Douglas S, Veninga T, Schild SE. A validated score for patients with metastatic spinal cord compression from non-small cell lung cancer. BMC Cancer. 2012;12:302.
32. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomized trial. Lancet. 2005;366:643–648.
33. Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol. 2015;33(30):3475–3484.
34. Clinical Practice Guidelines in Oncology: small cell lung cancer. V.3.2017. National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed August 30, 2017.
35. Xie SS, Li M, Zhou CC, Song XL, Wang CH. Prophylactic cranial irradiation may impose detrimental effect on overall survival in patients with nonsmall cell lung cancer: a systematic review and meta-analysis. PLoS One. 2014;9(7):e103431.
36. Lewis MS, Wahner Hendrickson A, Moynihan TA. Oncologic emergencies: pathophysiology, presentation, diagnosis, and treatment. CA: Cancer J Clin 2011;61(5):287–314.
37. Mikkelson T, Paleologos NA, Robinson PD, et al. The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010;96(1):97–102.
38. Payne H, Adamson A, Bahl A, et al. Chemical- and radiation-induced hemorrhagic cystitis: current treatments and challenges. BJU Int. 2013;112(7):885–897.
39. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009;27(1):127–145.
40. Body JJ, Niepal D, Tonini G. Hypercalcemia and hypocalcemia: finding the balance. Support Care Cancer. 2017;25(5):1639–1649.
41. Wilson FP, Berns JS. Tumor lysis syndrome: new challenges and recent advances. Adv Chronic Kidney Dis. 2014;21(1):18–26.

100 Parenteral Nutrition

Melissa R. Pleva and Michael D. Kraft

LEARNING OBJECTIVES

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

LO

1. List appropriate indications for parenteral nutrition (PN) in adult patients.
2. Describe the components of PN and their role in nutrition support therapy.
3. List key elements of nutrition assessment and factors considered in assessing an adult patient's nutritional status and nutritional requirements.
4. List important recommendations to improve PN safety.
5. Explain important pharmaceutical and compounding concerns with PN admixtures.
6. Develop a plan to design, initiate, and adjust a PN formulation for an adult patient based on patient-specific factors.
7. Describe the etiology and risk factors for PN macronutrient-associated complications in adult patients receiving PN.
8. Describe the etiology and risk factors for refeeding syndrome, as well as measures to prevent refeeding syndrome.
9. Design a plan to assess the efficacy and monitor for safety, as well as fluid, electrolyte, vitamin, and trace element abnormalities in adult patients receiving PN.

INTRODUCTION

Malnutrition in hospitalized patients is associated with significant complications (eg, increased infection risk, poor wound healing, prolonged hospital stays, increased mortality), especially in surgical and critically ill patients.[1] Maintaining adequate nutritional status, especially during periods of illness and metabolic stress, is an essential part of patient care. *Nutrition support therapy* refers to the administration of nutrients via the oral, enteral, or parenteral route for therapeutic purposes.[1]

KEY CONCEPT Parenteral nutrition (PN), also called total parenteral nutrition (TPN), is the intravenous (IV) administration of fluids, macronutrients, electrolytes, vitamins, and trace elements for the purpose of weight maintenance or gain, to preserve or replete lean body mass and visceral proteins, and to support anabolism and nitrogen balance when the oral or enteral route is not feasible or adequate. PN is a potentially lifesaving therapy in patients with intestinal failure but can be associated with significant complications.

Desired Outcomes and Goals

The goals of nutrition support therapy include:

- Correction or avoidance of nutritional deficiencies
- Weight maintenance (or weight gain in malnourished patients and growing children)
- Preservation or repletion of lean body mass and visceral proteins
- Support of anabolism and nitrogen balance and improvement of healing
- Correction or avoidance of fluid, electrolyte, vitamin, and trace element abnormalities
- Improving clinical outcomes

Indications for PN Therapy

PN can be a lifesaving therapy in patients with intestinal failure, but the oral or enteral route is preferred when providing nutrition support therapy. Compared with PN, enteral nutrition is associated with a lower risk of hyperglycemia and fewer infectious complications (eg, pneumonia, intraabdominal abscess, catheter-related infections).[1–3] However, if used appropriately, PN can be safe and effective and can improve nutrient delivery. Indications for PN are listed in Table 100–1.[1,2,4] PN should be reserved for patients with altered intestinal function or absorption or when the gastrointestinal (GI) tract cannot be used. The anticipated duration of adequate PN therapy should be at least 5 to 7 days because shorter durations are unlikely to have a beneficial effect on a patient's clinical and nutritional outcomes.[1,2]

LO 1

PN COMPONENTS

LO 2

PN should provide a *balanced* nutrition formula, including macronutrients, micronutrients, fluids, and electrolytes. Macronutrients, including amino acids, dextrose, and injectable lipid emulsions (ILE; also known as IV lipid emulsion or IV fat emulsion), are important sources of structural and energy-yielding substrates. In a balanced PN formulation for adult patients, total daily calories are typically provided as 10% to 20% from amino acids, 50% to 60% from dextrose, and 15% to 30% from ILE. Amino acids may provide more than 20% of

Table 100–1

Indications for Parenteral Nutrition in Adults[1,2,4]

- Bowel obstruction
  - Physical or mechanical (eg, tumor compressing intestinal lumen)
  - Functional (eg, ileus, colonic pseudo-obstruction)
- Major small bowel resection (eg, short-bowel syndrome)
  - Adult patients with < 100 cm of small bowel distal to the ligament of Treitz without a colon
  - Adult patients with < 50 cm of small bowel if the colon is intact
- Diffuse peritonitis
- Intestinal fistulas if EN cannot be provided above or below the fistula
- Pancreatitis—if patients have failed EN beyond the ligament of Treitz or cannot receive EN (eg, because of intestinal obstruction)
- Severe intractable vomiting or diarrhea
- Preoperative nutrition support in patients with moderate to severe malnutrition who cannot tolerate EN and in whom surgery can be delayed safely for at least 7 days

the total daily calories in patients with conditions that increase protein requirements (eg, severe thermal injury, healing wounds, cachexia, treatment with continuous renal replacement therapy, hypocaloric feeding). Electrolytes and micronutrients, including vitamins and trace elements, are required to support essential biochemical reactions and maintain cellular homeostasis. Patients require individual adjustments of PN components based on their nutritional status, nutritional requirements, underlying disease state(s), degree of metabolic stress, clinical status, and organ functions.

LO 2

Macronutrients

▶ *Amino Acids*

LO 2

Amino acids, the building blocks of proteins, are an essential component of PN admixtures. KEY CONCEPT Amino acids are provided to preserve or replete lean body mass and visceral proteins, to promote protein anabolism and wound healing. Amino acids also provide a source of energy, providing 4 kcal/g (17 kJ/g).

Patient Encounter Part 1

RK is a 64-year-old woman with a history of hypertension and colon cancer, status post colon resection and colostomy, followed by chemotherapy, and subsequent colon reanastomosis. She was admitted approximately 2 weeks ago with signs and symptoms consistent with a bowel obstruction. She was taken to the OR for an **exploratory laparotomy** and found with multiple adhesions causing small bowel obstructions in two locations. She underwent a small bowel resection (jejunum) and extensive lysis of adhesions, and was discharged 8 days ago. RK is readmitted with foul-smelling drainage from her surgical incision × 2 days along with nausea, decreased appetite, and decreased oral intake (~30% of estimated energy requirements) for the past 2 to 3 days. Since her diagnosis of colon cancer, she has had weight loss, poor oral intake, and malnutrition. Most recently, she reports an unintentional weight loss of about 12 lb (5.5 kg) over the past 4 to 5 weeks.

Past Medical History

- Hypertension × 10 years
- Colon cancer diagnosed 2 years ago, status post colectomy, chemotherapy, and reanastomosis
- Malnutrition since diagnosis of colon cancer

Past Surgical History

- Colon resection with colostomy, colostomy takedown with reanastomosis 2 years ago
- Exploratory laparotomy with small bowel resection and lysis of adhesions due to small bowel obstruction (> 100 cm of small intestine remaining, ileocecal valve intact, part of the colon remaining)

Family History

- Mother and father: Hypertension
- Grandmother: Chronic constipation

Social History

- 30 pack-year smoking history, quit 2 years ago; patient reports only occasional alcohol; no recreational drugs

Medications Prior to Admission

- Hydrochlorothiazide 50 mg orally daily
- Docusate 100 mg orally twice daily
- Metformin 500 mg orally twice daily

Allergies

- NKDA

Physical Examination

- Ht 157 cm (~5′2″); actual body wt 53 kg (116 lb); ideal body wt 50 kg (110 lb); T 37.2°C (99.0°F); HR 83 beats/min; BP 138/82 mm Hg; RR 14 breaths/min; alert and oriented × 3; mucous membranes and skin appear cool and dry; lungs clear

Abdomen: Soft, tender around incision, faint bowel sounds, drainage of apparent enteric contents from surgical incision

Physical examination otherwise unremarkable

Diagnoses

Likely enterocutaneous fistula, probably from small bowel/jejunum (most recent surgery/small bowel resection), mild dehydration, and malnutrition

Plan

The patient was admitted to the hospital (non-ICU) for evaluation of a possible enterocutaneous fistula. The team performed a fistulogram and confirmed presence of an enterocutaneous fistula apparently originating in the proximal- to mid-jejunum. Given the patient's recent surgery, surgical intervention was deemed to not be an appropriate option at this time. A drain was placed into the fistula to control drainage and quantify output; the fistula drained approximately 600 mL in the first 24 hours. Against medical orders, the patient drank approximately 1 L of water, and the following day her fistula drained approximately 1500 mL of fluid. It is now hospital day #2.

Is PN therapy indicated in this patient? Why or why not?

Parenteral crystalline amino acid solutions are supplied by various manufacturers in various concentrations (eg, 7%, 8%, 8.5%, 10%, 15%, and others). Different formulations are tailored for specific age groups and disease states. Specialized formulations for patients with acute kidney injury contain higher proportions of essential amino acids. Formulations for patients with hepatic encephalopathy contain higher amounts of branched-chain and lower amounts of aromatic amino acids. These specialized formulations have not been clearly shown to improve patient outcomes and are not routinely used in clinical practice. Crystalline amino acid solutions have an acidic pH (pH ≈ 5–7) and may contain inherent electrolytes (eg, sodium, potassium, acetate, phosphate).

▶ *Dextrose*

LO 2

KEY CONCEPT Dextrose (D-glucose) is the major energy source, and it is vital for cellular metabolism, body protein preservation, and cellular growth. The central nervous system, red blood cells, and the renal medulla depend primarily on dextrose as a source of energy.

Typically, a 70% (70 g/100 mL) parenteral dextrose (hydrous dextrose) stock solution is used in PN compounding. Hydrous dextrose provides 3.4 kcal/g (14.2 kJ/g). A dextrose infusion rate of 2 mg/kg/min in adult patients is typically sufficient to suppress gluconeogenesis and spare proteins from being used for energy.[5] Dextrose infusion rate in hospitalized adult patients should not exceed 4 to 5 mg/kg per minute when PN is infused over 24 hours.[6,7] Use adjusted body weight (AdjBW), rather than actual weight, in obese patients when calculating the dextrose infusion rate.

▶ *Lipid Injectable Emulsions*

LO 2

KEY CONCEPT Injectable lipid emulsions (ILE) are provided to prevent or treat **essential fatty acid deficiency** (EFAD) and as an energy source. ILE particles consist of a triglyceride (TG) core surrounded by a layer of egg phospholipids (PL) (emulsifiers). These particles carry a negative charge on their surface that creates repulsive electrostatic forces between droplets and maintains the stability of the emulsion. Glycerol is added to adjust the tonicity, and water is the solvent. The negative charges on the surface of lipid particles can be disrupted by cations, especially divalent cations (eg, calcium, magnesium) and trivalent cations (eg, iron), and extreme pH changes, particularly acidic pH.[8] **Creaming**, **coalescence**, and **oiling out** are signs of a destabilized ILE. If there is any apparent disruption to ILE, it should *not* be infused into a patient.

ILEs differ in their concentration (10%, 20%, and 30%), caloric density by volume, natural source of fats/triglycerides, and ratio of phospholipids to triglycerides (PL:TG ratio). **Table 100–2** shows a comparison of standard commercially available ILEs in the United States. Most standard ILEs in the United States contain long-chain triglycerides derived from soybean oil. Because of the addition of PL emulsifiers and glycerol, the caloric density of ILEs by weight is approximately 10 kcal/g (42 kJ/g; dietary fat is ~9 kcal/g [38 kJ/g]). Compared with the 10% ILE, 20% and 30% ILEs have a lower PL:TG ratio and lower PL content, and this translates to better plasma clearance compared to the 10% ILE.[9] The 30% ILE is only approved by the Food and Drug Administration (FDA) for infusion in a total nutrient admixture (TNA) and should neither be infused directly into patients nor via Y-site injection.

More recently, the FDA approved two additional ILE products for use in adult patients in the United States: SMOFLipid and Clinolipid (Table 100–2). SMOFLipid is a combination of soybean oil, medium-chain triglycerides (MCTs), olive oil, and fish oil (30%/30%/25%/15%, respectively). Clinolipid is a mixture of refined olive and soybean oil (80%/20%, respectively), but this product is not yet on the market in the United States. Both alternative combinations of oil sources result in a reduced amount of omega-6 fatty acids and SMOFLipid has a higher concentration of omega-3 fatty acids. This may have a positive impact on inflammation and immune function, but significant data demonstrating improved clinical outcomes are lacking.[10] The optimal role of these ILE products in patient care is not yet known.

ILE particles are hydrolyzed in the bloodstream by **lipoprotein lipase** to release free fatty acids and glycerol. Fatty acids are taken up into adipose tissue for storage (triglycerides), oxidized to energy in various tissues (eg, skeletal muscles), or recycled in the liver to make lipoproteins.

The essential fatty acids that cannot be produced endogenously in humans are linoleic acid (C18:2 n-6) and α-linolenic acid (C18:3 n-3) (long-chain fatty acids). Arachidonic acid (C20:4 n-6) is also essential but can be synthesized in vivo from linoleic acid. Adult patients should receive a minimum of 2% to 4% of total daily calories as linoleic acid and 0.25% to 0.5% of total daily calories as α-linolenic acid to prevent essential fatty acid deficiency.[7] This can be achieved by providing a minimum of ~100 g (500 mL of 20%) of soybean oil-based ILE per week (in a single dose, or divided doses) for most adult patients. The typical daily dose of ILE in adults is about 0.5 to 1 g/kg/day (or ~15–30% of total daily calories). The maximum dose is 2.5 g/kg/day[7] or 60% of total daily calories, although doses this high are rarely used in practice and should be avoided to prevent complications.

Biochemical evidence of essential fatty acid deficiency (eg, decreased serum linoleic acid, α-linolenic acid, and arachidonic acid concentrations; elevated mead acid concentrations; elevated triene-to-tetraene ratio) can develop in well-nourished adult patients within about 2 to 4 weeks of receiving PN without ILE, and clinical manifestations (eg, dry skin, skin **desquamation**, hair loss, hepatomegaly, anemia, **thrombocytopenia**, poor wound healing) may begin to appear after an additional 1 to 2 weeks.[11]

Complications and safety concerns related to the administration of ILE include severe hypertriglyceridemia, infection, **anaphylactic** reactions, and infusion-related reactions. Patients with a history of hypertriglyceridemia, acute kidney injury, chronic kidney disease, hepatic dysfunction, severe metabolic stress, or **pancreatitis** (particularly if caused by hypertriglyceridemia) may have reduced lipid clearance and be at risk of developing hypertriglyceridemia. ILE should be temporarily withheld in adult patients with serum triglyceride concentrations exceeding 400 mg/dL (4.52 mmol/L).

ILEs support the growth of bacterial and fungal pathogens; bacterial growth is slower in TNAs than in ILE alone due to the acidic pH of amino acid solutions and higher osmolarity of PN formulations.[7,12,13] Because of this, the Centers for Disease Control and Prevention (CDC) recommends that TNA infusions be completed within 24 hours of initiation. Recent guidelines suggest that ILE infusion should be completed ideally within 12 hours if administered from the original manufacturer container (within 24 hours if 12 hours are not feasible for medical reasons), but completed within 12 hours if repackaged/transferred to another container and infused separately from a 2-in-1 PN admixture (although repackaging/transfer to another container was not recommended).[14]

Patients with an allergy to eggs, soybean, or legumes may develop cross-allergic reactions to ILE. Additionally, patients with an allergy or hypersensitivity to fish, olives, or other ingredients may develop cross-allergic reactions to SMOFLipid. Rarely, infusion-related adverse effects may occur with rapid infusion, including fever, chills, headache, palpitations, dyspnea,

Table 100–2

Comparison of Lipid Injectable Emulsion Products Approved in the United States

Brand Names	Intralipid			Nutrilipid	Liposyn III			SMOFLipid	Clinolipid
Oil source(s)	Soybean oil			Soybean oil	Soybean oil			Soybean oil (30%) MCT (30%) Olive oil (25%) Fish oil (15%)	Olive oil (80%) Soybean oil (20%)
Concentration	10%	20%	30%[a]	20%	10%	20%	30%[a]	20%	20%
Linoleic acid[b] (%)	44–62			48–58	54.5			14–25	13.8–22
α-Linolenic acid[c] (%)	4–11			4–11	8.3			1.5–3.5	0.5–4.2
Phospholipids (egg yolk) (%)	1.2			1.2	1.2	1.2	1.8	1.2	1.2
PL:TG ratio	0.12	0.06	0.04	0.06	0.12	0.06	0.06	0.06	0.06
Caloric density[d] (kcal/mL)	1.1	2	3	2	1.1	2	3	2	2
Approximate osmolality[e] (mOsm/kg water) or osmolarity (mOsm/L)	300 mOsm/kg	350 mOsm/kg	310 mOsm/kg	390 mOsm/kg	284 mOsm/L	292 mOsm/L	293 mOsm/L	380 mOsm/kg	340 mOsm/kg
Approximate mean pH (range)	8 (6–8.9)			6.8 (6–8.9)	8.3 (6–9)		8.4 (6–9)	6–9	6–9

[a]Only approved for compounding in a 3-in-1 admixture, not for direct patient administration

[b]Omega-6 (ω-6) fatty acid

[c]Omega-3 (ω-3) fatty acid

[d]One kcal/mL is equivalent to 4.19 kJ/mL.

[e]One mOsm/kg is equivalent to mmol/kg.

PL, phospholipid; TG, triglyceride.

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Table 100–3

Approximate Daily Maintenance Electrolyte Requirements for Adults[7,14]

Electrolyte	Approximate Daily Maintenance Requirements[a]	Electrolyte Salts Used in PN	Maximum Suggested Concentration in PN
Sodium	1–2 mEq/kg (mmol/kg)	Chloride, acetate, phosphate	154 mEq/L (mmol/L, equivalent to normal saline)
Potassium	1–2 mEq/kg (mmol/kg)	Chloride, acetate, phosphate	120 mEq/L (mmol/L) (central PN)
Phosphorus	20–40 mmol (~10–15 mmol per 1000 kcal [2.4–3.6 mmol per 1000kJ])	Sodium phosphate, potassium phosphate	See text section on calcium–phosphate solubility Maximum calcium + magnesium = 20 mEq/L in 3-in-1 admixture
Calcium	10–15 mEq (5–7.5 mmol)	Gluconate	
Magnesium	8–20 mEq (4–10 mmol)	Sulfate	20 mEq/L (10 mmol/L)[b]
Chloride	[c]	Sodium, potassium	Linked to limitations of sodium and potassium. Usual ratio of chloride to acetate ~1:1 to 1.5:1
Acetate	[c]	Sodium, potassium	
Conversions	1 mmol potassium phosphate = 1.47 mEq potassium 1 mmol sodium phosphate = 1.33 mEq sodium 1 gram of calcium gluconate = 4.65 mEq (2.32 mmol) calcium 1 gram of magnesium sulfate = 8.1 mEq (4 mmol) magnesium		

[a]Electrolyte requirements are adjusted based on serum electrolyte concentrations and vary depending on kidney function, gastrointestinal losses, nutritional status, specific metabolic and endocrine functions, and medication therapy that affect electrolyte losses or retention.

[b]For 3-in-1 formulations only.

[c]As needed to maintain acid–base balance; linked to amounts of sodium and potassium provided (as chloride and acetate salts).

chest tightness, and nausea. Extending the ILE infusion time can minimize infusion-related adverse events and improves ILE clearance. The maximum recommended infusion rate of ILE is 0.11 g/kg/hour.[7]

► *Fluid*

KEY CONCEPT PN should not be used to treat acute fluid abnormalities. PN should be adjusted to provide maintenance fluid requirements and to minimize worsening of underlying fluid disturbances, taking into account other fluids the patient is receiving. Daily maintenance fluid requirements for adults can be estimated with the following equation:

LO 2

$$\text{Total daily maintenance fluid requirements} = 1500\ \text{mL} + (20\ \text{mL/kg} \times [\text{Wt (kg)} - 20])^*$$

For patients with significant fluid deficits, it is safer and more cost effective to correct fluid abnormalities using standard IV fluids (eg, 0.9% sodium chloride in water, dextrose 5% and 0.45% sodium chloride in water +/– 20 milliequivalents (mEq)/L (mmol/L) of potassium chloride, lactated Ringer's solution). Minimizing PN fluid volume may be indicated in patients with fluid overload, patients with oliguric or anuric acute kidney injury, or those with congestive heart failure or symptomatic pleural effusion. It is reasonable to provide total daily fluid requirements (maintenance requirements and replacement for GI or other abnormal losses) in the PN admixture in patients who require long-term PN if stability and compatibility limits are maintained with dilution of the PN admixture.

*For patients > 60 years old, use 15 mL/kg for every kilogram above 20 kg.

Micronutrients

KEY CONCEPT Electrolytes, vitamins, and trace elements are essential for numerous biochemical and metabolic functions and should be added to PN daily unless otherwise not indicated.

► *Electrolytes*

KEY CONCEPT Electrolytes are essential for many metabolic and homeostatic functions, including enzymatic and biochemical reactions, maintenance of cell membrane structure and function, neurotransmission, hormone function, muscle contraction, cardiovascular function, bone composition, and fluid homeostasis. The causes of electrolyte abnormalities in patients receiving PN may be multifactorial, including altered absorption and distribution; excessive or inadequate intake; altered hormonal, neurologic, and homeostatic mechanisms; altered excretion and losses via the GI tract (eg, gastric, diarrhea, ostomy, enterocutaneous fistula) and kidneys; changes in fluid status and fluid shifts; and medication therapies. PN should not be used to treat acute electrolyte abnormalities but should be adjusted to meet maintenance requirements and to minimize worsening of underlying electrolyte disturbances.

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Electrolytes that are included routinely in PN admixtures include sodium, potassium, phosphorus (as phosphate), calcium, magnesium, chloride, and acetate. Always assess the patient's kidney function when determining electrolyte doses in PN admixtures. Typical daily electrolyte maintenance requirements for adults with normal kidney function are listed in Table 100–3.[7,15] For additional details regarding management of fluid, electrolyte, and acid–base disorders, refer to Chapters 27 and 28.

LO 2

LO 5 **Calcium–Phosphate Solubility** The FDA published a safety alert in response to two deaths from microvascular pulmonary emboli associated with calcium–phosphate precipitation in PN.[16] Because calcium and phosphate can bind and precipitate in solution, caution must be exercised when mixing these two electrolytes in PN admixtures. Several factors can affect calcium–phosphate solubility, including:

- *Amino acid brand and concentration:* Primary factor that affects pH of the PN admixture. The pH of amino acid stock solutions may vary between commercial products. In general, the higher the final amino acid concentration, the lower the pH of the final admixture (ie, closer to pH of the amino acid solution). Phosphates can also bind with amino acids, leaving fewer phosphates available to bind with calcium.
- *pH:* Largely affected by the amino acid brand and concentration, to a lesser extent by the dextrose concentration; the lower the solution pH, the less chance for calcium–phosphate precipitation. Monobasic phosphates predominate at low pH, leaving fewer free dibasic phosphates for precipitation with divalent calcium; monobasic calcium phosphate is more soluble than dibasic calcium phosphate.
- *Calcium salt:* Calcium gluconate is the preferred calcium salt in PN because it has a lower dissociation constant in solution with less free calcium available at a given time to bind phosphate.
- *Time:* The longer calcium and phosphate are in solution, the more calcium and phosphate will dissociate over time and increase the risk for calcium–phosphate precipitation.
- *Temperature:* As temperature increases, more calcium and phosphate dissociate and increase the risk of calcium–phosphate precipitation.
- *Order of mixing:* Calcium and phosphate should not be added simultaneously or consecutively when compounding PN admixtures (eg, add phosphate first, then add other PN components, and then add calcium near the end of compounding). The volume in the PN admixture at the time calcium is added (not necessarily the final volume) must be used to determine the maximum calcium that can be added.

When compounding PN admixtures, use calcium–phosphate solubility curves (based on the specific brand and final concentration of amino acids and dextrose) to determine safe and appropriate calcium and phosphate concentration limits.

Acetate Acetate is converted to bicarbonate at a 1:1 molar ratio. Bicarbonate should *never* be added to or co-infused with PN admixtures. This can lead to the release of carbon dioxide and result in the formation of insoluble calcium or magnesium carbonate salts.

► *Vitamins*

LO 2 Water-soluble and fat-soluble vitamins in the parenteral multivitamin products are essential cofactors for numerous biochemical reactions and metabolic processes. Parenteral multivitamins are added daily to the PN admixture. Water-soluble vitamins, with the exception of vitamin B_{12}, are generally readily excreted and not stored in the body in significant amounts. Deficiencies of water-soluble vitamins can occur rapidly in the absence of adequate vitamin supplementation in PN. Severe refractory lactic acidosis and deaths were reported in patients who received PN without added thiamine. Thiamine is an essential cofactor in carbohydrate metabolism (via the tricarboxylic acid cycle). Deficiency of thiamine pyrophosphate prevents the formation of acetyl-CoA from pyruvate, which is instead converted to lactate via anaerobic metabolism, resulting in lactic acidosis. Parenteral multivitamin products contain 150 mcg of vitamin K in accordance with FDA recommendations. A parenteral adult multivitamin formulation is available without vitamin K, but standard compounding of PN formulations should include a product that contains vitamin K unless otherwise indicated.

► *Trace Elements*

LO 2 Trace elements are essential cofactors for numerous biochemical processes. Trace elements added routinely to PN include zinc, selenium, copper, manganese, and chromium (Table 100–4). Various individual and multi-ingredient parenteral trace element formulations can be added to PN admixtures. Trace element supplementation in PN should be individualized, especially for long-term PN-dependent patients, rather than using a fixed dose of multi-trace element products.[17] Zinc is important for wound healing. Patients with high-output enterocutaneous fistulas, diarrhea, burns, and large open wounds may require additional zinc supplementation. Patients may lose as much as 12 to 17 mg zinc per liter of GI output; however, 12 mg/day may be adequate to maintain positive zinc balance in these patients.[18] Patients with chronic severe diarrhea, malabsorption, high-output enterocutaneous fistula, or short-bowel syndrome may also have increased selenium losses and may require additional selenium supplementation. Chromium is a cofactor for glucose metabolism, and patients with chromium deficiency may exhibit glucose intolerance; however, chromium deficiency is a rare cause of hyperglycemia. Patients who are chronically dependent on PN may accumulate chromium and manganese, resulting in high serum levels because these are known contaminants of parenteral products that are used in the making of PN, and manganese content of multitrace element products is higher than the recommended daily dose.[7,17] Patients with cholestasis (serum direct bilirubin concentrations that exceed 2 mg/dL [34.2 μmol/L]) should have manganese and possibly copper

LO 2 **Table 100–4**

Approximate Daily Maintenance Trace Element Requirements for Adults[7,a]

Zinc (Zn)	Selenium (Se)	Copper (Cu)	Manganese (Mn)	Chromium (Cr)
2.5–5 mg	20–60 mcg	0.3–0.5 mg	0.06–0.1 mg	10–15 mcg

[a]Requirements may vary based on patients' kidney function, liver function, gastrointestinal losses, nutritional status, specific metabolic and endocrine functions, serum levels, and medication therapy. Contamination of some PN ingredients with trace elements (eg, chromium, manganese) can contribute significantly to the total amount the patient receives. Monitor serum trace element levels in patients receiving long-term PN therapy.

LO 2

restricted to avoid accumulation and possible toxicity because both elements undergo biliary elimination. However, copper deficiency resulting in anemia, pancytopenia, and death has occurred in PN-dependent patients when copper was omitted from the PN admixture. Because copper deficiency has been reported to occur anywhere between 6 weeks and 12 months after copper elimination from PN,[19] serum copper concentrations must be regularly monitored (eg, every 6–12 weeks) when copper is omitted from PN admixtures. Trace element status should initially be monitored approximately every 3 months in patients at risk for trace element deficiency or accumulation. When stable, serum trace element concentrations can be monitored every 6 to 12 months. These levels should always be interpreted by a knowledgeable nutrition support professional, in context of the clinical stability of the patient and combined with a clinical assessment of signs and symptoms of deficiency or toxicity.

PN Additives

In general, additives in PN admixtures should be avoided or minimized to limit the risk of incompatibilities and potential safety risks. Some medications are compatible with PN admixtures and appropriate for administration over a prolonged infusion time (eg, 12–24 hours), and it may be reasonable to add these to PN admixtures when indicated.

▶ *Regular Insulin*

Regular insulin may be added to PN admixtures for glycemic control. The dose depends on the patient's clinical condition, severity of hyperglycemia, predisposing factors for hyperglycemia, renal function, and daily insulin requirements. Generally, after the patient is receiving his or her goal dextrose dose in PN, about 50% to 70% of the total insulin units administered over the previous 24 hours as sliding scale or continuous infusion can be added to the next PN admixture. In patients with diabetes, typical IV insulin doses in the PN admixture to maintain euglycemia range from 0.05 to 0.2 unit of insulin per gram of dextrose in PN. Caution should be used when insulin is added to PN to avoid hypoglycemia, especially when reversible causes of hyperglycemia have resolved (eg, stress, acute pancreatitis, corticosteroids therapy) or more than one form of insulin therapy is used concurrently. Adding insulin to PN (vs a continuous IV infusion) does not provide the flexibility of frequent titration. Other forms of insulin should not be added to PN admixtures because they are not a true solution (eg, NPH insulin) and/or their pharmacokinetics/duration of action may not be appropriate for infusion over a prolonged time.

▶ *Histamine-2 Receptor Antagonists*

Intravenous histamine-2 receptor antagonists (eg, ranitidine, famotidine) are compatible with PN admixtures and can be added when indicated.

▶ *Parenteral Iron*

Chronic PN-dependent patients are at risk for iron-deficiency due to underlying clinical conditions and the lack of regular iron supplementation in PN. Parenteral iron dextran should be used with caution due to its infusion-related adverse effects. Iron dextran is compatible with 2-in-1 PN formulations, but is not commonly added to PN admixtures due to incompatibility with ILE. Other parenteral iron formulations (eg, iron sucrose, ferric gluconate) should NOT be added to PN admixtures due to a lack of compatibility data.

▶ *Other Additives*

Other nonnutrient additives should only be included in PN admixtures if there are data supporting physicochemical compatibility and stability and if there are clinical data demonstrating the efficacy and safety of use when administered in the manner of PN administration (ie, continuous infusion over ~12–24 hours).[14]

NUTRITION ASSESSMENT AND NUTRIENT REQUIREMENTS

LO 3

A nutrition assessment is used to determine a patient's nutritional status, identify patients with malnutrition, identify risk factors for nutrition-related problems, identify or rule out specific nutrient deficiencies, and determine nutrient requirements.[1] A complete description of nutrition assessment is beyond the scope of this chapter, and a nutrition assessment should be completed by a health care professional with appropriate training and expertise (eg, dietitian, nutrition-certified pharmacist or nurse, physician). Briefly, key components of a nutrition assessment include:[1,20]

LO 3

- Patient history
- Anthropometric measurements including height, weight, ideal body weight (IBW), body mass index (BMI = weight [kg]/height [m^2]), and recent weight changes (intentional or unintentional) (refer to Chapter 102 for additional information)
- Physical examination of the musculoskeletal system (eg, biceps, triceps, quadriceps, temporalis, deltoid, and interosseous muscles) for loss of muscle mass or decreased grip strength, and examination of the skin and mucous membranes for abnormalities (eg, dry or flaky skin, bruising, edema, ascites, poorly healing wounds) and loss of subcutaneous fat
- Changes in eating habits, GI function, and associated GI symptoms
- Presence and severity of underlying and concurrent disease(s)
- Serum visceral protein concentrations (eg, albumin, prealbumin). Hypoalbuminemia at baseline or before hospitalization may indicate malnutrition, and severe hypoalbuminemia may be associated with poor outcomes. Serum albumin (half-life ~20 days) and prealbumin (half-life ~2 days) are negative acute phase proteins and therefore are neither sensitive nor specific indicators of nutritional status and protein stores in patients under metabolic stress or with evidence of inflammatory response. Measuring C-reactive protein (CRP), white blood cell count, and blood glucose levels may help assess inflammatory response. Synthesis and distribution of albumin and prealbumin may be altered, and serum concentrations are affected by nonnutritional factors, including hydration status, kidney function, and liver function.
- Biochemical evidence of vitamins, trace elements, and iron studies if clinical suspicion and minimal to no inflammation
- Functional assessment including handgrip strength

A diagnosis of malnutrition is made by identifying at least two of the following six characteristics:[20]

- Insufficient energy intake
- Weight loss
- Loss of muscle mass

- Loss of subcutaneous fat
- Localized or generalized fluid accumulation that may sometimes mask weight loss
- Diminished functional status as measure by hand grip strength

Using these criteria in combination with an assessment of inflammatory status, malnutrition may be defined as:[20]

- Without inflammation: Starvation-related malnutrition (pure chronic starvation, anorexia nervosa)
- Mild to moderate inflammation: Chronic disease-related malnutrition (organ failure, pancreatic cancer, rheumatoid arthritis, sarcopenic obesity)
- Marked inflammation: Acute disease or injury-related malnutrition (major infection, burns, trauma, closed head injury)

After performing a nutrition assessment, estimate the patient's daily energy and protein requirements (Table 100–5).[1,2,7,21,22] Indirect calorimetry involves measuring the volumes of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) to determine the resting metabolic rate (RMR) or resting energy expenditure (REE) and respiratory quotient (RQ = VCO_2/VO_2). The REE or RMR is the amount of calories required during 24 hours by the body in a nonactive state and is approximately 10% higher than the basal energy expenditure (BEE, metabolic activity required to maintain life) as it adjusts for the thermic effect of food and awake state. Critically ill patients may have variable energy expenditure (EE), and indirect calorimetry is a valuable tool in assessing EE in these patients. Indirect calorimetry requires specific equipment and trained personnel and therefore is not feasible in all settings.

More than 200 equations and derivations have been developed to predict EE for adults. The Harris-Benedict, Penn State, and Mifflin-St. Jeor equations are some of the most widely used, and they take into account several variables including a patient's sex, weight, height, age, and mechanical ventilation data to determine the REE (Table 100–5). A "stress" or "injury" factor is sometimes applied to estimate the daily total EE (TEE), although there is debate about the appropriateness and validity of this approach. Alternatively, EE can be estimated based on EE per body weight. However, dry weight or hospital

LO 3

Table 100–5

Estimating Daily Nutritional Requirements in Adults[1,2,7,20–22]

Determining Energy Expenditure	
Penn State equations (for critically ill, mechanically ventilated, nonobese adult patients)	RMR = (0.85 × BEE[a]) + (33 × V_E) + (175 × T_{max}) – 6433 RMR = (0.96 × BMR[b]) + (31 × V_E) + (167 × T_{max}) – 6212
Mifflin-St. Jeor equations (for nonobese and obese, noncritically ill adult patients)	Men: BMR = (10 × Wt) + (6.25 × Ht) – (5 × Age) + 5 Women: BMR = (10 × Wt) + (6.25 × Ht) – (5 × Age) – 161
Harris-Benedict equations (historical, not currently recommended for use in acute setting)	Men: BEE = 66.42 + (13.75 × Wt) + (5 × Ht) – (6.78 × Age) Women: BEE = 655.1 + (9.65 × Wt) + (1.85 × Ht) – (4.68 × Age) Energy expenditure then multiplied by a stress factor. To estimate the TEE: Bed rest ≈ 1.2 × BEE Ambulatory ≈ 1.3 × BEE Anabolic ≈ 1.5 × BEE Energy requirements should also be increased ~12% with each degree of fever above 37°C (98.6°F).
Energy expenditure per body weight (ie, kcal/kg)[c]	Range of ~20–30 kcal/kg/day, possibly up to 35 kcal/kg/day Maintenance ~20–25 kcal/kg/day Repletion, postoperative wound healing, critical illness, sepsis, severe trauma, severe burns ~25–30 kcal/kg/day, possibly up to 35 kcal/kg/day

Determining Amino Acid Requirements Patient Clinical Condition	Daily Amino Acid Requirements[d] (g/kg)
Maintenance or nonstressed	0.8–1
Repletion	1.3–2
Trauma, burns, sepsis, critical illness, wound healing	1.5–2
Hepatic failure with encephalopathy	0.8–1
Acute kidney injury, predialysis	0.8–1
Acute kidney injury receiving IHD	1.2–1.5
Chronic kidney disease receiving CAPD	1.2–1.5
Acute kidney disease receiving CRRT	1.5–2.5

[a]BEE calculated using the Harris-Benedict equation.

[b]BMR calculated using Mifflin-St. Jeor equation.

[c]One kcal/kg is equivalent to 4.184 kJ/kg.

[d]Amino acid requirements are based on actual body weight for normal body sized or malnourished adult patients and on ideal body weight (IBW) for obese patients.

BMR, basal metabolic rate; CAPD, continuous ambulatory peritoneal dialysis; CRRT, continuous renal replacement therapy; Ht, height (cm); IHD, intermittent hemodialysis; RMR, resting metabolic rate; TEE, total energy expenditure; T_{max}, maximum body temperature in degrees Celsius; V_E, minute ventilation in liters per minute; Wt, weight (kg).

admission weight should be used, and this estimation may not be appropriate in obese or elderly patients. There is debate over the best method to estimate energy requirements for obese patients. Indirect calorimetry would be the preferred method but may not always be available. Several equations have been developed to estimate EE in obese patients. Although there is no consensus on the weight used to estimate EE in obese patients, it is reasonable to use an AdjBW in obese patients to avoid overfeeding. AdjBW can be calculated with 25% to 50% of the difference between the actual weight and IBW added to the IBW. Using a 25% difference in calculating the AdjBW further avoids overfeeding when estimating energy requirements:

$$\text{AdjBW} = \text{IBW} + (0.25 \times [\text{Actual weight} - \text{IBW}])$$

Hypocaloric feeding is another approach for nutrient dosing in obese critically ill patients (discussed below).

Amino acid requirements are based on the patient's nutritional status, clinical condition(s), kidney function, and liver function. Amino acids are needed in adequate amounts to facilitate anabolism, restore lean body mass, and promote wound healing while avoiding adverse effects from excessive amino acid loading (eg, azotemia). No evidence-based data are available confirming the optimal body weight (actual, ideal, or adjusted) to use for dosing amino acids in adult patients. It is suggested to dose amino acids based on actual body weight for normal body sized or malnourished adult patients (ie, when actual weight is at or below IBW) and based on IBW or AdjBW for obese patients.

Hypocaloric nutrition support is an approach to dosing nutrition therapy for obese patients (BMI ≥ 30 kg/m^2). Hypocaloric feeding involves providing high doses of protein (≥ 2–2.5 g/kg IBW/day) to support anabolism with lower amounts of total calories (~11–14 kcal/kg [~46–59 kJ/kg] actual weight/day or ~22–25 kcal/kg [~92–105 kJ/kg] IBW/day) with primary goals to promote net protein anabolism and avoid hyperglycemia or exacerbation of metabolic stress in critically ill patients.[2,21] Other benefits could include avoiding fat weight gain or promoting fat weight loss. Most data with hypocaloric feeding are in critically ill adult patients, but this approach has been used in other patients. Hypocaloric feeding should not be used in patients with kidney or liver failure. The optimal safe duration of hypocaloric feeding is unknown.

Permissive underfeeding refers to providing a lower calorie nutrition support regimen to critically ill adult patients for a short period of time during the initial phase of high metabolic stress. The aims of permissive underfeeding are to avoid the burden of caloric intake on worsening metabolic stress and the negative effects of carbohydrate loading and associated hyperglycemia, increased carbon dioxide production, and fat accumulation. Typically, a permissive underfeeding PN regimen provides about 60% to 80% of daily energy requirements. Because the optimal amount of calories for critically ill patients is not well defined, strong clinical evidence to support the use of permissive underfeeding is also lacking. Severe or prolonged underfeeding should be avoided because it can result in energy deficit to the patient with the consequences of increased infectious complications with negative outcomes.

PARENTERAL NUTRITION SAFETY

Serious and sometimes fatal adverse events have occurred with inappropriate use of PN. Shortages of key PN components have also presented challenges to meet nutritional needs of patients requiring PN therapy. The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) has published several key PN safety documents, including comprehensive safe practice guidelines,[7] PN safety recommendations,[23] and revised guidelines that address PN ordering, order review, compounding, labeling, and dispensing.[14] A.S.P.E.N. has also provided guidance for managing shortages of PN components. These are essential resources for health care professionals for the safe and efficacious use of PN therapy, and they represent the standards of practice as related to PN prescribing, compounding, stability, compatibility, labeling, administration, and quality assurance. There are several key points and recommendations in these documents to improve the safety of the PN use process, including:

LO 4

- Adopting published guidelines and literature
- Developing standardized processes for PN prescribing, order verification, compounding, labeling, dispensing, administering, and monitoring
- Developing PN-specific policies and procedures
- Develop education and competency assessments at least annually for all health care professionals involved in the PN use process
- Optimizing electronic health records (EHR) and clinical decision support for PN orders
- Build, test, and heed clinical decision support warnings in EHR systems and in automated compounding devices
- Avoiding use of handwritten PN orders and eliminating transcription of PN orders
- Matching templates between ordering/EHR, compounding software/automated compounding devices, and PN labels
- PN use process and development of policies, procedures, education, and competencies should include health care professionals with expertise in nutrition support, preferably from multiple disciplines.

Although application of these guidelines is voluntary, health care professionals who are involved in prescribing, compounding, dispensing, administering, and monitoring PN therapy should review and apply them to their practice.

PREPARING THE PN PRESCRIPTION: ADMINISTRATION, COMPOUNDING, AND PHARMACEUTICAL ISSUES

LO 5

After performing a nutrition assessment and estimating nutritional requirements, determine the optimal route to provide nutrition support therapy (eg, oral, enteral, or parenteral). If PN is indicated, venous access for PN infusion must be obtained. Finally, formulate a PN prescription and administer PN according to safety guidelines.

Route of PN Administration: Peripheral Versus Central Vein Infusion

KEY CONCEPT PN can be administered via a smaller peripheral vein or via a larger central vein (Figure 100–1). Peripheral PN (PPN) is generally reserved for short-term administration (up to 7 days) when central venous access is not available. PN formulations are hyperosmolar, and PN infusion via a peripheral vein can cause thrombophlebitis. Factors that increase the risk of **phlebitis** include high solution osmolarity, extreme pH, rapid infusion rate, vein properties, catheter properties (eg, diameter, material), and infusion time via the same vein.[23] The osmolarity of PPN admixtures should be limited to ≤ 900 milliosmoles (mOsm)/L to minimize the risk of phlebitis. The approximate osmolarity

LO 5

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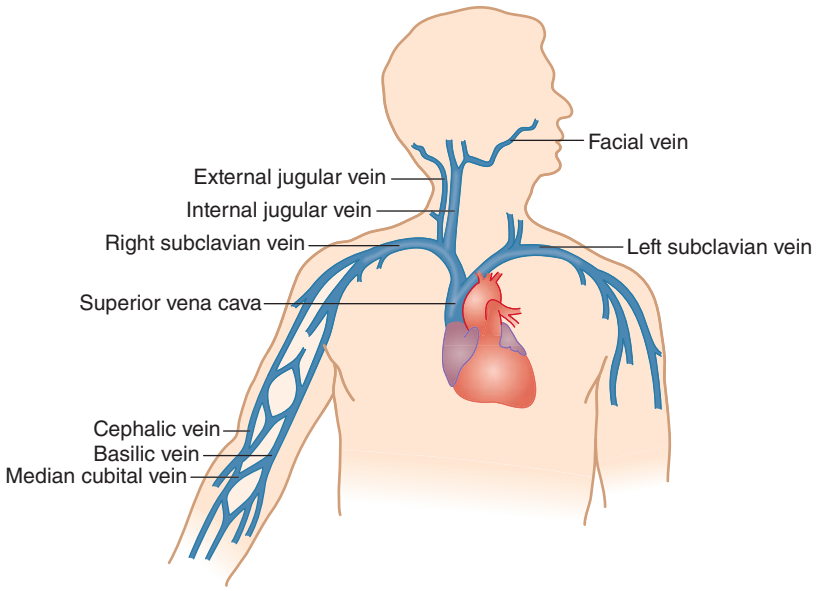

FIGURE 100–1. Selected vascular anatomy. (Reprinted with permission from Krzywda EA, Andris DA, Edmiston CE, Wallace JR. Parenteral Access Devices. In: Gottschlich MM, ed. The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2007:300–322.)

of a PN admixture can be calculated from the osmolarity of the individual components:

- Amino acids ~10 mOsm/g (or 100 mOsm/L% final concentration in PN)
- Dextrose ~5 mOsm/g (or 50 mOsm/L% final concentration in PN)
- Sodium (chloride, acetate, and phosphate) = 2 mOsm/mEq (or 2 mOsm/mmol)
- Potassium (chloride, acetate, and phosphate) = 2 mOsm/mEq (or 2 mOsm/mmol)
- Calcium gluconate = 1.4 mOsm/mEq (2.8 mOsm/mmol)
- Magnesium sulfate = 1 mOsm/mEq (2 mOsm/mmol)

LO 5 PPN admixtures should be co-infused with ILE when using 2-in-1 PN because the iso-osmolarity and near-neutral pH of ILE may decrease the risk of phlebitis (Table 100–2). Infectious and mechanical complications may be lower with PPN compared with central venous PN administration. However, because of the risk of phlebitis, severe soft tissue damage if extravasation occurs, and osmolarity limit, PPN admixtures have low macronutrient concentrations and therefore usually require large fluid volumes to meet a patient's nutritional requirements. Given these limitations, every effort should be made to obtain central venous access and initiate central PN in patients who have an appropriate indication (Table 100–1).

LO 5 *Central PN* refers to the administration of PN via a large central vein, and the catheter tip must be positioned in the superior vena cava (Figure 100–2). Central PN allows the infusion of a highly concentrated, hyperosmolar nutrient admixture. The typical osmolarity of a central PN admixture is about 1500 to 2000 mOsm/L. Central veins have much higher blood flow and the PN admixture is diluted rapidly on infusion, so phlebitis is usually not a concern. Patients who require PN therapy for longer periods of time (> 7 days) should receive central PN. Central PN requires placement of a central venous catheter and an x-ray to confirm placement of the catheter tip. A commonly used central catheter for PN infusion is a peripherally inserted central venous catheter (PICC), which is inserted into a peripheral vein but the catheter tip is placed in the superior vena cava (Figure 100–3). Central venous catheter placement may be associated with complications, including **pneumothorax**, arterial injury, **air embolus**, venous thrombosis, infection, **chylothorax**, and **brachial plexus** injury.[1,24]

Types of PN Formulations: 3-in-1 Versus 2-in-1

LO 5 KEY CONCEPT PN admixtures can be prepared by mixing all components into one bag, or ILE may be infused separately (via a Y-site infusion or through a separate IV catheter or lumen). When all components are mixed together, it is referred to as a 3-in-1 admixture or TNA.[25] When dextrose, amino acids,

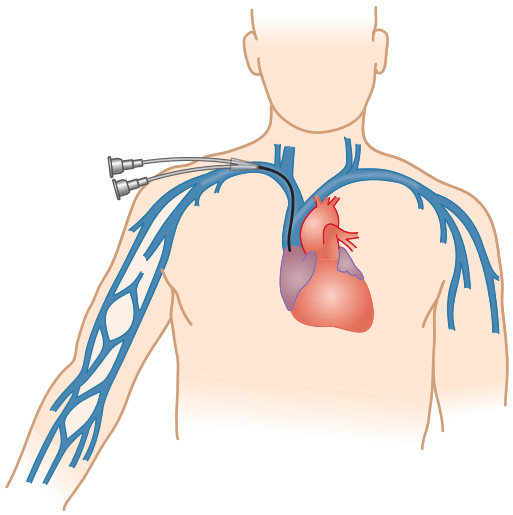

FIGURE 100–2. Percutaneous nontunneled catheter. (Reprinted with permission from Krzywda EA, Andris DA, Edmiston CE, Wallace JR. Parenteral Access Devices. In: Gottschlich MM, ed. The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2007:300–322.)

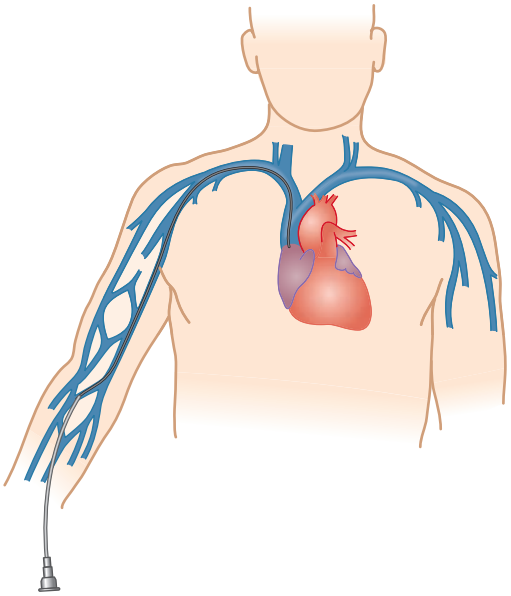

FIGURE 100–3. Peripherally inserted central venous catheter. (Reprinted with permission from Krzywda EA, Andris DA, Edmiston CE, Wallace JR. Parenteral Access Devices. In: Gottschlich MM, ed. The A.S.P.E.N. Nutrition Support Core Curriculum: A Case-Based Approach—The Adult Patient. Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2007:300–322.)

and all other PN components are mixed together without ILE, this is referred to as a 2-in-1 PN admixture. There are various advantages and disadvantages to using either TNA or 2-in-1 PN admixtures (Table 100–6). With a 2-in-1 PN admixture, ILE can be infused separately on a daily or intermittent basis. When ILE is mixed in the PN, the TNA becomes an emulsion with respect to physical and chemical characteristics. The final concentration of ILE in a 3-in-1 admixture should be greater than or equal to 2% (20 g/L) to prevent compromising the stability of the emulsion.[24] Electrolyte, dextrose, and amino acid concentrations may also be more limited in a 3-in-1 admixture.

LO 4 LO 5 The FDA has provided recommendations for safe infusion of PN admixtures containing calcium and phosphate:

- A 0.22-μm air-eliminating in-line filter should be used for infusion of non–ILE-containing PN.
- A 1.2-μm in-line filter should be used for the infusion of a TNA because it can remove large and unstable fat droplets and particulate matter.[25] (A 0.22-μm filter cannot be used on the TNA or ILE infusion line because the average size of ILE particles is ~0.3 to 0.5 μm.)[26]

LO 4 Medications should not be admixed or coinfused with PN unless necessary, and it should only be done if reasonable and safe (based on toxicity profile, pharmacokinetic, and pharmacodynamic considerations).[23] *Always* consult compatibility data before adding a medication to or coinfusing with a PN admixture. Many IV medications have limited compatibility with 3-in-1 formulations but may be coinfused with a 2-in-1 formulation.[27,28] Some medications can be coinfused at the Y-site, few medications can be mixed directly into the PN admixture or coinfused with ILE, and some cannot be mixed or coinfused with the PN admixture.[27,28]

Standardized, Commercially Available (Premixed) PN Formulations

A standardized, commercially available PN formulation is a product available from a manufacturer that requires fewer compounding steps before administration.[29] These products usually contain amino acids and dextrose in a two-chamber bag, with or without electrolytes. Vitamins and trace elements must be manually added. ILE can be added to create a TNA or infused separately. Potential advantages of standardized commercial PN products include improvements in safety (both decreased compounding errors and microbiologic contamination) and reduced costs.[29] The safety advantages are logically related to fewer manual manipulations of the system, but clinical trial data are lacking. Cost advantages have been demonstrated in some trials, with others finding no difference or increased costs. Limitations with the use of these products in the United States include relatively low amino acid concentrations, only 1- and 2-L volumes, limited

LO 5

Table 100–6

Potential Advantages and Disadvantages of Using 3-in-1 (TNA) or 2-in-1 PN Admixtures

	3-in-1 (TNA)	2-in-1
Advantages	Simplified regimen for patient Increased patient compliance at home Decreased labor (less nursing time) Decreased supply and equipment costs Decreased risk of contamination (less manipulation; all components aseptically compounded) Inhibited bacterial growth vs separate ILE Minimize infusion-related reactions from ILE and possibly improved lipid clearance (if infused over > 12 hours) Decreased vein irritation (with PPN)	Improved stability compared with TNA Increased number of compatible medications Decreased bacterial growth (in dextrose–amino acid component) compared with TNA Easier visual inspection Can use 0.22-μm bacterial retention filter
Disadvantages	Decreased stability compared to 2-in-1 PN Cannot use 0.22-μm bacterial retention filter; must use 1.2-μm filter Increased bacterial growth compared with 2-in-1 PN Visual inspection is difficult Limited compatibility with medications	Increased labor and costs (if ILE infused separately) Increased vein irritation with PPN, especially if not coinfused with ILE

ILE, IV lipid emulsion; PN, parenteral nutrition; PPN, peripheral parenteral nutrition; TNA, total nutrient admixture.

Patient Encounter Part 2

It is now hospital day #3. Given that RK has malnutrition, an enterocutaneous fistula originating from the jejunum with high output (> 500 mL/day, increased when the patient drank water), and had recent abdominal surgery, the surgery team decided to manage RK conservatively: control fistula drainage, nothing oral status, and begin parenteral nutrition (PN) support today. A peripherally inserted central catheter (PICC) was placed for PN therapy.

Laboratory Data

Na = 134 mEq/L (mmol/L), K = 3.2 mEq/L (mmol/L), Cl = 91 mEq/L (mmol/L), HCO_3 = 24 mEq/L (mmol/L), BUN = 6 mg/dL (2.1 mmol/L), serum creatinine = 0.4 mg/dL (35 µmol/L), blood glucose = 91 mg/dL (5.1 mmol/L), total Ca = 8.4 mg/dL (2.10 mmol/L)], ionized Ca = 2.38 mEq/L (1.19 mmol/L), Mg = 1.5 mg/dL (0.62 mmol/L), phosphorus = 2.5 mg/dL (0.81 mmol/L), TG = 129 mg/dL (1.46 mmol/L), albumin = 2.9 g/dL (29 g/L), WBC count = 8,300/mm^3 (8.3 × 10^9/L), hemoglobin = 11.4 mg/dL (114 g/L or 7.08 mmol/L), hematocrit = 35.1% (0.35), and platelets = 204,000/mm^3 (204 × 10^9/L)

Determine appropriate nutritional goals for RK (calorie and protein requirements).

What other patient data should be collected to help formulate a PN prescription?

variability in electrolyte content, and no formulations available for neonates and infants. These limitations may make standardized commercial PN admixtures less appropriate for some patients (eg, critically ill, obese, those with organ dysfunction or who require fluid restriction).

Formulating a PN Admixture and Regimen

After completing a full nutrition assessment; estimating the patient's daily fluid, energy, and protein requirements (Table 100–5); and determining if PN is indicated (Table 100–1), develop an appropriate PN prescription.

Initiating PN

LO 6 LO 7

Exercise caution when initiating PN to avoid hyperglycemia and fluid and electrolyte abnormalities. After determining the goal daily PN volume, initiate PN at a lower infusion rate (eg, ~50% of goal for anywhere from ~6 to 24 hours) on day 1 with no more than 150 to 200 g of dextrose per day (or a maximum initial dextrose infusion rate of ~2 mg/kg per minute). Then increase PN to goal over the following ~24 hours, provided that glycemic control is maintained and the patient does not experience significant fluid or electrolyte abnormalities. Monitor electrolytes daily and correct as needed. Advance PN more slowly and cautiously in patients with severe malnutrition and monitor for refeeding syndrome (see Complications of PN).

Patient Encounter Part 3

The surgical team asks for your recommendations for PN therapy for RK.

Develop a plan for a complete and balanced PN prescription for amino acids (including fluid, total calories, dextrose, amino acids, ILE, electrolytes, vitamins, trace elements, and any additives) and explain the rationale supporting your PN formulation and plan.

How should this PN admixture be initiated and titrated to goal?

Would you recommend any other treatments before initiating PN? (Hint: Is this patient at risk for refeeding syndrome?)

Cycling PN

PN should be administered over 24 hours in most hospitalized patients to minimize glucose, fluid, and electrolyte abnormalities. However, administering PN via an infusion over less than 24 hours, or *cycling PN*, may be advantageous in certain patients and situations. Cycling PN typically involves administering the same PN volume over a goal infusion time, usually over 12 to 18 hours, rather than over 24 hours. Begin with PN infusion over 24 hours; then taper the PN infusion to the goal cycle over 2 to 4 days (eg, 24 hours, then 18–20 hours the next day, then 14–16 hours the next day, and then 12 hours the next day). A longer goal cycle may limit adverse effects related to rate of fluid and dextrose administration (hyper- and hypoglycemia). Titrate the PN infusion rate up over 1 to 2 hours to peak rate to avoid hyperglycemia and taper down over 1 to 2 hours at the end of the cycle to avoid reactive hypoglycemia. Most home infusion pumps can be programmed to cycle a given PN volume automatically over a given time. However, the clinician may have to develop an appropriate PN cycle if the infusion pump cannot be programmed for an automatic cycle.

LO 6

Cyclic PN has the following potential advantages:

- It may improve the quality of life of patients receiving home PN by allowing the patient time off of PN to engage in normal activities of daily living.
- While data are limited, it may help prevent and alleviate PN-associated liver disease by avoiding continuous compulsive nutrient overload on the liver.[30]

Concerns with cycling PN include hyperglycemia with high infusion rates, reactive hypoglycemia when PN infusion is stopped, and fluid and electrolyte abnormalities. Random capillary blood glucose concentrations should be checked ~2 hours after reaching goal rate, 15 to 60 minutes after PN stops, and intermittently during the PN cycle as needed for glycemic control. During cyclic PN infusion, the potassium infusion rate should not exceed 10 mEq/h (mmol/h) if the patient is not on a cardiac monitor. If nocturnal cyclic PN infusion interferes with patient's sleep pattern by causing overdiuresis, the PN cycle can be extended over a longer infusion time or PN can be infused during other times of the day that are most convenient to the patient.

Transition to Oral or Enteral Nutrition

The goal is to transition the patient to enteral or oral nutrition and taper off PN as soon as indicated. After initiation of enteral or oral nutrition, monitor the patient for glucose, fluid, and electrolyte abnormalities. When oral nutrition intake is inconsistent, perform calorie counts to determine the adequacy of nutrition via the oral route. When the patient is tolerating more than 50% of total estimated daily calorie and protein requirements via the oral or enteral route, decrease PN by about 50%.

PN can be stopped when the patient is tolerating at least 75% of total daily calorie and protein requirements via the oral or enteral route, assuming that intestinal absorption is maintained.

COMPLICATIONS OF PN

KEY CONCEPT PN therapy is associated with significant complications, both with short- and long-term therapy (Table 100–7). Many complications are related to overfeeding (Table 100–8).

Hyperglycemia

LO 7

Hyperglycemia is one of the most common complications associated with PN therapy. The rate of dextrose oxidation may be reduced in patients with stress and hypermetabolism, patients with diabetes or acute pancreatitis, and patients receiving certain medications (eg, corticosteroids, vasopressors, octreotide, and tacrolimus).[31,32] Uncontrolled hyperglycemia can lead to fluid and electrolyte disturbances, hyperglycemic hyperosmolar nonketotic syndrome, hypertriglyceridemia, and an increased risk of infection.[33] Hyperglycemia in critically ill patients may be more a reflection of illness severity than from dextrose infusions, provided that the patient is not being overfed with dextrose.[34] Critical illness is associated with increased endogenous glucose production (caused by increased glycogenolysis and gluconeogenesis) and insulin resistance. Therefore, critically ill patients have lower tolerance for dextrose infusion compared with nonstressed patients. A portion of daily calories (~20% to 30%) can be administered via ILE to help decrease hyperglycemia, provided that the patient does not have hypertriglyceridemia. Overfeeding (with dextrose and with total calories) must always be avoided. Most recent data suggests that moderate glucose control is indicated in critically ill patients (eg, capillary glucose concentrations between ~140 and 180 mg per dL [7.8 and 10.0 mmol/L]).[35] Refer to the section on "PN Additives: Regular Insulin" regarding management of hyperglycemia with insulin.

Hypoglycemia

LO 7

Hypoglycemia can occur in patients when PN is interrupted suddenly (reactive hypoglycemia), especially when patients are treated with insulin or as a result of insulin overdosing in PN.[1] It is essential to prevent hypoglycemia and, if it occurs, identify and treat it promptly. Reactive hypoglycemia typically is rare and usually can be avoided by tapering PN over 1 to 2 hours before discontinuation rather than abruptly stopping the infusion (especially if the patient is receiving insulin in PN or if the patient is not receiving oral or enteral nutrition). Reactive hypoglycemia generally occurs within 15 to 60 minutes after stopping PN (especially in neonatal patients), although it can occur later than this after discontinuing PN.[1] Capillary blood glucose concentrations should be monitored about 15 to 60 minutes after stopping PN infusion to detect any potential hypoglycemia. If PN is interrupted abruptly (eg, because of lost IV access), infusing an IV solution containing dextrose 10% in water at the same rate as PN should prevent hypoglycemia. In patients with poor venous access, reduce the PN infusion rate by 50% for 1 hour before discontinuing. Another alternative to prevent reactive hypoglycemia is to provide a glucose source via the oral or sublingual route when feasible.

LO 7

Table 100–7

Complications Associated with Parenteral Nutrition

Short Term	Long Term
Hyperglycemia	Infectious complications
Hypoglycemia	Liver toxicity
Electrolyte abnormalities	Vitamin abnormalities
Refeeding syndrome	Trace element abnormalities
Acid–base disturbances	Metabolic bone disease
Hyperlipidemia	Catheter/mechanical complications
Hypercapnia	
Infectious complications	
Catheter/mechanical complications	

LO 7

Table 100–8

Consequences of Overfeeding

Source of Overfeeding	Consequences
Dextrose	Hyperglycemia, hypertriglyceridemia, hepatic steatosis, hypercapnia; hyperglycemia may cause fluid and electrolyte disturbances and increased infection risk
IV lipid emulsions	Hypertriglyceridemia, hyperlipidemia, hepatic steatosis
Amino acids	Azotemia
Total calories	Hepatic steatosis, cholestasis, hypercapnia

Hyperlipidemia/Hypertriglyceridemia

Patients receiving ILE may be at risk for hyperlipidemia and hypertriglyceridemia. Hyperlipidemia in patients receiving PN may lead to a reduction in pulmonary gas diffusion and pulmonary vascular resistance.[36] Severe hypertriglyceridemia (especially serum triglyceride concentrations exceeding 1000 mg/dL or 11.30 mmol/L) can precipitate acute pancreatitis.[37] Hypertriglyceridemia may develop as a result of increased fatty acid synthesis caused by hyperglycemia, impaired ILE clearance, in patients with history of hyperlipidemia, obesity, diabetes, alcoholism, kidney failure, liver failure, multiorgan failure, sepsis, or pancreatitis, or as a result of medications (eg, propofol, corticosteroids, cyclosporine, and sirolimus).[38,39] Hyperglycemia is probably one of the most common causes of hypertriglyceridemia in patients receiving PN.

LO 7

A higher PL:TG ratio has been proposed to cause the appearance of the abnormal lipoprotein X particles in the blood.[9,38] Lipoprotein X may compete with ILE particles for metabolism by lipoprotein lipase. It is preferred to use ILE with a lower PL:TG ratio, especially in patients with hypertriglyceridemia, because they have improved clearance compared with emulsions with a higher PL:TG ratio (Table 100–2).[9,38]

Monitor serum triglyceride concentrations regularly during PN therapy (Table 100–8). If a patient develops hypertriglyceridemia, identify and correct the underlying cause(s) if possible. Prolonging the infusion of ILE may improve lipid clearance. If a patient is receiving propofol, ILE should be withheld and the triglyceride load and calories from the 10% ILE in propofol should be taken into account (Table 100–2). ILE should be held when the serum is lipemic or when serum triglyceride concentrations are greater than 400 mg/dL (4.52 mmol/L). When this occurs, restart ILE when the serum triglyceride concentration is approximately 200 to 400 mg/dL (2.26 to 4.52 mmol/L) (or less) and administer only

two to three times per week to prevent EFAD. Avoid completely holding ILE for more than 3 to 4 weeks due to risk of EFAD.

Hypercapnia

LO 7 Hypercapnia can develop as a result of overfeeding with dextrose and/or total calories.[1,40] Excess carbon dioxide production and retention can lead to acute respiratory acidosis. Excess carbon dioxide will also stimulate an increase in respiratory rate, and this increase in respiratory workload could cause respiratory insufficiency that may require mechanical ventilation. Reducing total calorie and dextrose intake would result in resolution of hypercapnia if due to overfeeding.

Liver Complications

The incidence of liver complications associated with PN ranges from approximately 7% to 84%, and end-stage liver disease historically developed in as many as 15% to 40% of adult patients on long-term PN (likely lower in current practice with avoidance of overfeeding).[38] Patients may develop a mild increase in liver transaminases within 1 to 2 weeks of initiating PN, but this generally resolves as PN continues, provided overfeeding is avoided. Severe liver complications include hepatic **steatosis**, **steatohepatitis**, cholestasis, and **cholelithiasis**.[38]

LO 7 Hepatic steatosis is usually a result of excessive administration of carbohydrates or fats, but deficiencies of carnitine, choline, and essential fatty acids also may contribute. Hepatic steatosis can be minimized or reversed by avoiding overfeeding, especially from dextrose and ILE.[38] Cholestasis is a common and potentially LO 7 serious complication in PN-dependent patients. Factors that predispose PN patients to cholestasis include overfeeding, bowel rest, long duration of PN, short-bowel syndrome, bacterial overgrowth and translocation, and sepsis.[38] Patients may exhibit increased liver transaminase, alkaline phosphatase and gamma-glutamyl transferase concentrations, and mainly increased bilirubin concentrations with jaundice. The most sensitive marker of cholestasis is increased serum conjugated bilirubin concentration of greater than 2 mg/dL (34.2 μmol/L).[38] Cholestasis generally is reversible if PN is discontinued before permanent liver damage occurs. Serum liver function tests may take up to 3 months to return to normal after discontinuing PN. Steps to prevent cholestasis associated with PN include early enteral or oral feedings, using a balanced PN formulation, avoiding overfeeding, using cyclic PN infusion, and treating and avoiding sepsis.[38] Limiting soy-based ILE infusion to one or two times weekly at a dose adequate to prevent essential fatty acid deficiency may also decrease serum bilirubin concentrations and improve cholestasis.[41] Pharmacologic treatments include ursodeoxycholic acid (ursodiol), which may improve bile flow and reduce the signs and symptoms of cholestasis. Ursodiol is only available in an oral dosage form, and absorption may be limited in patients with intestinal resections.

LO 7 Cholelithiasis can develop as a result of decreased gallbladder contractility, especially in the absence of enteral or oral intake. Lack of intestinal stimulation reduces secretion of cholecystokinin, a peptide hormone secreted in the duodenum that induces gallbladder contractility and emptying. The best prevention of cholelithiasis is early initiation of enteral or oral feeding.

Monitor liver function tests, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, conjugated bilirubin, unconjugated bilirubin, and γ-glutamyl transferase at the initiation of PN therapy and regularly thereafter during PN therapy. The frequency of monitoring liver function tests depends on the presence or absence of liver disease, ranging from once weekly in the acute setting to monthly or less frequently in stable home PN patients.

Manganese Toxicity

LO 7 Manganese accumulation can occur in patients with cholestasis or in patients receiving long-term PN therapy. Neurotoxicity is the most common manifestation (headache, somnolence, weakness, confusion, tremor, muscle rigidity, altered gait, and masklike face [a Parkinson-like syndrome]), but liver toxicity also may occur.[38] Periodically monitor blood manganese concentrations in patients on long-term PN. Patients with cholestasis receiving PN may require restriction of manganese in PN to prevent accumulation and possible toxicity.

Metabolic Bone Disease

LO 7 Metabolic bone disease (MBD) is a condition of bone demineralization leading to **osteomalacia**, **osteopenia**, or **osteoporosis** in patients receiving long-term PN. MBD may occur in as many as 40% to 100% of patients receiving long-term PN.[38] Often patients are asymptomatic, although symptoms can include bone pain, back pain, and fractures. Patients often have increased serum alkaline phosphatase concentrations, low to normal parathyroid hormone (PTH) concentrations, normal 25-hydroxyvitamin D and low 1,25 dihydroxyvitamin D concentrations, hypercalcemia or hypocalcemia, and hypercalcuria.[42] Because patients may be asymptomatic, diagnosis can be incidental. Radiographic techniques commonly used in diagnosing bone disease include quantitative computed tomography (CT) and bone mineral density.[42]

LO 7 Factors that can predispose patients to developing MBD include deficiencies of phosphorus, calcium, and vitamin D; aluminum toxicity; amino acids and hyperosmolar dextrose infusions; chronic metabolic acidosis; corticosteroid therapy; and lack of mobility.[38,42] Calcium deficiency (caused by decreased intake or increased urinary excretion) is one of the major causes of MBD in patients receiving PN. Provide adequate calcium and phosphate with PN to improve bone mineralization and help to prevent MBD. Administration of amino acids and chronic metabolic acidosis also appears to play an important role.

Aluminum toxicity appears to play a role in the development of MBD in patients on long-term PN, possibly by impairing calcium bone fixation, inhibiting the conversion of 25-hydroxyvitamin D to the active 1,25-dihydroxyvitamin D, and/or reducing PTH secretion.[38,42] The FDA issued a rule specifying acceptable LO 4 aluminum concentrations in large-volume parenterals,[43] LO 7 indicating that products contain no more than 25 mcg/L (0.93 μmol/L) of aluminum and defined a safe upper limit for parenteral aluminum intake at less than 4 to 5 mcg/kg/day. Pharmacies should use products with the lowest labeled aluminum content for the making of PN. Patients who are chronically dependent on PN should have their serum aluminum concentrations routinely monitored or whenever MBD is suspected or diagnosed.

Encourage patients on long-term PN to engage in regular low-intensity exercise. Yearly bone density measurements also should be performed on patients on long-term PN and when MBD is suspected.

Refeeding Syndrome

Refeeding syndrome describes the metabolic derangements that occur during nutritional repletion of patients who are starved, underweight, or severely malnourished.[44] Hypophosphatemia and hypokalemia (along with associated complications) are

the classic signs and symptoms, but refeeding syndrome encompasses a constellation of fluid and electrolyte abnormalities affecting neurologic, cardiac, hematologic, neuromuscular, and pulmonary systems. The most severe cases of refeeding syndrome have resulted in cardiac failure, seizures, coma, and death.[44] The reintroduction of energy substrates, especially carbohydrates, increases metabolism and utilization of glucose as the predominant fuel source. This increases insulin secretion and demand for phosphorylated intermediates of glycolysis (eg, ATP and **2,3-diphosphoglycerate** [2,3-DPG]), inhibits fat metabolism, and causes an intracellular shift of phosphorus, potassium, and magnesium. These changes, in combination with preexisting low total body stores of phosphorus, potassium, and magnesium and enhanced cellular uptake of phosphorus during anabolic refeeding, result in hypophosphatemia, hypokalemia, and hypomagnesemia. Vitamin deficiencies (eg, thiamine) also may exist or be precipitated during refeeding. High carbohydrate intake increases the demand for thiamine, which can precipitate thiamine deficiency and cause lactic acidosis and neurologic abnormalities,[44] as well as myocardial dysfunction and congestive heart failure. Other metabolic alterations that may occur include expansion of the extracellular water compartment and fluid intolerance.

LO 8

The primary goal is preventing refeeding syndrome when initiating PN in high-risk patients (eg, prolonged lack of adequate nutritional intake, significant weight loss, or moderate to severe malnutrition). When initiating nutrition support, the rule of thumb to prevent refeeding syndrome is to "start low and go slow." Initiate PN cautiously (eg, ~25%–33% of estimated nutritional or dextrose requirements, or ~20 kcal/hour [84 kJ/hour]) and gradually increase to goal over 3 to 5 days.[44,45] Correct electrolyte abnormalities before initiating PN and provide supplemental phosphate, potassium, and magnesium in and/or outside of PN. Doses of IV phosphate up to 0.64 to 1 mmol/kg may be used to treat severe hypophosphatemia (in patients with normal kidney function), and doses can be repeated as needed until serum phosphorus concentration has normalized.[46] Provide supplemental oral or IV thiamine 100 mg/day for about 1 week in addition to the standard multivitamin in PN. Assess patients for fluid balance, signs of edema, fluid overload, and weight gain, and consider minimizing fluid and sodium intake during the first few days of PN.[44] Monitor patients closely for signs and symptoms of refeeding syndrome until they are tolerating PN at goal for a few days:

LO 8

- Vital signs, mental status, and neurologic and neuromuscular function at least every 4 to 8 hours
- Pulse oximetry and any electrocardiographic changes when indicated
- Serum laboratory values (including sodium, potassium, phosphorus, and magnesium) at least once a day

If a patient develops severe hypophosphatemia and/or other signs or symptoms of refeeding syndrome, decrease nutritional intake (eg, back to the amount provided on day 1, or ~20 kcal/hr [84 kJ/hr]) and gradually increase back to goal over 3 to 5 days.[45]

Infectious Complications

Patients receiving central PN are at increased risk of developing infectious complications caused by bacterial and fungal pathogens.[1,47] Earlier studies found that patients without malnutrition who receive early PN (eg, within 48 hours of ICU admission) may have a higher incidence of infectious complications than patients who do not receive PN or receive late PN initiation (eg, > 7 days after ICU admission).[2,3,48] However, more recent studies have not demonstrated this same risk (potentially due to avoiding overfeeding, improvements in catheter care, glycemic control, and other aspects of ICU care).[49,50] Strict aseptic techniques must be used when placing the catheter along with continuous care of the catheter and infusion site. Catheter-related bloodstream infections are a common complication in long-term PN patients, often requiring hospital admission for parenteral antimicrobial therapy and/or removal of the catheter. Contamination of the PN admixture is possible but rare if protocols are followed for aseptic preparation of PN admixtures.

Mechanical Complications

Mechanical complications of PN are related to venous catheter placement and the equipment used to administer PN. A central venous catheter must be placed by a trained professional, and risks associated with placement include pneumothorax, arterial puncture, bleeding, hematoma formation, venous thrombosis, and air embolism.[1] Over time, the venous catheter may require replacement. Problems with the equipment include malfunctions of the infusion pump, IV tubing sets, and filters.

MONITORING PN THERAPY

KEY CONCEPT When initiating PN, patients should have important baseline laboratory values checked to assess electrolyte status, organ function, and nutritional status. Thereafter, these and other nutritional parameters should be monitored routinely or as indicated. Random capillary blood glucose concentrations also should be monitored every 6 to 8 hours when initiating PN, and regular insulin should be administered to control blood glucose concentrations as needed (**Table 100–9**).

SUMMARY AND CONCLUSION

PN is an effective and potentially lifesaving therapy for patients who cannot receive adequate oral or enteral nutrition. The PN use process and PN orders are complex, and there are a number of significant safety concerns with PN ordering and order review, compounding, and administration. PN therapy can be associated with significant adverse effects and metabolic, infectious, and mechanical complications. Health care professionals must take appropriate steps to optimize the safety of PN therapy and the PN use process to minimize the risk of adverse effects and complications, and patients must be monitored closely while receiving PN to optimize outcomes.

Patient Encounter Part 4

The surgical team plans to initiate PN for RK per your recommendations. Laboratory data were listed previously.

What monitoring parameters related to PN therapy should you follow in RK after initiating PN? List monitoring parameters and frequency.

What potential complications of PN should you monitor for in RK?

What special considerations must be made when developing a plan for nutrition support therapy and a PN formulation for patients with severe malnutrition?

LO 9

Table 100–9

Suggested Frequency of Monitoring Parameters in Hospitalized Patients Receiving PN

Parameters	Initial	Daily (Unstable)	2–3 × Weekly (Stable)	Weekly	As Indicated
BUN, creatinine	X	X	X		
Sodium, potassium, chloride, bicarbonate	X	X	X		
Glucose	X	X	X		
Calcium, phosphorus, magnesium albumin, AST, ALT, LDH, alkaline phosphatase, total bilirubin	X	X	X		
Conjugated bilirubin	X			X	X
Prealbumin[a]	X				X
Triglycerides	X			X	X
RBC count, hemoglobin, hematocrit, WBC count ± differential, platelets, PTT	X				X
PT or INR				X	X
Nitrogen balance					X
Zinc, selenium, chromium, copper, manganese, iron					X
TIBC, ferritin					X
Vitamin concentrations					X
Blood cultures					X
Body weight	X	X	X		

[a]Only recommended/indicated in the absence of inflammatory response.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; TIBC, total iron-binding capacity; WBC, white blood cell.

Patient Care Process: Parenteral Nutrition

Collect Information:

- Perform a medication history for use of prescription and nonprescription medications and dietary supplements. Identify allergies to medications and other substances.
- Review the medical history and physical assessment findings.
- Review diet/nutritional intake history (or perform this history if not available).
- Identify lifestyle habits, preferences and beliefs, health goals, and socioeconomic factors that affect medication and food access and other aspects of care.

Assess the Information:

- Determine whether the patient is taking any substance that could adversely affect nutritional status, nutrient intake, or interact with prescribed medications or specialized nutrition support.
- Review relevant laboratory tests pertinent to nutrition status and fluid/electrolyte balance (eg, electrolytes, lipids, liver panel, renal function, A1C, basic metabolic profile, complete blood count).
- Determine whether the patient is at risk of refeeding syndrome or short- or long-term complications of parenteral nutrition (PN).
- Determine or assess appropriateness of the patient's macronutrient goals.
- Assess the efficacy, safety, and patient adherence of current pharmacotherapy and specialized nutrition support.
- Identify any significant adverse drug effects or drug–drug or drug–nutrient interactions.

Develop a Care Plan:

- If patient is at risk for refeeding, develop a plan for preventing refeeding while initiating and advancing PN.
- Develop an initial, and subsequently a goal, PN formulation that is appropriate, safe, and pharmaceutically stable/compatible.
- Once stabilized on goal nutrition regimen, determine monitoring plan appropriate for the patient's current clinical status.
- Develop cycle regimen for PN if patient has an indication for cycling PN.
- If patient is unable to take oral medications, determine which medications can be given via alternate routes or identify other medication changes needed to address comorbid conditions.

Implement the Care Plan:

- Educate the patient about changes in drug and nutrition therapy, medication administration, potential adverse effects, and how to manage and report adverse effects that occur.
- Review the patient's practices and technique for self-administration of PN (including sterile technique) if patient will self-manage at home.

(*Continued*)

Patient Care Process: Parenteral Nutrition (*Continued*)

- Address any patient concerns about PN and its management.
- Determine whether the patient has insurance coverage for home PN if indicated.

Follow-up: Monitor and Evaluate:

- Follow up at regular intervals (frequency as appropriate for clinical status and stability of PN regimen) with laboratory monitoring.
- Review PN adherence, administration technique, any changes in oral or enteral nutrition intake, and gastrointestinal function (indication for PN).
- Review physical examination, lab tests, and results of other diagnostic tests to assess for short- and long-term complications of PN.

Abbreviations Introduced in This Chapter

AdjBW	Adjusted body weight
ALT	Alanine aminotransferase
A.S.P.E.N.	American Society for Parenteral and Enteral Nutrition
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
CT	Computed tomography
2,3-DPG	2,3-Diphosphoglycerate
FDA	Food and Drug Administration
GI	Gastrointestinal
IBW	Ideal body weight
ILE	Lipid injectable emulsion
kcal	Kilocalorie(s)
kJ	Kilojoule(s)
LDH	Lactate dehydrogenase
MBD	Metabolic bone disease
mEq	Milliequivalents
mmol	Millimoles
mOsm	Milliosmoles
PL	Phospholipid(s)
PN	Parenteral nutrition
PPN	Peripheral parenteral nutrition
PTH	Parathyroid hormone
TG	Triglyceride
TNA	Total nutrient admixture
TPN	Total parenteral nutrition

REFERENCES

1. American Society for Parenteral and Enteral Nutrition Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Enteral Nutr. 2002;26:1SA–138SA.
2. McClave SA, Taylor BE, Martindale RG, et al., and the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2016;40:159–211.
3. Peter JV, Moran JL, Phillips-Hughes J. A meta-analysis of treatment outcomes of early enteral versus early parenteral nutrition in hospitalized patients. Crit Care Med. 2005;33:213–220.
4. Worthington P, Balint J, Bechtold M, et al. When is parenteral nutrition appropriate? A consensus recommendation. JPEN J Parenter Enteral Nutr. 2017;41:324–377.
5. Wolfe RR, Allsop JR, Burke JF. Glucose metabolism in man: responses to intravenous glucose infusion. Metabolism. 1979;28:210–220.
6. Ahrens CL, Barletta JF, Kanji S, et al. Effect of low-calorie parenteral nutrition on the incidence and severity of hyperglycemia in surgical patients: a randomized, controlled trial. Crit Care Med 2005;33:2507–2512.
7. The American Society for Parenteral and Enteral Nutrition. Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices of parenteral nutrition. JPEN J Parenter Enteral Nutr. 2004;28(suppl):S39–S70.
8. Mirtallo JM, Dasta JF, Kleinschmidt KC, Varon J. State of the art review: intravenous fat emulsions: current applications, safety profile, and clinical implications. Ann Pharmacother. 2010;44:688–700.
9. Ferezou J, Bach AC. Structure and metabolic fate of triacylglycerol- and phospholipid-rich particles of commercial parenteral fat emulsions. Nutrition. 1999;15:44–50.
10. Biesboer AN, Stoehr NA. A product review of alternative oil-based intravenous fat emulsions. Nutr Clin Pract. 2017;31:610–618.
11. Hamilton C, Austin T, Seidner DL. Essential fatty acid deficiency in human adults during parenteral nutrition. Nutr Clin Pract. 2006;21:387–394.
12. Crocker KS, Noga R, Filibeck DJ, Krey SH, Markovic M, Steffee WP. Microbial growth comparisons of five commercial parenteral lipid emulsions. JPEN J Parenter Enteral Nutr. 1984;8:391–395.
13. D'Angio R, Quercia RA, Treiber NK, et al. The growth of microorganisms in total parenteral nutrition admixtures. JPEN J Parenter Enteral Nutr. 1987;11:394–397.
14. Boullata JI, Gilbert K, Sacks G, et al.; and the American Society for Parenteral and Enteral Nutrition A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling and dispensing. JPEN J Parenter Enteral Nutr. 2014; 38:334–377.
15. Sheldon GF, Grzyb S. Phosphate depletion and repletion: relation to parenteral nutrition and oxygen transport. Ann Surg. 1975;182:683–689.
16. Food and Drug Administration. Safety alert: hazards of precipitation associated with parenteral nutrition. Am J Hosp Pharm. 1994;51:1427–1428.
17. Btaiche IF, Carver PL, Welch KB. Dosing and monitoring of trace elements in long-term home parenteral nutrition patients. JPEN J Parenter Enteral Nutr. 2011;35(6):736–747.
18. Jeejeebhoy K. Zinc: an essential trace element for parenteral nutrition. Gastroenterology. 2009;137(5 suppl):S7–S12.
19. Shike M. Copper in parenteral nutrition. Gastroenterology. 2009;137(5 suppl):S13–S17.
20. White JV, Guenter P, Jensen G, Malone A, Schofield M, the Academy Malnutrition Work Group, the ASPEN Malnutrition Task Force, and the ASPEN Board of Directors. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: Characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN J Parenter Enteral Nutr. 2012;36:275–283.

21. Dickerson RN. Specialized nutrition support in the hospitalized obese patient. Nutr Clin Pract. 2004;19:245–254.
22. Brown RO, Compher C, A.S.P.E.N. Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support in adult acute and chronic renal failure. JPEN J Parenter Enteral Nutr. 2010; 34:366–377.
23. Ayers P, Adams S, Boullata J, et al.; and American Society for Parenteral and Enteral Nutrition. A.S.P.E.N. parenteral nutrition safety consensus recommendations. JPEN J Parenter Enteral Nutr. 2014; 38:296–333.
24. Gura KM. Is there still a role for peripheral parenteral nutrition? Nutr Clin Pract. 2009;24:709–717.
25. Driscoll DF. Lipid injectable emulsions: 2006. Nutr Clin Pract. 2006;21:381–386.
26. Driscoll DF, Bacon MN, Bistrian BR. Effects of in-line filtration on lipid particle size distribution in total nutrient admixtures. JPEN J Parenter Enteral Nutr. 1996;20:296–301.
27. Trissel LA, Gilbert DL, Martinez JF, Baker MB, Walter WV, Mirtallo JM. Compatibility of parenteral nutrient solutions with selected drugs during simulated Y-site administration. Am J Health Syst Pharm. 1997;54:1295–1300.
28. Trissel LA, Gilbert DL, Martinez JF, Baker MB, Walter WV, Mirtallo JM. Compatibility of medications with 3-in-1 parenteral nutrition admixtures. JPEN J Parenter Enteral Nutr. 1999;23:67–74.
29. Miller SJ. Commercial premixed parenteral nutrition: is it right for your institution? Nutr Clin Pract. 2009;24:459–469.
30. Stout SM, Cober MP. Metabolic effects of cyclic parenteral nutrition infusion in adults and children. Nutr Clin Pract. 2010;25:277–281.
31. Watters JM, Norris SB, Kirkpatrick SM. Endogenous glucose production following injury increases with age. J Clin Endocrinol Metab. 1997;82:3005–3010.
32. Campbell IT. Limitations of nutrient intake. The effect of stressors: trauma, sepsis and multiple organ failure. Eur J Clin Nutr. 1999;53(suppl 1):S143–S147.
33. Butler SO, Btaiche IF, Alaniz C. Relationship between hyperglycemia and infection in critically ill patients. Pharmacotherapy. 2005;25:963–976.
34. Atkinson M, Worthley LI. Nutrition in the critically ill patient: Part I. Essential physiology and pathophysiology. Crit Care Resusc. 2003;5:109–120.
35. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–1297.
36. Suchner U, Katz DP, Fürst P, et al. Effects of intravenous fat emulsions on lung function in patients with acute respiratory distress syndrome or sepsis. Crit Care Med. 2001;29:1569–1574.
37. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–3421.
38. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition in adults, part 1 and part 2. Am J Health Syst Pharm. 2004;61:1938–1949, 2050–2059.
39. Devlin JW, Lau AK, Tanios MA. Propofol-associated hypertriglyceridemia and pancreatitis in the intensive care unit: an analysis of frequency and risk factors. Pharmacotherapy. 2005;25:1348–1352.
40. McClave SA, Lowen CC, Kleber MJ, McConnell JW, Jung LY, Goldsmith LJ. Clinical use of the respirator quotient obtained from indirect calorimetry. JPEN J Parenter Enteral Nutr. 2003;27:21–26.
41. Cober MP, Teitelbaum DH. Prevention of parenteral nutrition-associated liver disease: lipid minimization. Curr Opin Organ Transplant. 2010;15:330–333.
42. Ferrone M, Geraci M. A review of the relationship between parenteral nutrition and metabolic bone disease. Nutr Clin Pract. 2007;22:329–339.
43. Department of Health and Human Services, Food and Drug Administration. Aluminum in large and small volume parenterals used in total parenteral nutrition. Fed Regist. 2000(Docket No. 90N-0056);65:4103–4111.
44. Kraft MD, Btaiche IF, Sacks GS. Review of the refeeding syndrome. Nutr Clin Pract. 2005;20:625–633.
45. Doig GS, Simpson F, Heighes PT, et al. for the Refeeding Syndrome Trial Investigators Group. Restricted versus continued standard caloric intake during the management of refeeding syndrome in critically ill adults: a randomised, parallel-group, multicentre, single-blind controlled trial. Lancet Respir Med. 2015;3:943–952.
46. Brown KA, Dickerson RN, Morgan LM, Alexander KH, Minard G, Brown RO. A new graduated dosing regimen for phosphorus replacement in patients receiving nutrition support. JPEN J Parenter Enteral Nutr. 2006;30:209–214.
47. Beghetto MG, Victorino J, Teixeira L, de Azevedo MJ. Parenteral nutrition as a risk factor for central venous catheter-related infection. JPEN J Parenter Enteral Nutr. 2005;29:367–373.
48. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365:506–517.
49. Doig GS, Simpson F, Sweetman EA, et al. for the Early PN Investigators of the ANZICS Clinical Trials Group. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition. JAMA. 2013;309:2130–2138.
50. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomized controlled clinical trial. Lancet. 2013;381:385–393.

101 Enteral Nutrition

Sarah J. Miller

LEARNING OBJECTIVES

LO

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

1. Discuss how gut structure and function impact choice of feeding route and outcome of feeding.
2. Estimate kilocalorie and protein requirements of an enteral feeding candidate and design an enteral nutrition (EN) regimen to meet these.
3. Evaluate patient-specific parameters to determine whether EN is appropriate.
4. Compare clinical efficacy, complications, and costs of EN versus parenteral nutrition (PN).
5. Formulate a monitoring plan for an EN patient.
6. Select appropriate medication administration techniques for an EN patient.

INTRODUCTION

Enteral nutrition (EN) is broadly defined as delivery of nutrients via the gastrointestinal (GI) tract. The terms *enteral nutrition* and *tube feedings* are often used synonymously. Formulas for EN usually are delivered in the form of commercially prepared liquid preparations, although some products are produced as powders for reconstitution, and a few patients may be appropriate for delivering specific blenderized foods down their feeding tubes.[1] Nonvolitional feedings in patients who cannot meet nutritional requirements by oral intake include EN and **parenteral nutrition** (PN), which are collectively known as *specialized nutrition support* (SNS).

Several organizations have issued clinical guidelines on the use of EN. These include the American Society for Parenteral and Enteral Nutrition (ASPEN), European Society for Clinical Nutrition and Metabolism (ESPEN), and a Canadian team known as Critical Care Nutrition.[2–5] ASPEN and the Society for Critical Care Medicine (SCCM) have jointly issued guidelines for SNS in critically ill patients.[6]

GI TRACT STRUCTURE AND FUNCTION

Anatomy and Absorptive Function

With normal volitional feeding, food is ingested via the mouth. There, the process of breaking down complex foodstuffs into simpler forms that can be absorbed by the small bowel begins. Solid food is chewed in the mouth, and enzymes begin digestion. Presence of food in specific regions of the GI tract triggers release for many enzymes and GI hormones. Food is swallowed and passes through the esophagus and the esophageal sphincter to the stomach, where additional digestive enzymes and acids further break it down. The stomach also mixes and grinds.

The food, now in a liquid form known as *chyme*, passes through the pyloric sphincter into the duodenum, where stomach acid is neutralized. The food then passes from the duodenum into the jejunum, where most absorption of digested carbohydrate and protein occurs. Most fat absorption occurs within the jejunum and ileum, the final segment of the small bowel. In the small bowel, breakdown of carbohydrate, protein, and fat occurs both within the lumen and at the intestinal mucosal membrane surface. The absorptive units on the intestinal mucosal membrane are infoldings known as *villi*. These villi are made up of epithelial cells called *enterocytes*. Projections from these enterocytes called *microvilli* increase surface area of the small bowel and make up the *brush-border membrane*.

Digestive substances secreted by the pancreas play a role in food breakdown. Large amounts of sodium bicarbonate neutralize stomach acid. Digestive substances flow from the pancreas through the pancreatic duct. The pancreatic duct typically joins the hepatic duct to become the common bile duct that empties through the sphincter of Oddi into the duodenum. Bile salts secreted by the liver help emulsify fat and facilitate fat absorption. Bile flows through bile ducts into the hepatic duct and common bile duct. Bile is stored in the gallbladder until needed to aid fat digestion, at which time it empties through the cystic duct to the common bile duct to the duodenum. Pathways through which carbohydrate, protein, and fat are digested and absorbed through the small bowel are illustrated in **Figure 101–1**.

Remaining undigested food passes from the ileum through the ileocecal valve to the colon. A major role of the colon is fluid absorption. Some water and sodium absorption is facilitated by short-chain fatty acids (SFCAs) formed from digestion of certain dietary fibers by colonic bacterial enzymes.

Gut Immune Function

The gut plays significant immune roles. The distal small bowel and colon host many bacteria and their endotoxins, and it is important that these organisms not gain access to internal systems of the body. This function is known globally as the *gut barrier function*.[7] Normal flora of the gut comprise one component. Normal flora, particularly some anaerobes, help to prevent overgrowth of potential pathogens. A second component involves mechanical factors. These include a mucus layer that prevents adherence of bacteria. Peristalsis of the small bowel prevents stasis of bacteria. **Gut-associated lymphoid tissue** (GALT), prominent in the small bowel, serves as a local immune

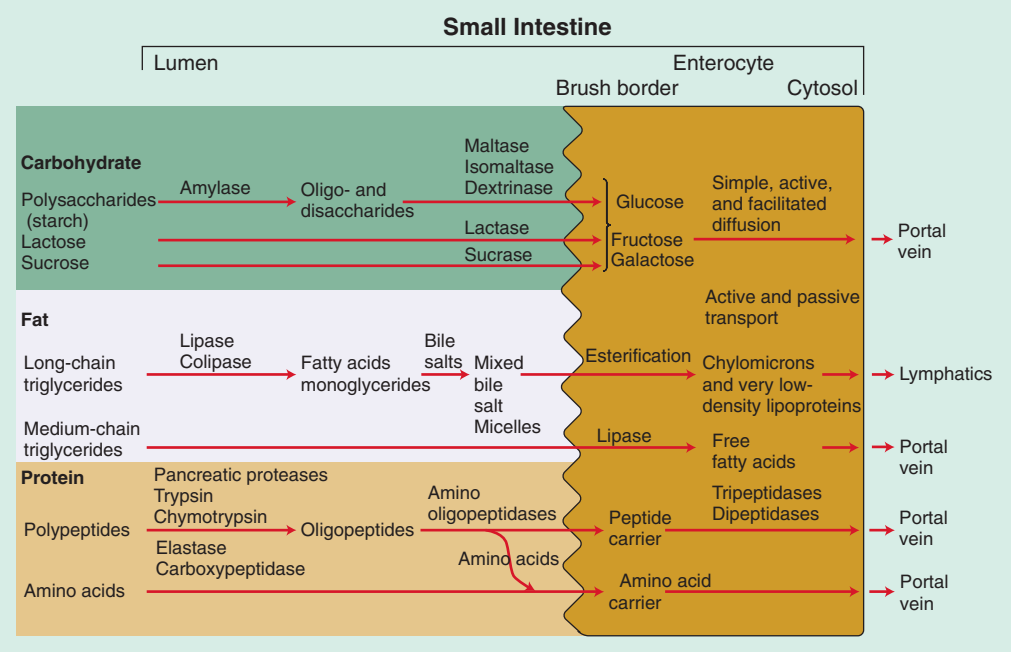

FIGURE 101–1. Schematic of carbohydrate, fat, and protein digestion. (From Kumpf VJ, Chessman KH. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014:2428.)

system. Secretory immunoglobulin A produced at the mucosal surface in response to food prevents bacteria from invading the surface.

PATIENT SELECTION

In general, KEY CONCEPT EN is the preferred route if the gut can be used safely in patients who cannot meet nutritional requirements by oral intake. If the gut functions, EN is usually preferred over PN. The timing of SNS (either EN or PN) is controversial, but definitive guidelines for these therapies state that SNS should be started when intake has been inadequate for 7 to 14 days or if inadequate oral intake is anticipated for at least 7 to 14 days.[2] Previously well-nourished patients can better afford not being fed for longer periods than previously poorly nourished patients. Patients in the intensive care unit (ICU) probably benefit from early EN started within 24 to 48 hours of admission to the ICU.[4,6] Ethical questions come into play when consideration is given to starting (or stopping) EN in seemingly futile situations. Methods for assessing nutritional status and designing SNS regimens are covered in Chapter 100. Generally, nonobese hospitalized patients require 20 to 35 total kcal/kg of body weight/day (84–147 kJ/kg body weight/day) and 1.2 to 2 g protein/kg of body weight/day. Obese patients are often fed hypocaloric, high protein diets; guidelines state to start feedings at 1.2 g protein per kg of actual body weight (or 2–2.5 g per kg of ideal body weight) and no more than 14 kcal/kg actual body weight (59 kJ/kg actual body weight).[8]

LO 1

LO 2

Indications

Many potential indications for EN exist (Table 101–1). PN was used extensively in the past for many of these conditions. Advances in EN technology now allow many patients with these conditions to receive EN. EN is administered in both institutional and home settings.

Table 101–1

Potential Indications for EN

Neoplastic Disease
Chemotherapy
Radiation therapy
Upper GI tumors
Cancer cachexia

Organ Dysfunction
Liver disease/failure
Kidney insufficiency/failure
Cardiac cachexia
ARDS/ALI
Bronchopulmonary dysplasia
Congenital heart disease
Organ transplantation

Hypermetabolic States
Closed head injury
Burns
Trauma
Postoperative major surgery
Sepsis

GI Disease
Inflammatory bowel disease
Short-bowel syndrome
Esophageal motility disorder
Pancreatitis
Fistulas
Gastroesophageal reflux disease (severe)
Esophageal or intestinal atresia

Neurologic Impairment
Comatose state
Cerebrovascular accident
Demyelinating disease
Severe depression
Cerebral palsy

Other Indications
AIDS
Anorexia nervosa
Complications during pregnancy
Failure-to-thrive
Geriatric patients with multiple chronic diseases
Extreme prematurity
Inborn errors of metabolism
Cystic fibrosis

AIDS, acquired immune deficiency syndrome; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

From Kumpf VJ, Chessman KH. Enteral nutrition. In DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014.

Table 101–2

Contraindications and Precautions for EN

Severe hemorrhagic pancreatitis
Severe necrotizing pancreatitis
Necrotizing enterocolitis
Diffuse peritonitis
Small bowel obstruction
Paralytic ileus
Severe hemodynamic instability
Enterocutaneous fistulae
Severe diarrhea
Severe malabsorption
Severe GI hemorrhage
Intractable vomiting
Uncorrectable coagulopathy
Bowel ischemia

Contraindications and Precautions

LO 3

EN should be avoided or used with caution in certain conditions (Table 101–2). It is possible to use EN in some patients with these conditions depending on severity of illness, location of abnormality, and experience of practitioners delivering care. Feeding in the setting of hemodynamic instability is controversial; the 2016 ASPEN/SCCM critical care guidelines recommend withholding feedings in hypotension or when vasopressors are being initiated or escalated.[6]

Enteral Versus Parenteral Feeding

With advent of the technique of PN by large central vein in the late 1960s, this modality quickly became popular. PN was incorporated quickly into care of patients such as critically ill patients. The relative ease of PN administration, along with the perception that critically ill patients had prolonged high-energy expenditures, led to complications of overfeeding. Dextrose overfeeding led to hyperglycemia, carbon dioxide overproduction leading to delays in weaning from mechanical ventilation, and liver abnormalities owing to hepatic steatosis.

LO 4

The pendulum began to swing toward EN in the late 1980s and early 1990s as clinical studies showed better clinical outcomes with EN compared to PN. Some potential advantages of EN over PN are included here. First, EN is expected to preserve the gut barrier function better than PN. This could prevent translocation of bacteria and endotoxin from the gut lumen into the lymphatic system and systemic circulation, thus preventing infections. Some studies support that KEY CONCEPT EN is associated with fewer infectious complications than PN. EN is cited frequently as having a better overall safety profile than PN. Whereas PN is associated with more severe complications, such as pneumothorax and catheter sepsis, EN is associated with more nuisance complications, such as GI side effects. Another frequently cited advantage of EN over PN is that EN is less expensive. EN formulas typically are cheaper and less labor intensive to prepare than PN, although some specialty EN formulas approach the cost of PN formulas. Depending on the method of feeding tube placement, EN costs can mount if the tube must be placed by a radiologist or gastroenterologist rather than a bedside nurse.

Arguments in support of EN over PN have been questioned. Part of this questioning relates to the question of whether EN is beneficial compared with PN or whether PN as previously administered might have been detrimental. Overfeeding and hyperglycemia occur easily with PN, and the potential harm of hyperglycemia, especially in critical care populations, has been demonstrated, although the exact range optimal for glycemic control in ICU patients remains controversial and may differ for various subpopulations of the critically ill. Parenteral nutrition as it was historically delivered led to an increased risk of infection and perhaps caused more harm than good in many instances unless patients were severely malnourished.[9] Whether EN truly prevents infections and improves clinical outcomes or whether PN is detrimental continues to be debated and probably depends on the specific patient population. At present, EN is preferred by most experts over PN when the gut is functional. In Europe (more so than in North America), PN has been used to supplement EN during the first week of intensive care therapy when EN is not yet being tolerated at full rates.[3] This approach is currently discouraged by American and Canadian ICU guidelines.[4,6] Randomized controlled trials relating to EN versus PN and deliberate (permissive) underfeeding (setting caloric goals below what would be considered necessary to achieve energy balance) have yielded disparate results.[10-16]

ROUTES OF ACCESS[17]

There are several access sites for EN (Figure 101–2). The tip of the feeding tube can end up in the stomach, duodenum, or jejunum. Both advantages and disadvantages exist for each EN route (Table 101–3). Tube sizes vary from about 8 to 24 French (Fr).

Gastric Feeding

Gastric feedings are commonly used. They require an intact gag reflex and normal gastric emptying for safety and success. Certain patients, such as those who have suffered head trauma, may not empty their stomachs efficiently and therefore may not be good candidates for gastric feedings. In these patients, it may be impossible to achieve a gastric tube feeding rate to provide adequate nutrients. Pooling of formula in the stomach could increase risk of aspirating feeding formula into the lungs.

The nasogastric (NG) route is used most commonly for short-term enteral access. The major advantage of this route is that the tube can be placed quickly and inexpensively by the nurse at the bedside.

Gastrostomy tubes, in which an incision is made directly through the abdominal wall, are indicated for patients who can tolerate gastric feedings but in whom long-term feedings are anticipated. The most commonly placed gastrostomy tubes are either placed percutaneously by interventional radiology or are percutaneous endoscopic gastrostomy (PEG) tubes placed endoscopically. Gastrostomy tubes also can be placed laparoscopically or during an open procedure by a surgeon. Placement of a gastrostomy tube either endoscopically or surgically is more expensive than bedside orogastric (OG) or NG placement but can result in placement of a larger bore tube.

Postpyloric Feedings

KEY CONCEPT For patients intolerant of gastric feedings or in whom the risk of aspiration is high, feedings delivered with the tip of the tube in the jejunum are preferred. This bypasses the problem of poor gastric emptying and adds another barrier (pyloric sphincter) through which tube feedings must traverse before aspiration into the lungs. However, postpyloric feedings do not preclude the possibility of aspiration. Many patients with this complication aspirate their own nasopharyngeal secretions.

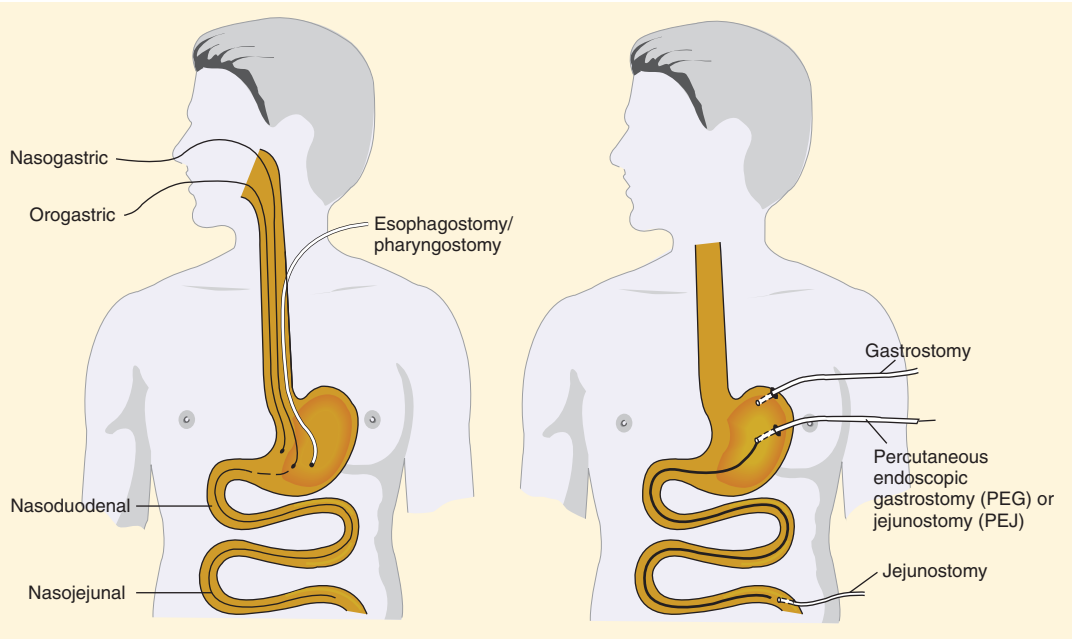

FIGURE 101–2. Access sites for tube feeding. (From Kumpf VJ, Chessman KH. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014:2431.)

Table 101–3

Options and Considerations in the Selection of Enteral Access

Access	EN Duration/Patient Characteristics	Tube Placement Options	Advantages	Disadvantages
Nasogastric or orogastric	Short term Intact gag reflex Normal gastric emptying	Manually at bedside	Ease of placement Allows for all methods of administration Inexpensive Multiple commercially available tubes and sizes	Potential tube displacement Potential increased aspiration risk
Nasoduodenal or nasojejunal	Short term Impaired gastric motility or emptying High risk of GER or aspiration	Manually at bedside Fluoroscopically Endoscopically	Potential reduced aspiration risk Allows for early post injury or postoperative feeding Multiple commercially available tubes and sizes	Manual transpyloric passage requires greater skill Potential tube displacement or clogging Bolus or intermittent feeding not tolerated
Gastrostomy	Long term Normal gastric emptying	Surgically Endoscopically Radiologically Laparoscopically	Allows for all methods of administration Low-profile buttons available Large-bore tubes less likely to clog Multiple commercially available tubes and sizes	Attendant risks associated with each type of procedure Potential increased aspiration risk Risk of stoma site complications
Jejunostomy	Long term Impaired gastric motility or gastric emptying High risk of GER or aspiration	Surgically Endoscopically Radiologically Laparoscopically	Allows for early post injury or postoperative feeding Potential reduced aspiration risk Multiple commercially available tubes and sizes Low-profile buttons available	Attendant risks associated with each type of procedure Bolus or intermittent feeding not tolerated Risk of stoma site complications

EN, enteral nutrition; GER, gastroesophageal reflux.

From Kumpf VJ, Chessman KH. Enteral nutrition. In DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014.

Nasoduodenal (ND) and nasojejunal (NJ) feeding tubes can be placed by trained, experienced nurses at the bedside. This is still a relatively inexpensive method of placement. Bedside electromagnetic transmitter devices (eg, CORTRAK, Corpak Medsystems) may be helpful in achieving postpyloric tube placement. In some institutions, ND or NJ placements are done in radiology by a radiologist using fluoroscopy to visualize tube advancement, increasing the cost of EN therapy. NJ tubes generally are preferred over ND tubes; placement of the tube tip distal to the **ligament of Treitz** may reduce risk of aspiration. Alternatively, during a laparotomy, the surgeon can place an ND or NJ tube.

Surgically placed jejunostomy tubes are placed through an incision in the abdominal wall. These tubes are sometimes placed during laparotomy following abdominal trauma. Alternatively, jejunal access can be obtained by placing a jejunal extension through a PEG tube; the resulting tube is sometimes referred to as a *PEGJ tube* or *G-J tube*. Another option is to place a **percutaneous endoscopic jejunostomy** (PEJ) tube directly; this is more technically difficult than PEG placement and is not available in most institutions.

METHODS OF DELIVERY

Enteral feedings are delivered by several different methods. Continuous infusion must be used when duodenal or jejunal feedings are administered; intermittent feedings directly into the small bowel generally result in GI intolerance. For gastric feedings, bolus or intermittent feedings could be administered instead of continuous feedings. Each method has advantages and disadvantages.

In hospitals, EN is delivered most commonly as a continuous infusion at a constant rate regulated by an infusion pump. A variation of continuous infusion is cyclic feeding, in which a constant rate is maintained over a certain number of hours daily; this method of administration is used commonly in long-term care or home settings. Sometimes EN is administered overnight. Continuous feedings are often started at a low rate and titrated up every few hours as the patient tolerates. Ideally the patient will reach goal rate of feeding within 1 to 2 days.

Intermittent feedings are used commonly in long-term care or home settings. Patients frequently are started with continuous feedings; transitioned to intermittent feedings given several times a day over about 30 to 45 minutes for each feeding; and eventually changed to bolus feedings administered over less than 10 minutes per feeding. Intermittent feedings may be administered by gravity flow adjusted with a roller clamp, although some institutions may use an infusion pump. Bolus feedings can be administered using a 60-mL syringe, although sometimes an infusion set and pump may be used. Intermittent and bolus feedings often are given in amounts of 240 to 480 mL per feeding, corresponding to one to two cans of formula.

Some institutions now have volume-based feeding protocols instead of rate-based. In these protocols, nurses are given the latitude to increase the rate after the feeding has been held such that the prescribed volume is administered over a 24-hour period.

EN FORMULAS

One advantage of EN over PN is the availability in the United States of certain nutrients in some EN formulations (eg, glutamine, medium-chain triglycerides [MCT]) that are not available for parenteral use. Many EN formulas are marketed commercially. Hospitals and long-term care facilities limit formularies of EN formulas, stocking only a limited number of products.

Polymeric Versus Oligomeric Formulas

A major criterion for categorizing EN products is whether macronutrients (particularly protein) are more intact (polymeric) or present in simpler forms (oligomeric). KEY CONCEPT Standard EN formulas are polymeric; these are appropriate for most patients. Oligomeric formulas should be reserved for patients with GI dysfunction.

Polymeric formulas typically contain intact proteins (most commonly casein and soy protein). They have low osmolality of 300 to 500 mOsm/kg (mmol/kg). These usually supply essential vitamins and minerals in amounts similar to the adequate intakes (AI) or Recommended Dietary Allowances (RDA) when the formula is delivered in amounts adequate to meet macronutrient requirements. The AI or RDA of a nutrient is the amount of that nutrient that must be consistently consumed by individuals to meet the needs of most of the population for that nutrient. Most modern formulas are lactose- and gluten-free. Products designed for use as oral supplements generally are polymeric and often have sucrose or other simple sugars added to improve taste.

Oligomeric formulas are also known as *chemically defined formulas*. These can be subcategorized based on whether the formula contains all free amino acids (elemental formulas) or peptides (peptide based) as the protein source. Some formulas contain a combination of free amino acids and small peptides. Dipeptides and tripeptides are absorbed more efficiently than free amino acids. Oligomeric formulas may be better tolerated than polymeric formulas for patients with defects in GI function and may be particularly useful with severe pancreatic dysfunction or significantly decreased GI surface area. However, adaptation of the bowel is better when intact nutrients are supplied to patients with short-bowel syndrome, so those patients should be transitioned to intact nutrients as soon as possible.

Oligomeric formulas typically are more expensive than polymeric formulas and have higher osmolality. However, osmolality of these products usually does not exceed 700 mOsm/kg (mmol/kg), a value less than that of many oral medications or a regular diet. Sometimes enteral feedings are diluted to deliver extra water required by the patient; this practice generally is discouraged because of potential risk of formula contamination. Instead, it is better to give extra water as boluses through the tube. If medications are administered through the feeding tube, generous amounts of water should be used to flush the tube before and after each medication; this practice helps provide extra fluid and prevent problems with tube occlusion.

Oligomeric formulas are less palatable than polymeric formulas and are not designed for use as oral supplements. Many oligomeric formulas provide some fat calories as MCT, a fat source that is more readily absorbed and metabolized than long-chain triglycerides (LCTs) typically found in polymeric formulas. The MCTs do not require bile salts or pancreatic enzymes for absorption. Some elemental formulas contain a low proportion of fat (< 10% of total calories), which makes them useful in certain situations where fat needs to be restricted. The carbohydrate source in oligomeric formulas is less complex than in polymeric formulas, consisting of oligosaccharides rather than hydrolyzed starch.

Fiber Content

Another distinguishing factor of enteral formulas is whether or not they contain fiber. Both soluble and insoluble fibers may be included. Insoluble fiber exerts an effect on gut motility by drawing water into the intestine and decreasing transit time, thus preventing constipation. Soluble fiber can help to lower

blood cholesterol levels, regulate blood sugar, and prolong gastric emptying. Soluble fiber may also help control diarrhea. Cellulose gum is an example source of insoluble fiber. Oat fiber and guar gum provide primarily soluble fiber. Soy fiber not only provides primarily insoluble fiber but also some soluble fiber and is the most commonly used fiber source in tube feeding products. Fiber has been useful for regulating gut motility in some but not all clinical studies; it certainly can be useful in selected patients.[18] Some patients may experience GI discomfort secondary to gas production with introduction of fiber.

Fructooligosaccharides (FOS) are a form of soluble fiber that pass through the stomach and small bowel undigested and are fermented by colonic bacteria to the SCFAs butyrate, propionate, and acetate. The SCFAs serve as a fuel source for **colonocytes** and also serve other important functions.[19] The FOS are thus **prebiotics** that serve as fermentable substrates for normal flora of the colon. The SCFAs are not added directly to EN products because they would be absorbed completely before reaching the colon; rather, FOS are added, allowing bacterial degradation to form SCFAs. Products containing FOS are often avoided postoperatively due to increased gas, bloating, and abdominal distention with these products.

Caloric Density

Enteral feeding formulas can be categorized based on caloric density. Standard caloric density is 1 to 1.3 kcal/mL (4.2–5.4 kJ/mL). More calorically dense formulas containing 1.5 to 2 kcal/mL (6.3–8.4 kJ/mL) are available and have higher osmolality. Fluid-overloaded patients may benefit from more calorically dense formulas. As caloric content of a formula increases, the amount of free water decreases.

Protein Content

Protein content is an important factor in choosing an EN formula. Standard protein content in EN formulas is up to about 20% of total calories as protein. High-protein formulas containing 25% or more of total calories as protein are available for highly stressed patients with elevated protein needs. Low-nitrogen formulas containing less than 10% of total calories as protein for use in patients requiring protein restriction are also available. A wide range of protein is available, from about 35 to 95 g/L.

Carbohydrate Content

Common carbohydrate sources in tube feeding products include maltodextrin, corn syrup solids, and hydrolyzed cornstarch. Products containing simple sugars (often those intended for oral use) tend to be higher in osmolality.

Fat Content

Both MCTs and LCTs are used in tube feeding products. Corn, soy, sunflower, and safflower oils are standard sources of fat, providing mainly ω-6 polyunsaturated fatty acids (PUFAs). Some EN products contain higher quantities of ω-3 PUFAs from sources such as fish oil (ie, docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]). Other formulas contain higher quantities of monounsaturated fatty acids (MUFAs) from canola oil and high-oleic safflower or sunflower oils. The essential fatty acid (EFA) content (mainly linoleic acid) of EN formulas is important because EFA deficiency can be induced if at least 1% to 4% of total calories are not supplied as EFAs. MCT oil does not contain EFAs.

Vitamin, Mineral, and Electrolyte Content

Most EN products contain vitamins and minerals, including major electrolytes, in amounts adequate to deliver the RDA or AI when a standard volume of formula is delivered daily. Some specialty formulas (eg, renal formulas) may have altered amounts of certain micronutrients.

Specialty Formulas

Specialty formulas designed for use in specific clinical situations generally are more expensive than standard polymeric formulas. KEY CONCEPT Robust clinical trial data supporting use of specialty formulas in niche populations typically remain lacking in terms of improved patient outcomes. Manufacturers' websites should be consulted for the most current information on content of enteral formulas as changes do occur.

▶ *Stress and Trauma Formulas*

Historically, formulas aimed specifically for highly stressed, critically ill patients were enriched with branched-chain amino acids (BCAAs). The rationale was that skeletal muscle BCAAs are preferentially used for energy in critical illness. Provision of BCAAs might limit breakdown of muscle in these patients. Clinical data failed to support or refute benefit of these formulas unequivocally in terms of clinical outcomes.[4]

The newer generation of enteral feeding formulas marketed for use in these populations covers a broad spectrum of characteristics (**Table 101–4**). Whereas some are polymeric, others are oligomeric to address malabsorption that may accompany high stress. Some formulas marketed for use in critical illness are calorically dense (1.5–2 kcal/mL [6.3–8.4 kJ/mL]) to address fluid restrictions seen in this population, and others are less calorically dense. Most products contain generous amounts of protein to address requirements of highly stressed patients (**nonprotein kilocalorie to nitrogen ratios** typically between 75:1 and 125:1 [nonprotein energy to nitrogen ratio between about 300 and 500 kJ/g N]). Many products contain ingredients purported to increase immune function; the term *immunonutrition* is sometimes attached to these products.

Immune-enhancing ingredients present in some enteral feeding products include arginine, glutamine, ω-3 fatty acids, nucleic acids, and antioxidants. Few products contain all of these (see Table 101–4). Arginine is an important substrate for nitric oxide (NO) synthesis, and small amounts of NO have beneficial effects on immune function under certain conditions. Arginine has been purported to have a positive influence on lymphocyte and macrophage function. Glutamine is considered to be conditionally essential in critical illness and is a preferred fuel source for enterocytes. Supplementation with glutamine, either parenterally or enterally, may help maintain integrity of gut mucosa, preventing translocation of bacteria and endotoxin from the gut lumen into the lymphatic system and systemic circulation. However, glutamine supplementation remains controversial.[4,6,20,21] The ω-3 fatty acids, primarily from fish oils, are included in many immunonutrition products. Metabolites of ω-6 fatty acids include mediators such as prostaglandins, leukotrienes, and thromboxanes that are primarily proinflammatory and increase coagulation. Conversely, mediators produced from ω-3 fatty acids are less proinflammatory and decrease coagulation. Limited data support nucleic acids as immunomodulators. Quantities of antioxidants (particularly vitamin C, vitamin E, and β-carotene) higher than traditionally found in standard enteral formulas are added to some immunonutrition formulas to protect

Table 101–4

Selected Enteral Feeding Formulas Marketed for Use in Critical Illness, High-Stress, Pulmonary Disease and Ventilator-Dependent, or Trauma Patients[a]

Product Name/Manufacturer	kcal/mL	Protein (g/L)	Protein (g/1000 kcal)	Enriched Ingredients[b]
Peptamen 1.5/Nestle	1.5	68	46	MCT
Nutren 2.0/Nestle	2	84	42	MCT
Promote/Abbott	1	63	63	MCT
Impact/Nestle	1	56	56	Arginine, nucleotides, ω-3 fatty acids
Nutren 1.5/Nestle	1.5	68	46	
Pulmocare/Abbott	1.5	62	42	
Oxepa/Abbott	1.5	63	42	ω-3 fatty acids, γ-linolenic acid
Isosource 1.5 Cal/Nestle	1.5	68	46	
Two Cal HN/Abbott	2	84	42	
Nutren Pulmonary	1.5	68	46	MCT
Impact Peptide 1.5/Nestle	1.5	94	63	Arginine, nucleotides, ω-3 fatty acids, MCT
Pivot 1.5 Cal/Abbott	1.5	94	63	Arginine, ω-3 fatty acids
Vivonex Plus/Nestle	1	45	45	Glutamine, arginine
Vivonex RTF/Nestle	1	50	50	MCT[c]
Peptamen Intense VHP/Nestle	1	92	92	MCT, ω-3 fatty acids
Peptamen AF/Nestle	1.2	76	63	MCT, ω-3 fatty acids
Perative/Abbott	1.3	67	52	MCT, arginine
Vital AF 1.2 Cal/Abbott	1.2	75	63	MCT, ω-3 fatty acids

[a]One kcal is equivalent to 4.186 kJ.

[b]Formula considered enriched if following criteria met: arginine > 8.5 g/1500 kcal (6279 kJ); glutamine > 9 g/1500 kcal (6279 kJ); MCT > 30% of total fat; and ω-3 fatty acid ratio of ω-6 to ω-3 ≤ 2:1 or > 1.5 g/L ω-3 fatty acids.

[c]Low fat product.

MCT, medium-chain triglycerides.

body systems, including the immune system, from damage by oxygen-free radicals. KEY CONCEPT Use of enteral immunonutrition in certain clinical settings is widely accepted. Commercial immunonutrition products and/or specific ingredients found in these products have generally been found to have no benefit in terms of mortality rates.[4,22,23] However, infection rates, length of stay, and length of time on a ventilator may be decreased with these products. The 2016 ASPEN/SCCM ICU Guidelines support use of these formulas in traumatic brain injury and surgical ICU patients but not in medical ICU patients.[6] The best timing (initiation and duration) of delivery remains to be determined.

► *Pulmonary Formulas*

Enteral feeding formulas designed for use in patients with chronic obstructive pulmonary disease or receiving mechanical ventilation contain higher amounts of fat (40% to 55% of total kilocalories) than most formulas. The rationale for high fat content is that burning of fat for energy is associated with less carbon dioxide production compared with burning of carbohydrate. Less carbon dioxide production theoretically would be advantageous in patients with retention of this substance and might facilitate weaning from mechanical ventilation. Because part of the market targeted by the manufacturers of these products comprises mechanically ventilated patients, these products are included in Table 101–4. Carbon dioxide retention owing to carbohydrate administration was a problem previously when feeding was overzealous. However, at conservative calorie levels, standard enteral formulas usually can be given without fear of excess carbon dioxide production.

One formula, Oxepa (Nestle), has been studied specifically in critically ill patients with acute respiratory distress syndrome (ARDS), acute lung injury (ALI), and sepsis. This formula contains high quantities of the ω-3 fatty acids (EPA) and γ-linolenic acid (GLA). GLA is metabolized to a prostaglandin with vasodilatory properties. EPA is converted to prostaglandins and leukotrienes that are less proinflammatory than those derived from ω-6 fatty acids. This formula contains large quantities of antioxidants. Whereas the Canadian guidelines state that use of this formula should be considered in ALI and ARDS, the 2016 ASPEN/SCCM critical care guidelines do not endorse use of the product.[4,6]

► *Diabetic Formulas*

Similar to pulmonary formulas, formulas designed for patients with diabetes or stress-induced hyperglycemia are relatively high in fat and low in carbohydrates (Table 101–5). These formulas typically contain fiber (primarily soluble) because it plays some role in glycemic control. They also may contain fructose and MUFAs. Data support improved blood sugar control with use of these formulas in patients with diabetes.[24] Whether or not a diabetic EN formula is chosen, avoidance of overfeeding and maintenance of good glycemic control with insulin or other hypoglycemic medications are important in this population.

► *Renal Formulas*

Products designed for use in renal failure have high caloric density (1.8–2 kcal/mL [7.5–8.4 kJ/mL]) to decrease administered fluid (Table 101–6). The products vary in amounts of nutrients such as protein, potassium, phosphorus, and magnesium. Products low in protein (20–35 g/L) may be appropriate in chronic renal

Table 101–5

Selected Enteral Feeding Formulas Marketed for Use in Diabetes and Stress-Induced Hyperglycemia[a]

Product Name/Manufacturer	kcal/mL	% kcal as Fat	% kcal as Carbohydrate	Fiber (g/L)
Glytrol/Nestle	1	43	40	15
Glucerna 1.0 Cal/Abbott	1	49	34	14
Glucerna 1.2 Cal/Abbott	1.2	45	38	16
Glucerna 1.5 Cal/Abbott	1.5	45	35	16
Diabetisourse AC/Nestle	1.2	53	33	15

[a]1 kcal is equivalent to 4.186 kJ.

failure patients not yet receiving dialysis. On the other hand, removal of nitrogen by dialysis, coupled with the hypercatabolic, hypermetabolic condition seen in many acute renal failure patients, makes use of higher protein formulas (80–90 g/L) appropriate in these situations. Potassium, phosphorus, and magnesium contents of EN formulas designed for use in renal failure tend to be lower than standard formulas because these renally excreted electrolytes accumulate during renal failure.

Historically, elemental formulas designed for renal failure were enriched with essential amino acids (EAAs) and contained lesser amounts of nonessential amino acids (NEAAs) than standard formulas. Theoretically, EAAs could combine with urea nitrogen in the synthesis of NEAAs, leading to a decrease in blood urea nitrogen (BUN). The only situation in which such formulas may be appropriate is in patients with chronic renal failure who are not candidates for dialysis. Even in this setting, use of these products should be limited to no more than 2 or 3 weeks.[2] These formulas have been supplanted largely by polymeric formulas with protein content similar to standard EN formulas. Many dialysis patients tolerate standard, high-protein EN formulas, although electrolytes must be monitored closely.

▶ *Hepatic Formulas*

Specialized formulas for patients with hepatic insufficiency are limited in number. These are enriched with BCAAs while containing a reduced quantity of aromatic amino acids (AAAs) and methionine compared with standard formulas. These changes address high levels of AAAs and low levels of BCAAs found in the blood of patients with hepatic insufficiency. Theoretically, these products might help patients with hepatic encephalopathy (HE). Improvement in mortality attributable to these products has not been consistent.[2]

The ASPEN/SCCM guidelines for the ICU recommend against the use of protein restriction to reduce risk of development of HE.[6] These guidelines recommend use of standard EN formulas for ICU patients with acute or chronic liver disease. An example of a specialized hepatic formula is Hepatic-Aid II (Hormel Health Labs), a product supplied as a powder for reconstitution that requires vitamin, mineral, and electrolyte supplementation. A second product is NutriHep (Nestle), supplied as a liquid formula containing the recommended amounts of key vitamins, minerals, and electrolytes.

▶ *Wound Healing Formulas*

Tube feeding and oral supplement formulas designed for use in patients with wounds or decubitus ulcers typically supply high amounts of protein and calories. The antioxidant vitamins A, C, and E are frequently also found in high quantities as is zinc.

▶ *Modular Components*

Single nutrient components are frequently administered through feeding tubes to augment the composition of the EN formula. Protein modules are probably the most commonly used. These may be supplied as a liquid product or as a powder that must be reconstituted with water. Another modular component is fiber. These components are typically given as a bolus through the feeding tube rather than being added to the feeding formula.

Table 101–6

Selected Enteral Feeding Products Designed for Use in Renal Failure

Product Name/Manufacturer	Protein g/L	Protein (g/1000 kcal[a])	Characteristics
Nepro with Carb Steady/Abbott	81	45	Complete formula[b] for patients on dialysis
Novasource Renal/Nestle	91	46	Complete formula for patients with CKD or AKI on dialysis
Suplena with Carb Steady/Abbott	45	25	Complete formula with low amounts of protein for patients not on dialysis
Renacal/Nestle	34	17	For patients with AKI and severe electrolyte restriction not on dialysis

[a]1 kcal is equivalent to 4.186 kJ.

[b]Complete formula—contains all nutrients in amounts sufficient to meet needs of most patients in a volume equal to or less than that usually administered.

AKI, acute kidney injury; CKD, chronic kidney disease.

Patient Encounter Part 1

LT is a thin 50-year-old woman with a history of smoking, chronic obstructive pulmonary disease, and an eating disorder. Her sister reports that the patient has been on another of her "weird" diets and has lost about 15 pounds (6.8 kg) in the last couple of months. She is admitted with sepsis with a suspected pulmonary source. She requires mechanical ventilation and exhibits prerenal azotemia. She receives a 30 mL/kg bolus of normal saline as part of the sepsis protocol and is started on vasopressor therapy and antibiotics. She is started on propofol for sedation while on the ventilator.

LT responds somewhat slowly to the sepsis protocol and on day 3 is still requiring both norepinephrine and vasopressin for blood pressure support. The dietitian assesses her nutritional needs. Her dry weight is 55 kg, height is 66 inches (168 cm), body mass index is 20 kg/m^2.

Is there any concern regarding starting EN at this time?

If EN is not appropriate at this time, should PN be initiated?

MONITORING AND COMPLICATIONS

Although complications of EN generally are considered less serious than those of PN, some complications nevertheless can be dangerous or can lead to impaired delivery of desired nutrient load. Complications can be divided into four categories: GI, technical, infectious, and metabolic. The first three categories, along with common causes, are listed in Table 101–7. Patients on EN must be monitored for prevention of complications (Table 101–8). Monitoring of many parameters can become less frequent as patient condition stabilizes. Monitoring for efficacy of EN is also important.

LOS

GI Complications

KEY CONCEPT GI complications are the most common complications of EN limiting the amount of feeding that patients receive. Although diarrhea frequently is blamed on feeding formula or method of EN administration, other possible causes usually exist (see Table 101–7). In the inpatient setting, patients receiving EN frequently are very sick. Along these lines, *Clostridium difficile* colitis must be considered as a possible cause of diarrhea, especially in patients receiving antimicrobial therapy or proton pump inhibitors.[25] Antibiotic therapy is a major cause of diarrhea in acutely ill patients, including those receiving EN. A medication-related cause of diarrhea is the sorbitol content of medications.[26] Large quantities of sorbitol present in oral liquid medications can cause diarrhea. Unfortunately, sorbitol content of many medications is not listed on their labeling, and manufacturers frequently reformulate preparations to contain varying amounts of excipients, such as sorbitol.

Determining the cause of diarrhea is important to determine how to address the problem. Whereas *C. difficile* colitis should be treated with an appropriate antibiotic, medication-related diarrhea can be addressed by removal of the offending agent. Likewise, diarrhea secondary to malabsorption sometimes can be addressed by changing to an oligomeric EN formula. Antiperistaltic agents (eg, loperamide) may be useful in some noninfectious diarrhea.

On the other hand, constipation may occur in patients receiving EN, especially the elderly. Increased provision of fluid or fiber may be useful. Constipation may be drug related, in which case discontinuation or replacement of the offending drug may be beneficial.

Impaired gastric emptying is seen commonly in EN patients receiving gastric feedings and may be associated with nausea and vomiting. Impaired emptying may be related to disease process (eg, diabetic gastroparesis or sequelae to head injury) or to drug

Table 101–7

Complications of Tube Feeding

Complication	Causes
GI	
Diarrhea	Drug related Antibiotic-induced bacterial overgrowth Hyperosmolar medications administered via feeding tubes Antacids containing magnesium Malabsorption Hypoalbuminemia or gut mucosal atrophy Pancreatic insufficiency Inadequate GI tract surface area Rapid GI tract transit Radiation enteritis Tube feeding related Rapid formula administration Formula hyperosmolality Low residue (fiber) content Lactose intolerance Bacterial contamination
Nausea and vomiting	Gastric dysmotility (surgery, anticholinergic drugs, diabetic gastroparesis) Rapid infusion of hyperosmolar formula
Constipation	Dehydration Drug induced (anticholinergics) Inactivity Low residue (fiber) content Obstruction or fecal impaction
Abdominal distention or cramping	Too rapid formula administration
Technical	
Occluded feeding tube lumen	Insoluble complexation of enteral formula and medication(s) Inadequate flushing of feeding tube Undissolved feeding formula
Tube displacement	Self-extubation Vomiting or coughing Inadequate fixation (jejunostomy)
Aspiration	Improper patient position Gastroparesis or atony causing regurgitation Feeding tube malpositioned Compromised lower esophageal sphincter Diminished gag reflex
Peristomal excoriation	Improper skin and tube care GI tract secretions leaking peristomally
Infectious	
Aspiration pneumonia	Same as technical—aspiration comments Prolonged use of large-bore polyvinylchloride tube

GI, gastrointestinal.

From Janson DD, Chessman KH. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 5th ed. New York, NY: McGraw-Hill, 2005.

Table 101–8

Suggested Monitoring for Patients on Enteral Nutrition

Parameter	During Initiation of EN Therapy	During Stable EN Therapy
Vital signs	Every 4–6 hours	As needed with suspected change (ie, fever)
Clinical assessment		
Weight	Daily	Weekly
Total intake/output	Daily	As needed with suspected changed in intake/output
Tube-feeding intake	Daily	Daily
Enterostomy tube site assessment	Daily	Daily
GI tolerance		
Stool frequency/volume	Daily	Daily
Abdomen assessment	Daily	Daily
Nausea or vomiting	Daily	Daily
Gastric residual volumes	Every 4–8 hours (varies)	As needed when delayed gastric emptying suspected
Tube placement	Prior to starting; then ongoing	Ongoing
Laboratory		
Electrolytes, blood urea nitrogen/serum creatinine, glucose	Daily	Every 1–3 months
Calcium, magnesium, phosphorus	3–7 times/week	Every 1–3 months
Liver function tests	Weekly	Every 1–3 months
Trace elements, vitamins	If deficiency/toxicity is suspected	If deficiency/toxicity is suspected

EN, enteral nutrition.

From Kumpf VS, Chessman KH. Enteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, et al., eds. Pharmacotherapy: A Pathophysiologic Approach, 9th ed. New York, NY: McGraw-Hill, 2014.

therapy, most notably narcotics. Gastric residual checks frequently are measured in patients receiving gastric feedings (see Table 101–8). The 2016 ASPEN/SCCM critical care guidelines recommend against routine gastric residual check and suggest that, if such checks are performed, feedings should not be held for residual volumes less than 500 mL in absence of other signs of intolerance.[6] Approaches to the patient with delayed gastric emptying might include changing to a formula containing less fat because dietary fat is associated with slower gastric emptying. Metoclopramide often is given to patients receiving gastric feedings to facilitate gastric emptying. Erythromycin is an alternative that may be useful, although it is associated with drug–drug interactions. Patients with poor gastric emptying may be at higher risk of aspirating feedings into their lungs and should be considered for transition to postpyloric feedings. Postpyloric feedings may help relieve EN-related nausea and vomiting and are preferred for patients without an intact gag reflex. An important practice to help prevent aspiration is elevation of the head of the bed to at least 30 degrees during continuous feedings as well as during and for 30 to 60 minutes after intermittent and bolus feedings.

Technical Complications

Technical or mechanical complications are encountered frequently in EN patients. Tube occlusion most commonly is related to formula occlusion or medication administration through the tube. KEY CONCEPT An important practice to help prevent medication-related occlusion is adequate water flushing of the tube before, between, and after each medication administration. If intermittent feedings are used, water flushing after each feeding is recommended. Clearing of occlusions using water or pancreatic enzymes plus sodium bicarbonate can be attempted, and special devices and kits are available.[5,27]

Tube displacement is a potentially significant complication. This may be seen in an agitated patient pulling at the tube, or the tube tip may migrate spontaneously. If the tip of the tube is positioned in the tracheobronchial tree and feeding is delivered to this area, pneumonia, pneumothorax, and other problems could potentially occur. Location of the tip of a blindly placed feeding tube (eg, NG) should be confirmed initially by chest radiograph after placement and before use. For ongoing assessment of tube placement, auscultation and measurement of aspirate pH can be utilized.

Endoscopic and surgical feeding tubes can cause erosion of the exit site due to leakage of gastric or intestinal contents onto the skin. This complication must be addressed by good wound care and repair or replacement of the access device. Similarly, NG, ND, and NJ tubes can be complicated by nasopharyngeal irritation or necrosis. This is one reason why such tubes should be considered for short-term use only.

Infectious Complications

Infectious complications of EN include aspiration pneumonia and infections related to delivery of contaminated EN formula. Although GI infections owing to industrial contamination of enteral formulas have been reported uncommonly, formulas are more commonly seeded with organisms during the processes of transferring from can to delivery bag with ready-to-use formulas and during the process of reconstitution with powdered formulas. So-called closed systems of delivery, wherein the formulas come from the manufacturer premixed in a delivery bag, should help decrease possibility of formula contamination. Practice recommendations from ASPEN state that tap water may be inappropriate for formula reconstitution, medication dilution, tube flushing, and additional water provision in patients requiring EN.[5]

Metabolic Complications

Metabolic complications of EN most commonly include disorders of fluid and electrolyte homeostasis and hyperglycemia. More severely ill patients require more frequent monitoring (see Table 101–8). Both dehydration and fluid overload can occur. Careful monitoring of fluid inputs and outputs as well as body weight is important. Dehydration may be caused by either excessive fluid losses or inadequate fluid intake. The trend in the ratio of BUN to serum creatinine can be useful in helping monitor fluid status; a ratio greater than 15:1 (60:1 for SI mmol/L:mmol/L) may be an indicator of dehydration; high ratios may also be a result of high protein provision by the feeding. Attention should be paid to free-water content of EN formulas. Free-water content varies from about 70% to 85%; percentage-free water typically drops as caloric density of the formula rises. If dehydration develops, switching to a less calorically dense formula or using larger water flushes is appropriate. Fluid overload is reflected by increases

in weight, lower extremity edema, and pulmonary rales and particularly may be a problem in patients with renal or cardiac insufficiency. Use of a more calorically dense EN formula may be helpful, and diuretic therapy may be necessary. Fluid imbalances often are associated with abnormalities of sodium homeostasis that should be addressed in concert with fluid imbalance.

Hypokalemia, hypomagnesemia, and hypophosphatemia are some of the most common electrolyte abnormalities in sick, hospitalized patients. These can occur in context of the refeeding syndrome, which may be seen in chronically malnourished patients aggressively started on feeding. Careful monitoring of electrolytes, coupled with a feeding regimen increased gradually to goal rate over a period of several days, should help protect at-risk patients from this complication. Hypokalemia and hypomagnesemia also are associated with excessive losses through the GI tract or urine and are associated with various medications, including diuretics. Repletion may be accomplished enterally in nonsymptomatic patients or parenterally if the patient is symptomatic or the abnormality is severe. Enteral repletion with magnesium and phosphate can cause diarrhea. Hyperkalemia, hypermagnesemia, and hyperphosphatemia are less common and usually are associated with renal insufficiency. Hyperkalemia also is associated with medications, including potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Although hyperglycemia is less common with EN than PN, it can occur. Many severely ill patients (eg, septic, highly stressed) receiving EN have a metabolic milieu promoting hyperglycemia. For ICU patients with hyperglycemia receiving continuous EN, an IV insulin drip may be the most effective way to achieve good glycemic control. Scheduled intermediate or long-acting insulin plus nutritional and correctional regular or rapid acting insulin can be utilized after stabilization on the feeding regimen or for patients in whom insulin drips are not feasible.[28] Administration of a higher fat, lower carbohydrate EN formula may be useful in selected patients.

Monitoring for Efficacy and Outcome Evaluation

A useful physical measurement of EN efficacy in the long-term patient is body weight. Depending on the clinical situation, the goal may be weight gain, weight maintenance, or weight loss. Whereas day-to-day fluctuations in weight generally reflect fluid changes, week-to-week variations are more useful in determining if caloric provision is appropriate.

The amount of EN actually administered is often less than the amount ordered owing to interruptions in therapy. It is imperative to monitor volume of feedings actually received and to make adjustments in rates or amounts of EN as necessary.

Biochemical markers have been used historically to help interpret EN adequacy. Use of visceral proteins such as albumin or prealbumin is limited by the effects of inflammation on serum levels of these biomarkers.[29] In the acute phase of illness characterized by a proinflammatory state, proteins known as *acute-phase reactants* are preferentially synthesized. One of these measured clinically is C-reactive protein (CRP). In some patients with significant illness, prealbumin may not rise, even though the patient is receiving appropriate EN, until CRP begins to fall. Collection of urine to measure nitrogen balance can help analyze adequacy of caloric and protein provision.

In patients with wounds (eg, decubitus ulcers, surgical wounds), a goal of therapy is to facilitate wound healing. Monitoring status of the wound becomes part of ongoing nutritional assessment. In debilitated patients, particularly on long-term EN, measures of functional status such as grip strength and ability to perform activities of daily living become important components of nutritional assessment.

MEDICATION ADMINISTRATION IN PATIENTS RECEIVING EN

Medication Administration Through Feeding Tubes

If a patient receiving EN is alert and can swallow oral medications, then medications should be given by mouth. Many patients are not able to receive medications by this route, and the feeding tube may be considered as a delivery route. Effects of medication administration through feeding tubes on the delivery of both the drug and the EN formula nutrients have been inadequately studied.[30]

KEY CONCEPT Compatibility of medication with EN formula is of concern when administering medications through feeding tubes. An important technical complication of EN is tube occlusion, related most commonly to medication administration. Not only must compatibility of medication and EN formula be considered, but interactions between medications and the feeding tube itself must be considered. Strict protocols for flushing the tube before, between, and after administration of medications are important.[5] The best fluid for flushing is warm water. At least 15 mL of water should be used as a flush before and after medication administration through a feeding tube. Medications should be administered one at a time sequentially rather than being mixed together for simultaneous administration down the tube; ideally 15 mL of water should be used as a flush between medications. This should help prevent interactions between drugs within the tube itself that could lead to occlusion.

LO 6

Different dosage forms present unique challenges for administration through feeding tubes. Certain solid dosage forms should not be crushed because crushing would alter release characteristics.[31] For example, controlled-release, extended-release, and sustained-release preparations should not be crushed, nor should sublingual dosage forms. Enteric-coated dosage forms generally are designed to protect acid-labile medications from stomach acid; when these dosage forms reach the small bowel with its higher pH, the drug is released into an environment in which it is more stable. Alternatively, enteric-coated dosage forms protect the stomach from medications that could cause irritation. Thus, crushing the enteric coating defeats the purpose of the dosage form and could lead to decreased efficacy or increased adverse events.

Medications available commercially as compressed tablets can be crushed for administration through tubes. After crushing, the fine powder should be mixed with 10 to 30 mL of fluid

Patient Encounter Part 2

On day 4, vasopressor requirements are minimal and enteral feeding is infusing at a low rate via nasogastric tube. Propofol is changed to dexmedetomidine on day 5.

How does propofol affect the initial EN prescription?

What is refeeding syndrome and is this patient at risk? If so, how can it be prevented?

Design an enteral feeding regimen, including choice of formula, titration schedule, and goal rate, appropriate for this patient at this time.

(usually warm water) for administration. A powdered dosage form inside a hard-gelatin capsule can be poured out and mixed with water for administration through tubes. Soft-gelatin capsules can be dissolved in warm water. Some enteric-coated and delayed-release microencapsulated products can be opened and individually coated particles administered through the tube without crushing if the tube has a large enough diameter.

If a liquid dosage form of a medication exists, it would seem rational to use this for administration through a feeding tube. This may decrease potential for tube clogging but may, in some instances, decrease tolerability of medication administration. Sorbitol is an excipient found in many liquid medications in amounts sufficient to cause diarrhea.

Another potential problem with administration of liquid medications through feeding tubes is high osmolality of some products. Dilution of hypertonic medications with 30 to 60 mL of water or administration of smaller dosages more frequently may help prevent diarrhea. Although administration of IV medications through feeding tubes may be entertained, these dosage forms frequently are hypertonic and contain problematic excipients when given via the GI tract.

It is generally not recommended to mix medications directly into EN formula because physical incompatibilities might lead to tube occlusion. Limited data currently available indicate that acidic syrups and elixirs may be most harmful, causing physical incompatibility when admixed with EN formulas. It would seem logical that medications considered absorbed better in the fasted state either should be given between feedings on an intermittent feeding schedule or feedings should be held before and after medication administration. However, not all studies have supported this idea, therefore this issue deserves further study.

Location of feeding tube tip is important when considering medication administration. This is particularly true if the medication acts locally in the GI tract. For example, sucralfate and antacids act locally in the stomach; therefore, administration through a duodenal or jejunal tube is illogical. Likewise, for medications requiring acid for best absorption, administration directly into the duodenum or jejunum may result in suboptimal absorption. Absorption of drugs when administered directly into the small bowel, especially the jejunum, is a topic where more research would be useful.

Problem Medications

▶ *Phenytoin*

Certain medications present challenges when administered through feeding tubes. The medication studied most thoroughly is phenytoin. Most studies have shown significant decreases in phenytoin absorption when administered enterally to patients receiving EN. Several mechanisms have been proposed. Liberal dilution of phenytoin suspension before its administration down the tube may improve delivery. Many institutions hold tube feedings for 1 or 2 hours before and after administration of phenytoin, although some EN patients subjected to this routine still require high dosages to achieve therapeutic serum concentrations. Holding feeding around medication administration can make meeting nutritional requirements difficult with continuous feedings, especially if phenytoin is administered several times daily. Diligent monitoring of serum concentrations is necessary for the patient on EN receiving this medication. In some cases, use of IV phenytoin or another anticonvulsant may be prudent.

Patient Encounter Part 3

LT is extubated on day 13. Concern regarding her swallowing strength leads to a speech pathology consult. On day 14 an order to advance oral diet as tolerated is written following the speech pathology assessment.

How should the transition from EN to oral feedings be accomplished?

▶ *Warfarin*

EN formulas contain vitamin K, which can antagonize the pharmacologic activity of warfarin. Vitamin K content of EN formulas has been adjusted down over several decades, resulting in products that contain amounts of vitamin K unlikely to affect anticoagulation by warfarin significantly. However, inadequate warfarin anticoagulation in EN patients receiving formulas containing minimal vitamin K has been reported. A component of certain tube feedings, perhaps protein, may bind warfarin and result in suboptimal activity, as might the feeding tube itself. One small study indicated a better response in terms of the international normalized ratio (INR) when feedings were held for 1 hour before and after warfarin compared with administration of the drug without holding feedings.[32] When tube feedings are started, changed, or discontinued, INR should be monitored closely. Alternatively, a different oral anticoagulant may be considered to avoid the potential interaction with warfarin, especially for short-term tube feedings in hospitalized patients.

▶ *Fluoroquinolones*

Absorption of antimicrobial agents such as fluoroquinolones and tetracyclines that can be bound by divalent and trivalent cations potentially could be compromised by administration with EN formulas containing these cations. Fluoroquinolones (eg, levofloxacin and ciprofloxacin) have been best studied in this regard, and results of studies are not consistent.[33] Some institutions hold tube feedings for 1 to 2 hours or more before and after enteral dosages of fluoroquinolones. Not all fluoroquinolones are affected by the interaction, suggesting that a mechanism other than chelation by divalent cations may also be significant. Because ciprofloxacin absorption has been shown to be decreased with jejunal administration, this drug probably should not be given by jejunal tube.

SUMMARY AND CONCLUSION

EN is an important method of feeding patients who cannot or should not eat enough to meet nutrient requirements for a prolonged time. When the GI tract can be used safely, EN is preferred over PN. Various types of enteral access devices are available. Whereas tubes inserted through the nose often are adequate for patients expected to receive EN for a short time, devices that are more permanent are preferred for longer-term patients. Choice of whether to feed into the stomach or postpylorically is patient specific. Although numerous EN formulas are available, many products are very similar, making a limited formulary feasible. Data supporting many specialized types of EN formulas are limited. Although complications of EN tend to be less serious than those of PN, adverse effects encountered can be significant, and ongoing monitoring is necessary. Although medications can be administered through feeding tubes, various factors must be taken into account in each individual patient.

Patient Care Process

Collect Information:

- Based on patient's disease states and severity, estimate the amount of time until adequate oral intake resumes (Table 101–1).
- Are there any contraindications or precautions regarding use of EN (Table 101–2)? When the GI tract is nonfunctional, either PN or no SNS is indicated.
- If inadequate intake has occurred or is anticipated for 7 to 14 days, start SNS. The threshold for starting SNS is lower for previously malnourished patients. Critically ill patients at high nutritional risk should generally be started on EN within 24 to 48 hours of ICU admission.
- Choose the appropriate type of enteral access device based on expected duration of use and whether any condition exists which precludes gastric feeding (Table 101–3).
- Choose method of feeding administration (eg, intermittent or continuous) based on feeding location (ie, gastric versus postpyloric) and other patient factors.

Assess the Information:

- Are medications being administered down the feeding tube? If so, assess the appropriateness of this route.

Develop a Care Plan:

- Start tube feeding at full strength and increase rate as tolerated to goal that will meet patient's nutritional requirements.
- Develop plan to include monitoring at appropriate intervals for metabolic, GI, technical, or infectious complications (Table 101–8).
- Develop monitoring plan for adequacy of nutritional regimen. This may include serial weights, intakes and outputs, and a measure of functional status.

Implement the Care Plan:

- If patient is to be discharged home on EN, educate patient or caregiver on enteral access device care, feeding delivery, troubleshooting, and complications to observe for and who should be contacted when complications occur (Table 101–7).

Follow-up: Monitor and Evaluate:

- Adjust formula, rate of administration, and/or route of administration if intolerance develops or nutritional goals (eg, weight loss, weight maintenance, weight gain, maintenance of muscle mass, slowing of functional decline) are not met.

Abbreviations Introduced in This Chapter

AAA	Aromatic amino acid(s)
AI	Adequate intake
AKI	Acute kidney injury
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
ASPEN	American Society for Parenteral and Enteral Nutrition
BCAA	Branched-chain amino acid(s)
BUN	Blood urea nitrogen
CRP	C-Reactive protein
DHA	Docosahexaenoic acid
EAA	Essential amino acid(s)
EFA	Essential fatty acid(s)
EN	Enteral nutrition
EPA	Eicosapentaenoic acid
ESPEN	European Society for Clinical Nutrition and Metabolism
FOS	Fructooligosaccharide
Fr	French
GALT	Gut-associated lymphoid tissue
GI	Gastrointestinal
GLA	γ-Linolenic acid
HE	Hepatic encephalopathy
IBD	Inflammatory bowel disease
ICU	Intensive care unit
INR	International normalized ratio
LCT	Long-chain triglyceride
MCT	Medium-chain triglyceride
MUFA	Monounsaturated fatty acid
ND	Nasoduodenal
NEAA	Nonessential amino acid
NG	Nasogastric
NJ	Nasojejunal
NO	Nitric oxide
OG	Orogastric
PEG	Percutaneous endoscopic gastrostomy
PEJ	Percutaneous endoscopic jejunostomy
PN	Parenteral nutrition
PUFA	Polyunsaturated fatty acid
RDA	Recommended Dietary Allowance
SCFA	Short-chain fatty acid
SCCM	Society for Critical Care Medicine
SNS	Specialized nutrition support

REFERENCES

1. Fester TA. Home tube feeding with blenderized foods. Available from: oley.org/default.asp?page=HomeTF_BlenderFoods. Accessed July 27, 2018.
2. American Society for Parenteral and Enteral Nutrition Board of Directors. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. JPEN J Parenter Ent Nutr. 2002;26(suppl):1SA–138SA.
3. The European Society for Clinical Nutrition and Metabolism. ESPEN Guidelines on Adult Enteral Nutrition. Clin Nutr. 2006; 25:177–360.
4. Clinical practice guidelines. Critical care nutrition; Clinical Evaluation Research Unit. Available from: http://www.criticalcarenutrition.com. Accessed July 27, 2018.
5. Boullata JI, Carrera AL, Harvey L, et al. ASPEN safe practices for enteral nutrition therapy. JPEN J Parenter Enter Nutr. 2016;41:15–103.
6. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. JPEN J Parenter Ent Nutr. 2016;40:159–211.
7. Scaldaferri F, Pizzoferrato M, Gerardi V, Lopetuso L, Gasbarrini A. The gut barrier: new acquisitions and therapeutic approaches. J Clin Gastroenterol. 2012:46(suppl 1):S12–S17.
8. Choban P, Dickerson R, Malone A, Worthington P, Compher C. A.S.P.E.N. clinical guidelines: nutrition support of hospitalized adult patients with obesity. JPEN J Parent Ent Nutr. 2013; 37:714–744.
9. Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. N Engl J Med. 1991;325:525–532.

10. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011; 365:506–517.
11. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomized controlled clinical trial. Lancet. 2013:381:385–393.
12. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition. JAMA. 2013;309:2130–2138.
13. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. Intensive Care Med. 2011;37:601–609.
14. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. New Engl J Med. 2014;371:1673–1684.
15. Harvey SE, Harrison DA, Bear DE, et al. Trial of the route of early nutritional support in critically ill adults. New Engl J Med. 2014;371:1673–1684.
16. Peterson SJ, Lateef OB, Freels S, McKeever L, Fantuzzi G, Braunschweig CA. Early exposure to recommended calorie delivery in the intensive care unit is associated with increased mortality in patients with acute respiratory distress syndrome. JPEN J Parenteral Enteral Nutr. 2017 Jun 1. [Epub ahead of print.]
17. Blumenstein I, Shastri YM, Stein J. Gastroenteric tube feeding: techniques, problems and solutions. World J Gastroenterol. 2014;20:8505–8524.
18. Kamarul Zaman M, Chin KF, Rai V, Majid HA. Fiber and prebiotic supplementation in enteral nutrition: a systematic review and meta-analysis. World J Gastroenterol. 2015;21:5372–5381.
19. Robefroid M, Gibson GR, Hoyles L, et al. Prebiotic effects: metabolic and health benefits. Br J Nutr. 2010;104(suppl 2): S1–S63.
20. Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013;368:1489–1497.
21. Ziegler TR, May AK, Hebbar G, et al. Efficacy and safety of glutamine-supplemented parenteral nutrition in surgical intensive care units patients: an American multicenter randomized controlled trial. Ann Surg. 2016;273:646–655.
22. Braga M, Wischmeyer PE, Drover J, Heyland DK. Clinical evidence for pharmaconutrition in major elective surgery. JPEN J Parenter Enteral Nutr. 2013;37(suppl 5):66S–72S.
23. Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008;34:1980–1990.
24. Ojo O, Brooke J. Evaluation of the role of enteral nutrition in managing patients with diabetes: a systematic review. Nutrients. 2014;6:5142–5152.
25. Tariq R, Singh S, Gupta A, Pardi DS, Khanna S. Association of gastric acid suppression with recurrent Clostridium difficile infection: a systematic review and meta-analysis. JAMA Intern Med. 2017;177:784–791.
26. Edes TE, Walk BE, Austin JL. Diarrhea in tube-fed patients: feeding formula not necessarily the cause. Am J Med. 1990; 88:91–93.
27. Kozeniecki M, Fritzshall R. Enteral nutrition for adults in the hospital setting. Nutr Clin Pract. 2015;30:634–651.
28. Drincic AT, Knezevich JT, Akkireddy P. Nutrition and hyperglycemia management in the inpatient setting (meals on demand, parenteral, or enteral nutrition). Curr Diab Rep. 2017;17(8):59.
29. White JV, Guenter P, Jensen G, Malone A, Schofield M. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). JPEN J Parenter Enteral Nutr. 2012;36:275–283.
30. Wohlt PD, Zheng L, Gunderson S, Balzar SA, Johnson BD, Fish JT. Recommendations for the use of medications with continuous enteral nutrition. Am J Health-Syst Pharm. 2009;66:1458–1467.
31. Mitchell JF. Oral dosage forms that should not be crushed. Institute for Safe Medication Practices. Available from: http://www.ismp.org/tools/donotcrush.pdf. Accessed July 27, 2018.
32. Dickerson RN, Garmon WM, Kuhl DA, Minard G, Brown RO. Vitamin K-independent warfarin resistance after concurrent administration of warfarin and continuous enteral nutrition. Pharmacotherapy. 2008;28:308–313.
33. Rollins CJ. Drug-nutrient interactions. In: Mueller CM, ed. The A.S.P.E.N. Nutrition Support Core Curriculum, 2nd ed., Silver Spring, MD: A.S.P.E.N., 2012:298–312.

102 Overweight and Obesity

April Smith

LEARNING OBJECTIVES

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

1. Explain the underlying causes of overweight and obesity.
2. Identify parameters used to diagnose obesity and indicate the severity of disease.
3. Identify desired therapeutic goals for patients with obesity.
4. Recommend appropriate nonpharmacologic and pharmacologic therapeutic interventions for overweight or obese patients.
5. Implement a monitoring plan that will assess both the efficacy and safety of therapy initiated.
6. Educate patients about the disease state and associated risks, comprehensive lifestyle interventions, drug therapy, and surgical options necessary for effective treatment.

INTRODUCTION

Overweight and obesity are terms used to describe weight measurements greater than what is considered healthy for a given height.[1] KEY CONCEPT **Body mass index** (BMI), waist circumference (WC), comorbidities, and readiness to lose weight are used in the assessment of overweight or obese patients. BMI should be used to identify adults at increased risk for cardiovascular disease (CVD) and other obesity-related disorders. Evaluation of the patient's risk status involves not only calculation of the BMI but also the measurement of WC. KEY CONCEPT The presence of comorbidities (CVD, type 2 diabetes mellitus, and sleep apnea) and cardiovascular risk factors (cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose) requires identification and aggressive management for overall effective treatment of the overweight or obese patient to reduce their risk of mortality.[2] Obesity contributes to some of the leading causes of preventable death including hypertension, dyslipidemia, diabetes mellitus, CVD, stroke, sleep apnea, gallbladder disease, osteoarthritis, and certain cancers.[2] Obesity is officially recognized as a disease by the American Medical Association with a pathophysiological basis for metabolic and biochemical dysfunctions.

ETIOLOGY AND EPIDEMIOLOGY

Obesity is a multifactorial, complex disease that occurs because of an interaction between genotype and the environment. Although the etiology is not completely known, it involves overlapping silos of social, behavioral, hormonal, and genetic influence.[3] The majority of overweight or obese individuals are adults, but overweight or obesity is also prevalent in children between 2 and 19 years of age. Just over 1/3rd of US adults 20 years of age and older are currently considered obese. The prevalence of obesity in men and women of various racial and ethnic origins differs. Thirty-six percent of non-Hispanic white adults are obese, whereas approximately 40% of Hispanics and 50% of non-Hispanic blacks are obese.[4]

Thirty-two percent of children and adolescents aged 2 to 19 years are overweight or obese. Overweight children typically become overweight adults, but most obese adults were not overweight as children.[2,5,6,7] Psychosocial functioning also may be hindered because obese patients may be at risk for discrimination as well as higher risk of low self-esteem and depression.[2]

PATHOPHYSIOLOGY

The key factor in the development of overweight and obesity is the imbalance that occurs between energy intake and energy expenditure. The extent of obesity is determined by the length of time this imbalance has been present. The hormone leptin, released from adipose tissue, is generally thought to play a major role in long-term weight homeostasis.[8] Leptin increases signaling to the hypothalamus as fat stores rise[9] (**Figure 102–1**). In the setting of obesity, leptin levels remain high, but eating behavior does not seem to be impaired, which is thought to be due in part to leptin resistance. Energy intake is affected by environmental influences and various gut hormones, whereas genetic composition and metabolism affect energy expenditure.[8]

Energy Intake

Food intake is regulated by various receptor systems that comprise the gut-brain axis. Gut peptides travel via the vagus nerve or pass directly through the blood brain barrier to affect the appetite control centers in the hypothalamus (Figure 102–1). There are two groups of neurons in the arcuate nucleus (ARC) of the hypothalamus that send signals to higher brain centers and ultimately drive eating behavior. When neuropeptide Y or agouti-related peptide (NPY/AgRP) neurons in the ARC are stimulated by gut peptides such as ghrelin, eating ensues. When pro-opiomelanocortin or cocaine-amphetamine-regulated transcript (POMC/CART) neurons in the ARC are stimulated by various gut peptides or leptin, eating is halted. Stimulation of the following receptors increases and decreases food intake, respectively.

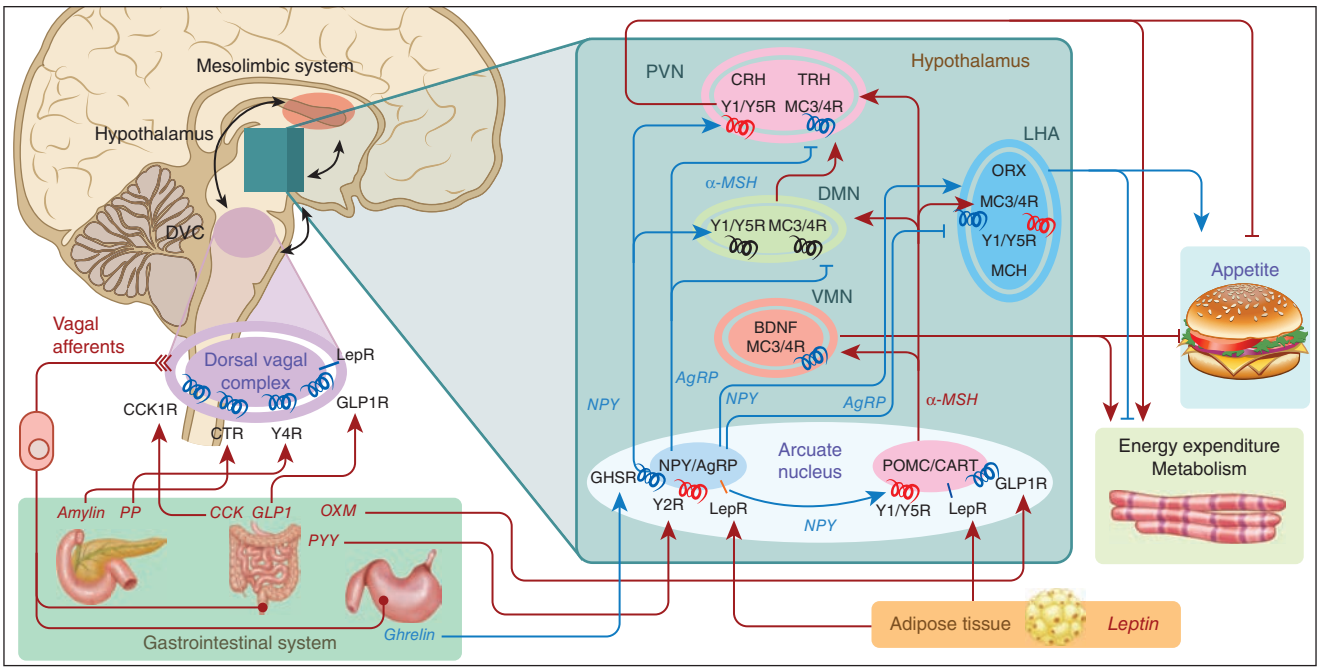

FIGURE 102–1. Central regulation of appetite and energy homoeostasis. The hypothalamus is the major site of integration of anorexigenic and orexigenic signaling. Peripheral satiety hormones, such as ghrelin from the stomach and leptin from adipose tissue, primarily bind and activate their cognate receptors directly in the hypothalamus, particularly in the arcuate nucleus, or in the dorsal vagal complex in the medulla, which communicates with the hypothalamus. Among the neurons in the arcuate nucleus there exist two populations of neurons: those expressing the orexigenic neuropeptide y (NPY) or agouti-related peptide (AgRP); and those expressing the anorexigenic pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). Several satiety hormones induce their anorectic effects by either inhibiting the activity of NPY/AgRP neurons or activating POMC/CART neurons. These neurons in the arcuate nucleus project to second-order neurons in other hypothalamic nuclei, including the paraventricular nucleus (PVN), dorsomedial nucleus (DMN), ventromedial nucleus (VMN), and lateral hypothalamic area (LHA). These second-order hypothalamic neurons express anorexigenic neuropeptides (corticotropin-releasing hormone [CRH], thyrotropin-releasing hormone [TRH], brain-derived neurotrophic factor [BDNF]) and orexigenic neuropeptides (orexin [ORX], melanin-concentrating hormone [MCH]), which modulate appetite and energy homeostasis. Furthermore, the regulation of energy balance involves an integration of signaling from the hypothalamus, brainstem, and reward pathways of the mesolimbic system. Symbols: blue receptor = activating; red receptor = inhibiting; blue arrow = appetite-stimulating; red arrow = appetite-suppressing. (From Kim GW, Lin JE, Blomain ES, et al. Antiobesity pharmacotherapy: new drugs and emerging targets. Clin Pharmacol Ther. 2014;95(1):53–66.)

▶ *Increase Food Intake*

- Serotonin 1A subtype (5-HT_{1A})
- Noradrenergic α_2
- Cannabinoid 1 (CB1)
- NPY/AgRP
- Melanin-concentrating hormone (MCH)
- Orexin

▶ *Decrease Food Intake*

- Serotonin 2C subtype (5-HT_{2C})
- Noradrenergic α_1 or β_2
- Histamine subtypes 1 and 3
- Dopamine 1 and 2
- CART/POMC
- α-melanocyte-stimulating hormone (α-MSH)

Targeting of this endogenous circuitry is a primary trait shared by many of the newer antiobesity medications on the market as well as those currently in development.

Energy Expenditure

A person's metabolic rate is the primary determinant of energy expenditure. The metabolic rate is enhanced immediately after food consumption and is directly related to the amount and type of food consumed.[10] After a period of weight loss, total energy expenditure is reduced.[10] Physical inactivity and/or endocrine-related disorders (eg, hypothyroidism and Cushing syndrome) may lower the metabolic rate, further contributing to the development of overweight and obesity.

LO 1

CLINICAL PRESENTATION AND DIAGNOSIS

LO 2

KEY CONCEPT BMI, WC, body fat percentage, comorbidities, and readiness to lose weight are used in the assessment of overweight or obese patients. Any interaction between a patient and a health care provider presents an opportunity to evaluate the patient's height and weight and calculate their BMI. These parameters should be measured no less than annually. The BMI is calculated using the measured weight in kilograms divided by the height in meters squared (kg/m^2) for all adult patients, regardless of gender, and is used to classify overweight or obesity. The greater the BMI in overweight and obese individuals, the greater the risk

LO 2

Table 102–1

BMI Classification

Adult	
Underweight	< 18.5 kg/m^2
Normal weight	18.5–24.9 kg/m^2
Overweight	25–29.9 kg/m^2
Obesity (Class 1)	30–34.9 kg/m^2
Obesity (Class 2)	35–39.9 kg/m^2
Extreme obesity (Class 3)	≥ 40 kg/m^2
Children (Only for Those > 2 Years of Age[a])	
Underweight	< 5th percentile
Healthy weight	5th–84th percentile
Overweight	85th–94th percentile
Obesity	≥ 95th percentile

[a]Weight for height values should be plotted and monitored over time for children < 2 years of age.

From Refs. 2 and 12.

of CVD, type 2 diabetes mellitus, and all-cause mortality.[11] The BMI distribution changes with age for children just as height and weight. Percentiles specific for age and gender are used to classify pediatric patients as overweight and obese as well as healthy and underweight. BMI is classified according to Table 102–1. WC should also be determined no less than annually for adult patients by placing a measuring tape at the top of the right iliac crest and proceeding around the abdomen, ensuring that the tape is tight but not constricting the skin. The value is measured after normal expiration. High-risk WC is defined as greater than 40 inches (102 cm) in men and greater than 35 inches (89 cm) in women.[13] Measurement of WC is not recommended for children and adolescents because reference values identifying risk are unavailable.[13] After obtaining patient-appropriate parameters, further assess the adult patient for the presence of obesity-related comorbidities and cardiovascular risk factors. KEY CONCEPT The presence of obesity-related comorbidities (CVD, type 2 diabetes mellitus, and sleep apnea) and cardiovascular risk factors requires identification and aggressive management for overall effective treatment of the overweight or obese patient. A patient is at very high absolute risk of a cardiovascular event if diagnosed with CVD, type 2 diabetes mellitus, or sleep apnea or if three or more of the following risk factors exist: cigarette smoking, hypertension, elevated low-density lipoprotein cholesterol, decreased high-density lipoprotein cholesterol, or impaired fasting glucose.[2] Aggressive disease management should be initiated and not limited to weight loss.

TREATMENT

Desired Outcome

KEY CONCEPT The treatment goals for overweight and obesity are to prevent additional weight gain, reduce and maintain a lower body weight, and control related risks. A 5% to 10% weight loss has been shown to improve obesity-related comorbidities such as hypertension, hyperlipidemia, and type 2 diabetes mellitus and thus serves as the initial goal for obesity treatment strategies.[11] A sustained 5% weight loss will likely reduce triglyceride and blood glucose values as well as risk for the development of type 2 diabetes mellitus.[11] Greater reductions in weight will reduce blood pressure and improve both low-density and high-density lipoprotein cholesterol. KEY CONCEPT Weight loss is indicated for patients with a BMI of 25 to 29.9 kg/m^2 with one or more indicators of increased CVD risk (eg, elevated WC, prediabetes or type 2 diabetes, hypertension, dyslipidemia, current cigarette smoker) or for any patient with a BMI of 30 kg/m^2 or greater. Weight loss should occur at a rate of 0.45 to 0.9 kg (1–2 lbs) per week, meeting the initial weight loss goal within the first 6 months of therapy. If the patient achieves a 5% to 10% loss in weight, weight loss maintenance strategies should be considered. KEY CONCEPT Weight maintenance occurs after successful achievement of weight loss.

For children or adolescents, a BMI below the 85th percentile is warranted, but is difficult to assess in frequent or short time periods. Serial weight measurements may better quantify energy balance. Goals are most likely accomplished through adaptation of lifelong healthy lifestyle habits. In doing so, weight loss or maintenance can be attained for some children. Others may need to incorporate changes that result in a negative energy balance or energy input less than energy output.[12–14]

General Approach to Treatment

KEY CONCEPT Treatment of obesity includes comprehensive lifestyle intervention (caloric-restricted diet, increased physical activity, and behavioral therapy to facilitate compliance with diet and exercise), pharmacologic treatment, surgical intervention, or a combination of modalities. Before initiating therapy, secondary causes of obesity (eg, hypothyroidism and Cushing syndrome) must be considered. Current treatment with medications that increase weight should be determined and, if present, alternative therapies should be suggested.[15,16] Table 102–2 provides a list of drugs commonly associated with weight gain. Therapy implemented to minimize associated risk(s) may not enhance

Table 102–2

Drugs Contributing to Weight Gain

- Anticonvulsants/mood stabilizers
  - Carbamazepine
  - Gabapentin
  - Pregabalin
  - Valproic acid
  - Lithium
- Antidepressants
  - Monoamine oxidase inhibitors (phenelzine)
  - Presynaptic α-2 antagonist (mirtazapine)
  - Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluvoxamine)
  - Serotonin and norepinephrine reuptake inhibitors (duloxetine)
  - Tricyclics (amitriptyline, imipramine)
- Antidiabetics
  - Insulin
  - Meglintinides
  - Sulfonylureas (glipizide, glyburide)
  - Thiazolidinediones
- Antipsychotics
  - Atypical (clozapine, olanzapine, paliperidone, risperidone)
  - Conventional (haloperidol)
- Others
  - Antihistamines
  - Some nonselective β-blockers
  - Corticosteroids
  - Hormonal contraceptives (depot injections)

From Refs. 15 and 16.

weight loss, but weight loss will positively address risk factors. Weight loss therapy should not be initiated in pregnant or lactating patients, decompensated psychiatric patients, or patients in whom reduced caloric intake can exacerbate an acute, serious illness.[2]

The treatment of pediatric obesity is a comprehensive strategy combined of four main pillars; regulating quality and quantity of food intake, encouraging at least 60 minutes of physical activity daily while also limiting screen time to less than 1–2 hours per day, sleep regulation, and pharmacotherapy for those who qualify.[12,15]

Nonpharmacologic Therapy

Weight loss therapy requires the creation of an energy deficit. This may be achieved through daily caloric restriction and increased physical activity. Comprehensive lifestyle intervention and behavior modification is foundational to weight loss and should be recommended for all overweight or obese patients, even when adjunctive therapy with medications, devices, or bariatric surgery has been implemented.[11] Table 102–3 indicates which treatment options may be appropriate according to BMI category.[13,17]

▶ *Reduced-Calorie Diet*

LO 4

Techniques to reduce dietary energy intake include adoption of a target energy intake less than that required for energy balance. This can usually be accomplished by reducing the energy intake by 500 kcal/day (2093 kJ/day) or greater from current intake. Recommend total intake of 1200 to 1500 or 1500 to 1800 kcals/day (5023–6279 or 6279–7534 kJ/day) for women and men, respectively. The choice of calorie-restricted diet is based on patient preference and current health status. A variety of diets, including but not limited to, high protein, low carbohydrate, low fat, Mediterranean and American Heart Association (AHA) Step-1 diet, can result in weight loss if reduction in dietary intake is achieved.[11] The AHA Step-1 diet restricts daily calories to a range of 1000 to 1200 kcal (4186–5023 kJ/day) for women weighing less than 75 kg (165 lbs) and 1400 to 1600 kcal (5860–6697 kJ/day) for all others. This daily limit should be considered after assessing a patient's normal daily caloric intake and ensuring that the initial caloric restriction does not exceed 500 to 1000 kcal (2093–4186 kJ/day). For example, a male patient who consumes 3000 kcal (12,557 kJ/day) should not reduce his daily caloric intake to less than 2000 kcal (8372 kJ/day) when initially implementing a dietary program. Further reduction to the target of 1600 kcal (6697 kJ/day) can be attempted when the patient has reduced calories successfully, as initially recommended, for a period agreeable to the practitioner and the patient.[2] Diets too restrictive in calorie reduction are successful initially, but fail in the long term because compliance is difficult to sustain.[18] Therefore, this less aggressive approach promotes gradual weight loss and weight maintenance. Consultation with a dietician is recommended when implementing a healthy meal plan tailored to the individual's nutritional needs.

Pediatric patients should be encouraged to consume three servings of protein daily, three servings of dairy daily, four to six servings of fruits and vegetables daily (majority from vegetables), avoid fast food, restrict dessert to special occasions only, and allowing the child to leave food on their plate if they feel full.[12]

▶ *Increased Physical Activity*

LO 4

Although diet and exercise contribute to weight loss, combining a reduced-calorie diet with increased physical activity results in greater weight loss compared with either therapy alone.[13] In addition, physical activity can help prevent weight regain and reduce related cardiovascular risks.[11] Slow titration of both the amount and intensity of aerobic physical activity is recommended for most patients.[2] A program that incorporates walking daily is a viable option for most patients. Suggest starting with 10 minutes of physical activity 3 days/week and titrate up to 30 minutes most days as tolerated for optimal weight maintenance.[2,11] Pediatric patients should engage in at least 60 minutes of moderate to vigorous activity daily and limit nonacademic sedentary time.[12]

LO 3 LO 4

▶ *Behavioral*

Eliminating barriers through behavior modification is necessary to gain maximal benefit from both dietary modification and exercise. Successful behavioral therapy includes regular self-monitoring of food intake, physical activity, and weight.[11,13]

LO 3 LO 4

Targeted behaviors should be recommended to pediatric patients and their families because healthy habits help prevent excessive weight gain. These include, but are not limited to:[12,14]

- Limit the consumption of sugar-sweetened beverages.
- Limit the amount of screen time (television, computer, etc) to 2 hours or less per day.
- Limit the number meals eaten at restaurants, especially those serving fast food.
- Limit portion size when preparing and serving meals.

Pharmacologic Therapy

KEY CONCEPT Pharmacotherapy in addition to comprehensive lifestyle intervention can be considered for patients with a BMI of 30 kg/m^2 or greater, or a BMI of 27 kg/m^2 or greater with other obesity-related co-morbidities. Obesity is a chronic

Table 102–3

Indications for Obesity Treatment by BMI Category

	BMI Category				
Treatment	25–26.9	27–29.9	30–34.9	35–39.9	> 40
Bariatric Surgery	No	No	Gastric banding with comorbidity	With comorbidity	Yes
Devices	No	No	Balloon	Aspire Assist Balloon vBloc[a] with comorbidity	Aspire Assist vBloc
Pharmacotherapy	No	With comorbidity	Yes	Yes	Yes
Lifestyle Modification (diet, activity, behavior)	Yes	Yes	Yes	Yes	Yes

[a]vBloc = vagal nerve block therapy

From Refs. 13 and 17.

disease that needs chronic treatment. There is no other chronic disease where therapy is withdrawn after a definitive time point. KEY CONCEPT Weight will likely be regained if lifestyle changes and/or therapeutic interventions are not continued indefinitely. Five drugs are approved for long-term use (at least 2 years) in promoting weight loss and preventing weight regain. If 4% to 5% weight loss is not achieved after 12 weeks of target dose therapy, the drug should be discontinued. Pharmacotherapy is not appropriate for women who are pregnant or lactating. Orlistat is the only agent approved for adolescent patients and is FDA approved for patients greater than 12 years of age.[19] All other pharmacotherapeutic agents are only approved for patients greater than 18 years of age. Table 102–4 summarizes currently available pharmacotherapeutic agents for weight management.

Table 102–4

Pharmacotherapy for the Treatment of Obesity

Drug	Dose	Side Effects	Warnings and Contraindications	Relative Monthly Cash Price
Phentermine (Adipex P, Lomaira)	8–37.5 mg daily (given in 1–3 divided doses)	Restlessness, tremor, palpitations or tachycardia, hypertension, cardiac valvulopathy pulmonary hypertension	Tolerance develops after a few weeks Do not discontinue abruptly from max dose (seizure possible), avoid alcohol, hypokalemia if used with diuretics, avoid in hepatic dysfunction, take in morning to avoid insomnia History of drug abuse, cardiovascular disease, hyperthyroidism, glaucoma, administration of a monoamine oxidase inhibitor within 14 days	~$50
Phentermine/ Topiramate (Qsymia) Risk Evaluation and Mitigation Strategy (REMS) Program—pregnancy warning; cleft palate	3.75/23 mg daily × 14 days, 7.5/46 mg × 12 weeks Titrate up to 11.25/69 mg × 14 days then 15/92 mg daily if first 12 weeks successful Max dose 7.5/46 mg for CrCL < 50 mL/min (0.84 mL/s)	Constipation, paresthesias, xerostomia, blurred vision, impaired cognition, headache, kidney stones, increased upper respiratory tract infection, tachycardia, metabolic acidosis	Do not discontinue abruptly from max dose, avoid alcohol, hypokalemia if used with diuretics, avoid in hepatic dysfunction, take in morning to avoid insomnia Glaucoma, hyperthyroidism, administration of a monoamine oxidase inhibitor within 14 days	~$200–250
Bupropion/ Naltrexone (Contrave)	8/90 mg ER tab titrate up by 1 tab each week over 4 weeks to 32/360 mg given twice daily Limit to 1 tab twice a day for moderate–severe renal, and 1 tab daily for hepatic dysfunction	Nausea, vomiting, constipation, headache, dizziness, tachycardia, hypertension, insomnia, mood disturbances—report suicidal ideation immediately	Don't take with high-fat meals, **potential drug interactions:** other serotonergic drugs, antipsychotics, clopidogrel, antiretrovirals Seizure disorder, uncontrolled hypertension, history of eating disorder, **chronic opioid use**, administration of a monoamine oxidase inhibitor within 14 days	~$250–300
Lorcaserin (Belviq, Belviq XR)	10 mg twice daily or 20 mg XR daily	Valvular heart disease, cognitive impairment/psychiatric disturbances, priapism, headache, dizziness, increased upper respiratory tract infection, nausea, constipation	Avoid if CrCL < 30 mL/min (0.50 mL/s), **drug–drug interactions with other serotonergic drugs**	~$250–300
Liraglutide 3 mg (Saxenda) REMS: Thyroid C-cell tumors, acute pancreatitis	0.6 mg subcutaneously daily, increase by 0.6 mg each week up to 3 mg	Nausea, vomiting, diarrhea, constipation, headache, dizziness, dyspepsia (delayed gastric emptying), increased heart rate, acute pancreatitis, cholelithiasis	↓ Sulfonylurea dose by 50% and do NOT use with insulin Personal or family history of medullary thyroid cancer or endocrine neoplasia type 2	~$100–1300
Orlistat (Xenical—prescription) (Alli—OTC)	Xenical 120 mg three times daily with meals Alli 60 mg three times daily with meals	Abdominal pain fecal urgency, leakage, incontinence flatulence, steatorrhea	Take a multivitamin containing vitamins A,D,E, and K Cholestasis, malabsorption syndromes	~$700–750 ~$50–100

From Refs. 19–26.

▶ *Agents for Long-Term Use*

Orlistat Orlistat promotes and maintains weight loss by acting locally in the GI tract. It inhibits pancreatic and gastric lipases, as well as triglyceride hydrolysis. As a result, undigested triglycerides are not absorbed, causing a caloric deficit and weight loss.[19] Two different orlistat products are available; prescription strength (Xenical 120 mg) and over the counter strength (Alli 60 mg) and both are taken with each meal. Initiate orlistat with a well-balanced but reduced-caloric meal containing no more than 30% of calories from fat. Orlistat may be taken during or up to 1 hour after the meal. If a meal is missed or contains little fat, the dose of orlistat may be omitted. Doses above 360 mg/day provide no greater benefit and thus are not recommended.[19] LO 4

Prescription strength orlistat in combination with diet, exercise, and behavior modification resulted in a significant reduction in BMI and WC in adolescents. In addition, orlistat-treated subjects exhibited minimal weight increase after 1 year.[19]

The safety and efficacy of orlistat have not been determined beyond 4 years of use. Orlistat's product label contains liver injury warning. Signs and symptoms of liver injury include itching, yellowing of the eyes or skin, dark urine, decreased appetite and light-colored stools. Orlistat should be stopped if the patient complains of these signs and symptoms. In addition, liver function tests should be assessed.[27] LO 5 LO 6

Orlistat reduces the absorption of some fat-soluble vitamins. Daily intake of a multivitamin containing fat-soluble vitamins is recommended. Because the absorption of vitamin K may be reduced in patients receiving orlistat therapy, closer monitoring of coagulation status should occur in patients also taking warfarin.[19] Simultaneous administration of orlistat and some other medications may cause reduced absorption of the other medication and put the patient at increased risk of clinical adverse effects. Patients should take levothyroxine 4 hours before or after the orlistat dose and be monitored for changes in thyroid function. Administration of orlistat in conjunction with cyclosporine can result in decreased cyclosporine plasma levels. Cyclosporine should be taken 2 hours before or after the dose of orlistat and cyclosporine levels should be monitored more frequently.[19] LO 5 LO 6

Lorcaserin Lorcaserin, a 5-HT_{2C} agonist, promotes satiety and decreases food consumption, however, the mechanism is unknown. Its use with other serotonin promoting drugs such as triptans, monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), bupropion, lithium, antipsychotics, St. John's wort, and dextromethorphan is extremely cautioned due to the potential for serotonin syndrome.

Almost 30% of diabetic patients taking lorcaserin experienced hypoglycemia. Blood glucose should be monitored closely in patients taking an antidiabetic medication and lorcaserin.[21]

Initiate lorcaserin 10 mg twice daily or 20 mg once daily of the extended release version in addition to a calorie-restricted diet and increased physical activity. Doses greater than 20 mg daily are not recommended and may result in the development of euphoria, altered mood, and hallucinations. Due to the potential for psychic dependence and abuse, lorcaserin is a federally controlled substance (CIV) in the United States.[21] LO 5 LO 6

Phentermine-topiramate Phentermine-topiramate is an extended-release combination product. Phentermine decreases food intake by increasing norepinephrine and dopamine release in the central nervous system (CNS) which suppresses appetite. Topiramate is an antiepileptic drug whose exact mechanism of action is unknown. It is thought to increase satiety and suppress appetite through multiple pathways.[22]

Phentermine-topiramate use is associated with increased heart rate. Monitor resting heart rate frequently and have patients report the presence of palpitations. Topiramate can increase a patient's risk for suicidal thoughts and behaviors and alter mood. Patients should be monitored for worsening depression, thoughts of suicide, and unusual mood or behavior. Topiramate is contraindicated in patients with glaucoma or hyperthyroidism. Cognitive impairment is also associated with use of phentermine-topiramate; patients should proceed with caution when operating hazardous machinery including driving a car until the extent of impairment is known. An increase in serum creatinine and decrease in both potassium and bicarbonate have been reported.[22]

Because topiramate is a known teratogen, use of phentermine-topiramate during pregnancy is contraindicated. All women of childbearing potential should have a documented negative pregnancy result before this drug is initiated and monthly while on therapy.

Coadministration of phentermine-topiramate and MAOI could result in a hypertensive crisis. Do not initiate phentermine-topiramate within 14 days of MAOI discontinuation. Phentermine-topiramate used in patients taking an oral contraceptive may cause irregular bleeding but not an increased risk of pregnancy. Advise patients to continue the oral contraceptives even if spotting occurs. LO 5 LO 6

Initiate phentermine-topiramate at a dose of 3.75 mg/23 mg daily and titrate to max dose as per Table 102–4. Discontinue drug or increase the dose of phentermine-topiramate if a 3% weight loss is not achieved in 12 weeks. If the decision is made to increase the dose, recommend 11.25 mg/69 mg daily for 14 days then increase to 15 mg/92 mg daily. Discontinue drug if a 5% weight loss is not achieved after 12 weeks at the highest drug dose. Due to the potential for drug abuse, phentermine-topiramate is a federally controlled substance (CIV).[22] Gradually discontinue the 15 mg/92 mg dose to prevent possible seizures from abrupt withdrawal.

Naltrexone-bupropion Naltrexone-bupropion is an extended-release combination product. The exact mechanisms by which this opioid antagonist/antidepressant combination product decreases food intake and weight are not fully known but involve two separate areas of the brain (hypothalamus and mesolimbic dopamine circuit).[23] LO 6

Patients taking this product should be monitored for emergence or worsening of suicidal thoughts and behaviors and neuropsychiatric reactions. Bupropion inhibits CYP2D6 and can therefore increase the concentration of antidepressants, antipsychotics, and β-blockers. When taken with a CYP2B6 inhibitor (eg, clopidogrel), the concentration of bupropion increases. Reduce maximum daily dose by half in these patients. CYP2B6 inducers may reduce bupropion efficacy.[23] LO 5 LO 6

Each extended release tablet contains 8 mg of naltrexone and 90 mg of bupropion. Patients should be advised to not cut, crush, or chew tablets. Patients should also avoid taking naltrexone-bupropion with high-fat meals to minimize the risk of enhanced bupropion absorption and subsequent seizure occurrence. To further reduce the risk of seizures, the dose must be titrated slowly as suggested in Table 102–4.

Liraglutide 3 mg Liraglutide is an injectable analog of GLP-1 with a sequence that is 97% homologous with endogenously produced GLP-1.[20] When liraglutide stimulates GLP-1 receptors

in the brain, signals of satiety are received and gastric emptying is delayed. A 50% dose reduction of sulfonylureas is recommended with concomitant administration of liraglutide 3 mg in patients with type 2 diabetes. Liraglutide 3 mg was not studied in patients currently using insulin; therefore, this combination should be avoided. Acute pancreatitis occurs in 0.3% of patients taking liraglutide.[20]

Liraglutide is administered subcutaneously at a starting dose of 0.6 mg daily and increased to a target dose of 3 mg as suggested in Table 102–4. The dose increase may be delayed by 1 week if the patient is experiencing intolerable gastrointestinal adverse effects.

► *Agents for Short-Term Use*

LO 4 LO 5 LO 6

Agents for short-term use are indicated as an adjunct to lifestyle modifications for no more than 12 weeks use.[22,28,29] They are structurally related to amphetamine and work to suppress appetite. They can cause CNS stimulation and carry a potential for abuse. They should also not be used concurrently or within 14 days of an MAOI. These agents are cheaper than chronic obesity medications, but often have more risky side effect profiles.

Phentermine An average weight loss of 3.6 kg (7.9 lbs) was demonstrated for patients treated with phentermine compared with placebo.[24]

Common adverse reactions seen with phentermine use include heart palpitations, tachycardia, elevated blood pressure, stimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, dry mouth, constipation, and diarrhea. Avoid phentermine in patients with CVD, hypertension, hyperthyroidism, and agitated states. Because phentermine is related to the amphetamines, the potential for abuse is high.[24] Alcohol is not recommended for patients prescribed phentermine.[24]

LO 5 LO 6

Phentermine is available as an immediate- and a sustained-release product. In conjunction with a healthy lifestyle, 30 to 37.5 mg of phentermine is administered once daily, typically before breakfast or 1 to 2 hours after the morning meal. The dosage should be individualized; some patients may be managed adequately at 15 to 18.75 mg/day, but a dose of 18.75 mg twice daily may be used to minimize side effects, excluding insomnia. To lessen the risk of insomnia, dosing phentermine in the evening should be avoided.[24] A lower dose, 8 mg tablet, is given three times daily prior to meals.

Diethylpropion and Phendimetrazine These older sympathomimetic amines exhibit pharmacologic activity similar to amphetamines, resulting in CNS stimulation and appetite suppression.

Use of diethylpropion for a period longer than 12 weeks is associated with an increased risk for development of pulmonary hypertension.[28] When used as directed, reported common CNS adverse effects of these amphetamine derivatives included restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, anxiety, tachycardia, palpitations, dry mouth, constipation, mydriasis, and blurred vision.[28,29] In addition, diethylpropion can decrease the seizure threshold.[28] These agents are contraindicated in patients with pulmonary hypertension, advanced arteriosclerosis, severe hypertension, hyperthyroidism, agitated states, or glaucoma. Because these medications are related to the amphetamines, the potential for abuse is high.[28]

Use of diethylpropion and phendimetrazine should be avoided in patients receiving or having received an MAOI within the preceding 14 days to prevent hypertensive crisis. Combination with other anorectic agents should be avoided.[28,29]

Patient Encounter 1, Part 1

A 44-year-old woman presents to your weight loss clinic for an initial evaluation. She reports that her glucose and blood pressure were elevated upon screening while attending a community health fair. She followed up with her primary care provider who recommended weight loss. The patient has gained 25 pounds (11.4 kg) since her last check up 2 years ago. She is not currently following any specific diet. She admits to eating fast food 2 to 3 days per week. The patient is recently divorced (1 year ago) and does not enjoy cooking for one. This patient is currently part of a walking group where she walks 20 minutes per day roughly 5 days per week. The patient does not smoke and consumes one glass of wine at least 4 nights per week. Her BMI is 33.1 kg/m^2 and her waist circumference is 39 inches (99 cm).

What classification of overweight and obesity is appropriate for this patient?

Does this patient have a high-risk waist circumference?

Does she have other risk factors that may contribute to morbidity or mortality?

What are the treatment goals for the patient?

What additional information do you need to know before creating a treatment plan for this patient?

LO 4

Diethylpropion is available as both an immediate- and a controlled-release product. In conjunction with a reduced-calorie diet and/or exercise, dose diethylpropion (immediate release) 25 mg three times a day before meals or 75 mg (controlled release) once a day, usually midmorning.[28] Dose phendimetrazine extended release (105 mg) in the morning, 30 to 60 minutes before the morning meal or 35 mg immediate release 2 to 3 times per day prior to meals. Phendimetrazine is a federally controlled substance (CIII).[29]

Surgical Intervention

LO 6

KEY CONCEPT Weight loss (bariatric) surgery is warranted when other treatment attempts have failed in severely obese patients (BMI ≥ 40 kg/m^2, or ≥ 35 kg/m^2 with obesity-related comorbidities).[2,13] Several surgical techniques exist; however, three are currently recognized as contemporary procedures: **gastric bypass**, which induces weight loss through both malabsorptive and restriction, **sleeve gastrectomy**, and **laparoscopic adjustable gastric banding (LAGB)**, which achieve weight loss through restriction of food intake only.[30] Currently, the sleeve gastrectomy is the most commonly performed bariatric surgery procedure.[31]

Surgical options for obesity provide the most effective and sustainable weight loss results and may produce a loss of two-thirds of **excess body weight** after 2 years.[2] Additionally, very favorable outcomes for obesity-related comorbid conditions are observed.[32] Risk versus benefit must be considered as complications are inherent to any surgical procedure, but the overall likelihood of major complications is less than 4%. Possible short-term complications include pulmonary embolism, wound infection, and anastomotic leak. The overall risk of mortality from bariatric surgery is about 0.1%. Several studies have compared mortality in obese patients who have underwent bariatric surgery to those who have not and consistently found reduced mortality rates in the surgical population.[32]

Patient Encounter 1, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Persistent lower back pain, occasional heartburn, depression, insomnia

FH: Father alive and 68 years of age; mother also alive (age 65) with history of obesity

SH: (–) Tobacco, (+) alcohol

Meds: Hydrocodone/acetaminophen 5/325 one tablet orally at bedtime, pantoprazole 40 mg orally each day, citalopram 20 mg orally each day, and quetiapine 12.5 mg orally at bedtime for sleep

ROS: (+) Heartburn; (–) chest pain, nausea, vomiting, diarrhea, change in appetite, shortness of breath, or cough

PE:

VS: BP 147/88 mm Hg, P 92 beats/min, RR 16 breaths/min, T 98.6°F (37.0°C)

Weight: Wt 193 lbs (87.7 kg); Ht 64" (163 cm)

Cardiovascular: Normal S_1S_2; no murmurs, rubs, gallops

Abdominal: Obese, soft, nontender, nondistended; (+) bowel sounds

Extremities: (–) Edema

Labs: Glucose (118 mg/dL[6.5 mmol/L]) and HbA1C (6.0% [0.06 or 42 mmol/mol Hgb]).

ECG: Normal; no evidence of past ischemia

Given this additional information, do you recommend weight loss? If so, how much weight should the patient lose and how fast?

What nonpharmacologic and pharmacologic treatments are available for the patient?

Would you recommend any changes to her current medication regimen to assist with her weight loss?

If you elected to start her on a pharmacotherapeutic agent for weight loss, what would you need to monitor and when would you recommend the patient come back for follow-up?

LO 6 Bariatric surgery is an alternative offered to adolescents because it results in substantial weight loss and medical health improvement.[33] Adolescent patients should be managed by a multidisciplinary team that can provide psychosocial, nutritional, and exercise support.[34] LO 6 Both adult and pediatric surgical patients must understand and commit to a substantial change in eating and activity patterns to maintain long-term weight reduction.

Postoperatively, healthcare providers should also make considerations for medication management as these procedures may alter drug and nutrient absorption.[35]

- If safe to do so for individual medications, crush tablets, open capsules, or use liquid formulations to replace sizeable pills until appropriate to restart solid foods (likely variable per program).
- Avoid nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, oral bisphosphonates, and potentially extended- or delayed-release products for malabsorptive procedures.
- Certain micronutrient supplements may be indicated depending on procedure type (eg, fat soluble vitamins, iron, vitamin B12).
- Nonoral routes of administration may be considered if available.

▶ *Devices*

Weight loss devices require a minimally invasive outpatient procedure since most of them are endoscopically placed.[17] There are currently three types of devices approved for use in adult patients by the FDA, vagal nerve blocking stimulators (vBloc), gastric balloons, and gastric emptying systems. Indications for use are dependent on BMI category and/or presence of obesity-related comorbidities (see Table 102–3) and some are only approved for short-term therapy (6 months).[13,17] Devices are associated with an overall equal to or greater weight loss profile compared to pharmacotherapy, but are not quite as effective as bariatric surgery.[17] Devices are associated with some similar adverse effects but an overall lesser serious complication rate compared to bariatric surgery.[17]

Vagal Nerve Block Stimulator The vBloc system contains a pacemaker-like device that is implanted under the skin and connects to electrodes that are attached to the vagus nerve.[36] It blocks hunger signals sent from the stomach to the brain along the vagus nerve. The vBloc system is not appropriate for patients with hepatic cirrhosis or those who have another electronic medical device already implanted.

Gastric Balloons Three medical-grade silicone gastric balloons are currently available for endoscopic placement and inflation in the stomach: Reshape, Orbera, and Obalon. The balloon reduces the amount of food that a patient can consume by taking up significant space in the stomach. After 6 months, balloons must be removed. Most common adverse events are nausea/vomiting, abdominal pain, and gastric ulcers.

Reduced Calorie Absorption System The AspireAssist device works by removing roughly one-third of the food consumed from the stomach before it reaches the intestinal

Patient Encounter 2, Part 1

A 41-year-old white man presents to your CVD risk reduction clinic. The patient currently denies chest pain, shortness of breath, dizziness, and lightheadedness. Upon review of previous progress notes, you discover that the patient's blood pressure has been elevated during the past three office visits. As a computer programmer, he finds himself sitting more than engaging in physical activity. He frequently eats fast food for lunch. Evenings are spent watching TV. He claims that his knee arthritis limits his exercise ability. The patient's BMI is 45 kg/m^2 and waist circumference is 47 inches (119 cm). He presents to the clinic today seeking recommendation for additional weight loss and says he is willing to make changes to better his health. He claims to have lost about 10 pounds (4.5 kg) since starting on Victoza for his diabetes.

What classification of overweight and obesity is appropriate for this patient?

Does this patient have a high-risk waist circumference?

Does he have other risk factors that may contribute to morbidity or mortality?

What are the treatment goals for the patient?

What additional information do you need to know before creating a treatment plan for this patient?

Patient Encounter 2, Part 2: Medical History, Physical Examination, and Diagnostic Tests

PMH: Occasional headache, Type 2 diabetes mellitus, hypertension, osteoarthritis of the left knee

FH: Father alive and 78 years of age; mother also alive and 77 years of age

SH: Drinks alcohol occasionally (socially) but denies any alcohol-related problems; distant history of substance abuse, mostly cocaine, but has been sober for 20 years

Meds: Lisinopril/hydrochlorothiazide 10/25 mg orally daily, aspirin 81 mg orally daily, metformin 1000 mg orally twice a day, Victoza 1.8 mg subcutaneously daily, atorvastatin 20 mg orally daily, Excedrin migraine 2 tabs orally as needed for headache, acetaminophen 650 mg orally four times a day as needed for knee pain

ROS: (–) Heartburn, regurgitation; (–) chest pain, nausea, vomiting, diarrhea, change in appetite, shortness of breath, or cough

VS: BP 134/92 mm Hg, P 92 beats/min, RR 15 breaths/min, T 98.7°F (37.1°C)

Weight: 289 lbs (131.3 kg)

Height: 68″ (173 cm)

Waist circumference: 47″ (119 cm)

10-year CVD risk: 7%

PE:

General: Well developed, in no acute distress

HEENT: Conjunctiva clear

CV: Regular rhythm, no S_3 or S_4 noted

Lungs: Clear to auscultation (CTA) bilaterally

Abd: Obese, soft, nontender, nondistended; (+) bowel sounds

Neuro: Normal gait, normal speech

Ext: (–) Edema

Labs:

Na: 142 mEq/L (mmol/L); **K:** 4.6 mEq/L (mmol/L); **Cl:** 107 mEq/L (mmol/L); **CO_2:** 23 mEq/L (mmol/L); **BUN:** 18 mg/dL (6.4 mmol/L); **Creatinine:** 0.9 mg/dL (80 µmol/L); **glucose:** 72 mg/dL (4.0 mmol/L) **HbA1C:** 6.9% (0.069; 52 mmol/mol Hgb)

TC: 213 mg/dL (5.51 mmol/L); **LDL:** 110 mg/dL (2.84 mmol/L); **HDL:** 30 mg/dL (0.78 mmol/L); **TG:** 152 mg/dL (1.72 mmol/L)

AST: 24 U/L (0.40 µkat/L); **ALT:** 30 U/L (0.50 µkat/L)

What would be the optimal treatment strategy for this patient?

tract; effectively reducing the calories absorbed from food.[17] A tube is placed into the stomach and connects to a small button on the outside of the abdomen. Roughly 20 to 30 minutes after a meal, the patient connects the tube to a handheld device that then pumps food out of the stomach and into the toilet. The most common adverse effects are abdominal discomfort and button site irritation.

OUTCOME EVALUATION

LO 5

Successful management of overweight and obesity is determined by the ability the treatment plan has to (a) prevent weight gain, (b) reduce and maintain a lower body weight, and (c) decrease the risk of obesity-related comorbidities. Obesity management may encompass more than weight loss or maintenance in the presence

Patient Care Process

Collect and Assess Information:

- Measure weight and height.
- Calculate and classify BMI.
- Medical history, current medications, and laboratory data for secondary causes of weight gain
- CVD risks and obesity-related comorbidities
- Current lifestyle and history of weight gain/loss
- Need to lose weight (candidates include obese patients or overweight patients with at least one indicator of increased CVD risk)
- Readiness to make lifestyle changes
- Weight loss goals

Develop and Implement a Care Plan:

- Comprehensive lifestyle intervention strategies (restricted caloric-diet, increased physical activity and behavioral therapy)
- Determine eligibility for obesity pharmacotherapy and, if so, verify if insurance coverage exists for the patient or if they qualify for any manufacturer offered discount cards
- If patient is already receiving an antiobesity medication, assess efficacy, safety, adherence, and potential drug, interactions.
- Manage CVD risk factors such as hypertension, dyslipidemia, etc.
- Encourage self-weighing, at least weekly, for better weight loss and maintenance over time.

Follow-Up: Monitor and Evaluate:

- In 2 weeks, assess weight, blood pressure, heart rate, and adherence with comprehensive lifestyle intervention. Assess weight monitoring log.
- Reassess patient in person, ideally monthly.
- Once weight loss is achieved, continue contact with the patient monthly. Address small weight gains and continued adherence with comprehensive lifestyle intervention.

of other conditions such as hypertension, type 2 diabetes mellitus, hyperlipidemia, CVD, sleep apnea, hypothyroidism, osteoarthritis, gallbladder disease, gout, or cancer. Measure blood pressure and heart rate before implementation of any therapy and assess basic metabolic panel, liver function tests, complete blood count, fasting lipid profile, thyroid function tests, and other laboratory studies at baseline and as clinically indicated. Additionally, obtain an electrocardiogram if recent results are unknown.[2]

LO3 LO5 When considering various approaches to behavioral therapy for weight loss, in-person, high-intensity (defined as a minimum of 14 sessions within 6 months) behavioral therapy is the most effective. During each session, assess compliance with comprehensive lifestyle intervention, as well as measure weight, blood pressure, and heart rate. Measure WC intermittently. Identify presence of adverse drug reactions or drug interactions if weight loss medications have been initiated.[2,13]

When the patient has achieved the recommended weight loss, he or she then enters the weight maintenance phase, which includes continued contact for education (no less than monthly), guidance, and risk factor assessment. Self-weighing, at least weekly, is associated with better weight maintenance over time. Counsel patient to address small weight gains before they become larger.[11]

LO3 LO5 If weight loss is not attained, further assess why the goals of therapy are unmet. Direct the interaction toward determining the motivation to lose weight, balance between caloric intake and physical activity, adherence to behavioral therapy, and determination of psychological stressors present.[2] Refer patient to a nutrition professional or for evaluation for bariatric surgery if eligibility criteria are met. If adjunctive pharmacotherapy has not been initiated, consider antiobesity drugs approved for long-term use.[26]

Abbreviations Introduced in This Chapter

ALT	Alanine aminotransferase
AST	Aspartate transaminase
BMI	Body mass index
CB1	Cannabinoid receptor
CNS	Central nervous system
CVD	Cardiovascular disease
FDA	Food and Drug Administration
5-HT_{1A}	Serotonin 1A subtype
5-HT_{2C}	Serotonin 2C subtype
GI	Gastrointestinal
MAOI	Monoamine oxidase inhibitor

REFERENCES

1. Defining Adult Overweight and Obesity. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/obesity/adult/defining.html. Accessed June 16, 2016.
2. U.S. Department of Health and Human Services, NIH-NHLBI. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults. NIH publication no. 00–4084. Bethesda, MD: National Institutes of Health, 2000.
3. Adult Obesity Causes and Consequences. Centers for Disease control and Prevention. Available from: https://www.cdc.gov/obesity/adult/causes.html. Accessed August 29, 2017.
4. Overweight and Obesity. Centers for Disease Control and Prevention. Available from: https://www.cdc.gov/obesity/data/adult.html. Accessed November 29, 2017.
5. Power C, Lake JK, Cole TJ. Body mass index and height from childhood to adulthood in the 1958 British born cohort. Am J Clin Nutr. 1997;66:1094–1101.
6. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa heart study. Pediatrics. 1999;103:1175–1182.
7. Must A, Jacques PF, Dallal GE, Bajema CJ, Dietz WH. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. N Engl J Med. 1992;327:1350–1355.
8. Chen Y. Regulation of food intake and the development of anti-obesity drugs. Drug Discov Ther. 2016;10(2):62–73.
9. Kim GW, Lin JE, Blomain ES, Waldman SA. Antiobesity pharmacotherapy: new drugs and emerging targets. Clin Pharmacol Ther. 2014;95(1):53–66.
10. Bray GA, Smith SR, DeJonge L, et al. Effect of diet composition on energy expenditure during weight loss: the POUNDS LOST study. Int J Obes. 2012;36(3):448–455.
11. Jenson MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guidelines for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society. Circulation. 2014;129:S1–S45.
12. Cuda SE, Censani M, Scinta W, Joseph M, Green R. Pediatric obesity algorithm, presented by the Obesity Medicine Association, 2016–2017. Available from: www.PediatricObesityAlgorithm.org. Accessed September 5, 2017.
13. Bays HE, Seger JC, Primack C, et al. Obesity algorithm, presented by the Obesity Medicine Association. www.obesityalgorithm.org. 2016–2017. Accessed September 5, 2017.
14. Spear BA, Barlow SE, Ervin C, et al. Recommendations for treatment and adolescent overweight and obesity. Pediatrics. 2007;120(suppl):S254–S288.
15. Malone M. Medications associated with weight gain. Ann Pharmacother. 2005;39:2046–2055.
16. Sheehan AH. Weight gain. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases: Prevention, Detection and Management, 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2010.
17. Abu Dayyeh BK, Edmundowicz S, Thompson CC. Clinical practice update: expert review on endoscopic bariatric therapies. Gastroenterology. 2017;152:716–729.
18. Wadden TA, Foster DD, Letizia KA. One-year behavioral treatment of obesity: comparison of moderate and severe caloric restriction and the effects of weight maintenance therapy. J Consult Clin Psychol. 1994;62:165–171.
19. Roche Laboratories. Xenical (Orlistat) package insert. Nutley, NJ: Roche Laboratories, 2009 (January).
20. Liraglutide (Saxenda) package insert (version 4). Novo Nordisk. Bagsvaerd, Denmark. Last updated May 2017. Available from: http://www.novo-pi.com/saxenda.pdf. Accessed August 31, 2017.
21. Arena Pharmaceuticals. Lorcaserin (Belviq) package insert. Zofingen, Switzerland: Arena Pharmaceuticals, 2017 (May).
22. Vivus, Inc. Phentermine-topiramate (Qsymia) package insert. Mountain View, CA. Vivus, Inc. 2014 (October).
23. Orexigen Therapeutics, Inc. Naltrexone-bupropion (Contrave) package insert. La Jolla, CA: 2017 (May).
24. Teva Pharmaceuticals. Adipex-P (Phentermine) package insert. Horsham, PA: 2017 (March).
25. LexiComp online database. AWP Pricing. Wolters Kluwer Clinical Drug Information, Inc. 2017.
26. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015;100(2):342–362.

27. FDA drug safety communication: completed safety review of Xenical/Alli (orlistat) and severe liver injury. Food and Drug Administration. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm. Accessed September 5, 2017.
28. Merrell Pharmaceuticals. Tenuate (Diethylpropion) package insert. Bridgewater, NJ: Merrell Pharmaceuticals, 2003 (November).
29. Valeant Pharmaceuticals North America. Bontril (Phendimetrazine) package insert. Aliso Viejo, CA; Valeant Pharmaceuticals North America. 2007 (March).
30. Bariatric Surgery Procedures. American Society for Metabolic and Bariatric Surgery. Available from: https://asmbs.org/patients/bariatric-surgery-procedures. Accessed September 10, 2017.
31. American Society for Metabolic and Bariatric Surgery. Estimate of Bariatric Surgery Numbers, 2011–2015. Available from: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers. Accessed September 10, 2017.
32. Kim J, Eisenberg D, Azagury D, DeMaria E, Campos GM. American Society for Metabolic and Bariatric Surgery position statement on long-term survival benefit after metabolic and bariatric surgery. SOARD. 2016;12:453–459.
33. Treadwell JR, Fang S, Schoelles K. Systematic review & meta analysis of bariatric surgery for pediatric obesity. Ann Surg. 2008;248(5):763–776.
34. Michalsky M, Reichard K, Inge T, Pratt J, Lenders C. ASMBS pediatric committee best practice guidelines. SOARD. 2012; 8:1–7.
35. Stein J, Stier C, Raab H, Weiner R. Review article: the nutritional and pharmacological consequences of obesity surgery. Aliment Pharmacol Ther. 2014;40:582–609.
36. Apovian CM, Shah SN, Wolfe BM, et al. Two-year outcomes of vagal nerve blocking (vBloc) for the treatment of obesity in the ReCharge trial. Obes Surg. 2017;27:169–176.

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Appendix A: Conversion Factors and Anthropometrics*

CONVERSION FACTORS

SI Units

SI (*le Systéme International d'Unités*) units are used in many countries to express clinical laboratory and serum drug concentration data.* Instead of using units of mass (eg, micrograms), the SI system uses moles (mol) to represent the amount of a substance. A molar solution contains 1 mole (the molecular weight of the substance in grams) of the solute in 1 L of solution. The following formula is used to convert units of mass to moles (mcg/mL to μmol/L or, by substitution of terms, mg/mL to mmol/L or ng/mL to nmol/L).

► *Micromoles per Liter*

$$\text{Micromoles per liter } (\mu\text{mol/L}) = \frac{\text{drug concentration (mcg/mL)} \times 1000}{\text{molecular weight of drug (g/mol)}}$$

► *Milliequivalents*

An equivalent weight of a substance is the weight that will combine with or replace 1 g of hydrogen; a milliequivalent is 1/1000 of an equivalent weight.

Milliequivalents per Liter

$$\text{Milliequivalents per liter (mEq/L)} = \frac{\text{weight of salt (g)} \times \text{valence of ion} \times 1000}{\text{molecular weight of salt}}$$

$$\text{Weight of salt (g)} = \frac{\text{mEq/L} \times \text{molecular weight of salt}}{\text{valence of ion} \times 1000}$$

Approximate Milliequivalents: Weight Conversions for Selected Ions

Salt	mEq/g Salt	mg Salt/mEq
Calcium carbonate ($CaCO_3$)	20.0	50.0
Calcium chloride ($CaCl_2 \cdot 2H_2O$)	13.6	73.5
Calcium gluceptate ($Ca[C_7H_{13}O_8]_2$)	4.1	245.2
Calcium gluconate ($Ca[C_6H_{11}O_7]_2 \cdot H_2O$)	4.5	224.1
Calcium lactate ($Ca[C_3H_5O_3]_2 \cdot 5H_2O$)	6.5	154.1
Magnesium gluconate ($Mg[C_6H_{11}O_7]_2 \cdot H_2O$)	4.6	216.3
Magnesium oxide (MgO)	49.6	20.2
Magnesium sulfate ($MgSO_4$)	16.6	60.2
Magnesium sulfate ($MgSO_4 \cdot 7H_2O$)	8.1	123.2
Potassium acetate ($K[C_2H_3O_2]$)	10.2	98.1
Potassium chloride (KCl)	13.4	74.6
Potassium citrate ($K_3[C_6H_5O_7] \cdot H_2O$)	9.2	108.1
Potassium iodide (KI)	6.0	166.0
Sodium acetate ($Na[C_2H_3O_2]$)	12.2	82.0
Sodium acetate ($Na[C_2H_3O_2] \cdot 3H_2O$)	7.3	136.1
Sodium bicarbonate ($NaHCO_3$)	11.9	84.0
Sodium chloride (NaCl)	17.1	58.4
Sodium citrate ($Na_3[C_6H_5O_7] \cdot 2H_2O$)	10.2	98.0
Sodium iodide (NaI)	6.7	149.9
Sodium lactate ($Na[C_3H_5O_3]$)	8.9	112.1
Zinc sulfate ($ZnSO_4 \cdot 7H_2O$)	7.0	143.8

Valences and Atomic/Molecular Weights of Selected Ions

Substance	Electrolyte	Valence	Atomic/Molecular Weight
Calcium	Ca^{2+}	2	40.1
Chloride	Cl^-	1	35.5
Magnesium	Mg^{2+}	2	24.3
Phosphate	HPO_4^{2-} (80%)	1.8	96.0[a]
(pH = 7.4)	$H_2PO_4^-$ (20%)		97.0
Potassium	K^+	1	39.1
Sodium	Na^+	1	23.0
Sulfate	SO_4^-	2	96.0[a]

[a]The atomic/molecular weight of phosphorus is only 31; that of sulfur is only 32.1.

*This appendix contains information from Appendices 1 and 2 of Smith KM, Riche DM, Henyan NN (eds.). Clinical Drug Data, 11th ed. New York: McGraw-Hill, 2010:1239–1246; With permission.

Anion Gap

The anion gap is the concentration of plasma anions not routinely measured by laboratory screening. It is useful in the evaluation of acid–base disorders. The anion gap is greater with increased plasma concentrations of endogenous species (eg, phosphate, sulfate, lactate, and ketoacids) or exogenous species (eg, salicylate, penicillin, ethylene glycol, ethanol, and methanol). The formulas for calculating the anion gap are as follows:

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

or

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-)$$

where the expected normal value for the first equation is 11 to 20 mmol/L and for the second equation is 7 to 16 mmol/L. Note that there is a variation in the upper and lower limits of the normal range.

Temperature

Fahrenheit to Celsius: (°F – 32) × 5/9 = °C
Celsius to Fahrenheit: (°C × 9/5) + 32 = °F
Celsius to Kelvin: °C + 273 = °K

Weights and Measures

▶ *Metric Weight Equivalents*

1 kilogram (kg) = 1000 grams
1 gram (g) = 1000 milligrams
1 milligram (mg) = 0.001 gram
1 microgram (mcg, μg) = 0.001 milligram
1 nanogram (ng) = 0.001 microgram
1 picogram (pg) = 0.001 nanogram
1 femtogram (fg) = 0.001 picogram

▶ *Metric Volume Equivalents*

1 liter (L) = 1000 milliliters
1 deciliter (dL) = 100 milliliters
1 milliliter (mL) = 0.001 liter
1 microliter (μL) = 0.001 milliliter
1 nanoliter (nL) = 0.001 microliter
1 picoliter (pL) = 0.001 nanoliter
1 femtoliter (fL) = 0.001 picoliter

▶ *Apothecary Weight Equivalents*

1 scruple (℈) = 20 grains (gr)
60 grains (gr) = 1 dram (ʒ)
8 drams (ʒ) = 1 ounce (℥)
1 ounce (℥) = 480 grains (gr)
12 ounces (℥) = 1 pound (lb)

▶ *Apothecary Volume Equivalents*

60 minims (m) = 1 fluidram (fl ʒ)
8 fluidrams (fl ʒ) = 1 fluid ounce (fl ℥)
1 fluid ounce (fl ℥) = 480 minims (m)
16 fluid ounces (fl ℥) = 1 pint (pt)

▶ *Avoirdupois Equivalents*

1 ounce (oz) = 437.5 grains
16 ounces (oz) = 1 pound (lb)

▶ *Weight/Volume Equivalents*

1 mg/dL = 10 mcg/mL
1 mg/dL = 1 mg%
1 ppm = 1 mg/L

▶ *Conversion Equivalents*

1 gram (g) = 15.43 grains (gr)
1 grain (gr) = 64.8 milligrams (mg)
1 ounce (℥) = 31.1 grams (g)
1 ounce (oz) = 28.35 grams (g)
1 pound (lb) = 453.6 grams (g)
1 kilogram (kg) = 2.2 pounds (lb)
1 milliliter (mL) = 16.23 minims (m)
1 minim (m) = 0.06 milliliter (mL)
1 fluid ounce (fl oz) = 29.57 milliliters (mL)
1 pint (pt) = 473.2 milliliters (mL)
1 US gallon = 3.78 liters (L)
1 Canadian gallon = 4.55 liters (L)
0.1 milligram = 1/650 grain
0.12 milligram = 1/540 grain
0.15 milligram = 1/430 grain
0.2 milligram = 1/320 grain
0.3 milligram = 1/220 grain
0.4 milligram = 1/160 grain
0.5 milligram = 1/130 grain
0.6 milligram = 1/110 grain
0.8 milligram = 1/80 grain
1 milligram = 1/65 grain

▶ *Metric Length Conversion Equivalents*

2.54 cm = 1 inch
30.48 cm = 1 foot
1 m = 3.28 feet
1.6 km = 1 mile

ANTHROPOMETRICS

Creatinine Clearance Formulas

▶ *Formulas for Estimating Creatinine Clearance in Patients with Stable Renal Function*

Cockcroft-Gault Formula

Adults (age 18 years and older)[1]:

$$\text{CrCl (men)} = \frac{(140 - \text{age}) \times \text{weight}}{\text{SCr} \times 72}$$

CrCl (women) = 0.85 × above value*

*Some studies suggest that the predictive accuracy of this formula for women is better *without* the correction factor of 0.85.

where CrCl is creatinine clearance (in mL/min), SCr is serum creatinine (in mg/dL [or μmol/L divided by 88.4]), age is in years, and weight is in kilograms.

Traub-Johnson Formula

Children (age 1–18 years)[2]:

$$\text{CrCl} = \frac{0.48 \times \text{height} \times \text{BSA}}{\text{SCr} \times 1.73}$$

where BSA is body surface area (in m^2), CrCl is creatinine clearance (in mL/min), SCr is serum creatinine (in mg/dL [or μmol/L divided by 88.4]), and height is in centimeters.

▶ *Formula for Estimating Creatinine Clearance from a Measured Urine Collection*

$$\text{CrCl (mL/min)} = \frac{U \times V}{P \times T}$$

where U is the concentration of creatinine in a urine specimen in mg/dL, V is the volume of urine in mL, P is the concentration of creatinine in serum at the midpoint of the urine collection period in mg/dL, and T is the time of the urine collection period in minutes (eg, 6 hours = 360 minutes; 24 hours = 1440 minutes). Procedures for obtaining urine specimens should stress the importance of complete urine collection during the collection time period.

▶ *IDMS-Traceable MDRD Equation (Used for Creatinine Methods with Calibration Traceable to IDMS)*

For creatinine in mg/dL:

$$X = 175 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

For creatinine in μmol/L:

$$X = 175 \times (\text{creatinine}/88.4)^{-1.154} \times \text{age}^{-0.203} \times \text{constant}$$

where X is the glomerular filtration rate, constant for white men is 1 and for women is 0.742, and constant for African Americans is 1.212.

Ideal Body Weight

IBW is the weight expected for a non-obese person of a given height. The IBW formulas below and various life insurance tables can be used to estimate IBW. Dosing methods described in the literature may use IBW as a method in dosing obese patients.

Adults (age 18 years and older)[3]:

IBW (men) = 50 + (2.3 × height in inches over 5 ft)
IBW (women) = 45.5 + (2.3 × height in inches over 5 ft)

where IBW is in kilograms.

Children (age 1–18 years)[2] under 5-feet tall:

$$\text{IBW} = \frac{\text{height}^2 \times 1.65}{1000}$$

where IBW is in kilograms and height is in centimeters.

Children (age 1–18 years) 5 feet or taller:

IBW (males) = 39 + (2.27 × height in inches over 5 ft)
IBW (females) = 42.2 + (2.27 × height in inches over 5 ft)

where IBW is in kilograms.

REFERENCES

1. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
2. Traub SI, Johnson CE. Comparison of methods of estimating creatinine clearance in children. Am J Hosp Pharm. 1980;37: 195–201.
3. Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm. 1974;8:650–655.

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Appendix B: Common Medical Abbreviations

These are the abbreviations used commonly in medical practice both in verbal communication and in the medical record.

A&O	alert and oriented
A&O×3	awake (or alert) and oriented to person, place, and time
A&O×4	awake (or alert) and oriented to person, place, time, and situation
A&P	active and present; anterior and posterior; assessment and plans; auscultation and percussion
A&W	alive and well
A1c	hemoglobin A1c
AA	aplastic anemia; Alcoholics Anonymous
AAA	abdominal aortic aneurysm
AAO	awake, alert, and oriented
AAO×3	awake and orientated to time, place, and person
ABC	absolute band counts; absolute basophil count; apnea, bradycardia, and cytology; aspiration, biopsy, and cytology; artificial beta cells
Abd	abdomen
ABG	arterial blood gases
ABO	blood group system (A, AB, B, and O)
ABP	arterial blood pressure
ABW	actual body weight
ABx	antibiotics
AC	before meals (*ante cibos*)
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitor
ACLS	advanced cardiac life support
ACS	acute coronary syndromes
ACTH	adrenocorticotropic hormone
AD	Alzheimer disease; right ear (*auris dextra*)
ADA	American Diabetes Association; adenosine deaminase
ADE	adverse drug effect (or event)
ADH	antidiuretic hormone
ADHD	attention-deficit hyperactivity disorder
ADL	activities of daily living
ADR	adverse drug reaction
AF	atrial fibrillation
AFB	acid-fast bacillus; aortofemoral bypass; aspirated foreign body
AFEB	afebrile
AI	aortic insufficiency
AIDS	acquired immune deficiency syndrome
AKA	above-knee amputation; alcoholic ketoacidosis; all known allergies; also known as
AKI	acute kidney injury
ALFT	abnormal liver function test
ALL	acute lymphoblastic leukemia; acute lymphocytic leukemia
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALT	alanine transaminase (SGPT); alanine aminotransferase
AMA	against medical advice; American Medical Association; antimitochondrial antibody
AMI	acute myocardial infarction
AML	acute myelogenous leukemia
Amp	ampule
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANLL	acute nonlymphocytic leukemia
AODM	adult-onset diabetes mellitus
AOM	acute otitis media
AP	anteroposterior
APAP	acetaminophen (acetyl-*p*-aminophenol)
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ARC	AIDS-related complex
ARD	acute respiratory disease; adult respiratory disease; antibiotic removal device; aphakic retinal detachment
ARDS	adult respiratory distress syndrome
ARF	acute renal failure; acute respiratory failure; acute rheumatic fever
AROM	active range of motion
AS	left ear (*auris sinistra*)
ASA	aspirin (acetylsalicylic acid)
ASCVD	arteriosclerotic cardiovascular disease
ASD	atrial septal defect
ASH	asymmetric septal hypertrophy
ASHD	arteriosclerotic heart disease
AST	aspartate transaminase (SGOT); aspartate aminotransferase
ATG	antithymocyte globulin
ATN	acute tubular necrosis
AU	each ear (*auris uterque*)
AV	arteriovenous; atrioventricular; auditory visual
AVR	aortic valve replacement
BBB	bundle branch block; blood–brain barrier
BC	blood culture
BCOP	Board Certified Oncology Pharmacist
BCP	birth control pill
BCPP	Board Certified Psychiatric Pharmacist
BCPS	Board Certified Pharmacotherapy Specialist
BE	barium enema

BG	blood glucose
bid	twice daily (*bis in die*)
BKA	below-knee amputation
BM	bone marrow; bowel movement; an isoenzyme of creatine phosphokinase
BMC	bone marrow cells
BMD	bone mineral density
BMI	body mass index
BMP	basic metabolic panel
BMR	basal metabolic rate
BMT	bone marrow transplantation
BP	blood pressure
BPD	bronchopulmonary dysplasia
BPH	benign prostatic hyperplasia
bpm	beats per minute
BR	bed rest
BS	bowel sounds; breath sounds; blood sugar
BSA	body surface area
BUN	blood urea nitrogen
Bx	biopsy
C&S	culture and sensitivity
CA	cancer; calcium
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CAH	chronic active hepatitis
CAM	complementary and alternative medicine
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CBD	common bile duct
CBG	capillary blood gas; corticosteroid-binding globulin
CC	chief complaint
CCA	calcium channel antagonist
CCB	calcium channel blocker
CCE	clubbing, cyanosis, edema
CCK	cholecystokinin
CCU	coronary care unit
CF	cystic fibrosis
CFS	chronic fatigue syndrome
CFU	colony-forming unit
CHD	coronary heart disease
CHF	congestive heart failure; chronic heart failure
CHO	carbohydrate
CI	cardiac index
CIWA	Clinical Institute Withdrawal Assessment
CK	creatine kinase
CKD	chronic kidney disease
CLL	chronic lymphocytic leukemia
CM	costal margin
CMG	cystometrogram
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
CN	cranial nerve
CNS	central nervous system
C/O	complains of
CO	cardiac output; carbon monoxide
COLD	chronic obstructive lung disease
COPD	chronic obstructive pulmonary disease
CP	chest pain; cerebral palsy
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase (BB, MB, and MM are isoenzymes)
CPP	cerebral perfusion pressure
CPR	cardiopulmonary resuscitation
CrCl	creatinine clearance
CRF	chronic renal failure; corticotropin-releasing factor
CRH	corticotropin-releasing hormone
CRI	chronic renal insufficiency; catheter-related infection
CRNA	Certified Registered Nurse Anesthetist
CRNP	Certified Registered Nurse Practitioner
CRP	C-reactive protein
CRTT	Certified Respiratory Therapy Technician
CSF	cerebrospinal fluid; colony-stimulating factor
CT	computed tomography; chest tube
cTnI	cardiac troponin I
CTZ	chemoreceptor trigger zone
CV	cardiovascular
CVA	cerebrovascular accident
CVC	central venous catheter
CVP	central venous pressure
Cx	culture; cervix
CXR	chest x-ray
CYP	cytochrome P450
D&C	dilatation and curettage
D_5W	5% dextrose in water
DBP	diastolic blood pressure
D/C	discontinue; discharge
DCC	direct-current cardioversion
DI	diabetes insipidus
DIC	disseminated intravascular coagulation
Diff	differential
DJD	degenerative joint disease
DKA	diabetic ketoacidosis
dL	deciliter
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DNR	do not resuscitate
DO	Doctor of Osteopathy
DOA	dead on arrival; date of admission; duration of action
DOB	date of birth
DOE	dyspnea on exertion
DOT	directly observed therapy
DPGN	diffuse proliferative glomerulonephritis
DPI	dry powder inhaler
DRE	digital rectal examination
DRG	diagnosis-related group
DS	double strength
d/t	due to
DTP	diphtheria–tetanus–pertussis
DTR	deep tendon reflex
DVT	deep vein thrombosis
Dx	diagnosis
EBV	Epstein-Barr virus
EC	enteric coated
ECF	extracellular fluid
ECG	electrocardiogram
ECHO	echocardiogram
ECT	electroconvulsive therapy
ED	emergency department
EEG	electroencephalogram
EENT	eyes, ears, nose, throat
EF	ejection fraction
EGD	esophagogastroduodenoscopy
EIA	enzyme immunoassay
ECG	electrocardiogram
EMG	electromyogram
EMT	Emergency Medical Technician
Endo	endotracheal, endoscopy
EOMI	extraocular movements (or muscles) intact
EPO	erythropoietin
EPS	extrapyramidal symptoms
ER	emergency room
ERCP	endoscopic retrograde cholangiopancreatography
ERT	estrogen replacement therapy
ESKD	end-stage kidney disease
ESLD	end-stage liver disease

ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ET	endotracheal
EtOH	ethanol
FB	finger breadth; foreign body
FBS	fasting blood sugar
FDA	Food and Drug Administration
FEF	forced expiratory flow rate
FEV_1	forced expiratory volume in 1 second
FFP	fresh-frozen plasma
FH	family history
FiO_2	fraction of inspired oxygen
FOBT	fecal occult blood test
FPG	fasting plasma glucose
FPIA	fluorescence polarization immunoassay
FSH	follicle-stimulating hormone
FTA	fluorescent treponemal antibody
FT_4	free thyroxine
F/U	follow-up
FUO	fever of unknown origin
Fx	fracture
g	gram
G-CSF	granulocyte colony-stimulating factor
G6PD	glucose-6-phosphate dehydrogenase
GB	gallbladder
GBS	group B *Streptococcus*; Guillain-Barré syndrome
GC	gonococcus
GDM	gestational diabetes mellitus
GE	gastroesophageal; gastroenterology
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	γ-glutamyl transferase
GGTP	γ-glutamyl transpeptidase
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GN	glomerulonephritis; graduate nurse
gr	grain
GT	gastrostomy tube
gtt	drops (*guttae*)
GTT	glucose tolerance test
GU	genitourinary
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
Gyn	gynecology
H&H, H/H	hemoglobin and hematocrit
H&P	history and physical examination
HA	headache
HAART	highly active antiretroviral therapy
HAMD	Hamilton Rating Scale for Depression
HAV	hepatitis A virus
Hb, hgb	hemoglobin
HbAlc	glycosylated hemoglobin (hemoglobin Alc)
HBIG	hepatitis B immune globulin
HBP	high blood pressure
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	hydrocortisone, home care
HCG	human chorionic gonadotropin
HCO_3	bicarbonate
Hct	hematocrit
HCTZ	hydrochlorothiazide
HCV	hepatitis C virus
HD	Hodgkin disease; hemodialysis
HDL	high-density lipoprotein
HEENT	head, eyes, ears, nose, and throat
HF	heart failure
HFA	hydrofluoroalkane
H flu	*Hemophilus influenzae*
HGH	human growth hormone
HH	hiatal hernia
Hib	*Hemophilus influenzae* type b
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HJR	hepatojugular reflux
HLA	human leukocyte antigen; human lymphocyte antigen
HMG-CoA	hydroxy-methylglutaryl coenzyme A
H/O	history of
HOB	head of bed
HPA	hypothalamic–pituitary axis
hpf	high-power field
HPI	history of present illness
HR	heart rate
H_2RA	H_2 receptor antagonist
HRSD	Hamilton Rating Scale for Depression
HRT	hormone-replacement therapy
HS	at bedtime (*hora somni*)
HSV	herpes simplex virus
HTN	hypertension
Hx	history
I&D	incision and drainage
I&O, I/O	intake and output
IBD	inflammatory bowel disease
IBW	ideal body weight
ICD	implantable cardioverter defibrillator
ICP	intracranial pressure
ICS	intercostal space; inhaled corticosteroid
ICU	intensive care unit
ID	identification; infectious disease
IDDM	insulin-dependent diabetes mellitus
IFN	interferon
Ig	immunoglobulin
IgA	immunoglobulin A
IgD	immunoglobulin D
IHD	ischemic heart disease
IJ	internal jugular
IM	intramuscular; infectious mononucleosis
INH	isoniazid
INR	international normalized ratio
IOP	intraocular pressure
IP	intraperitoneal
IPG	impedance plethysmography
IPN	interstitial pneumonia
IRB	institutional review board
ISA	intrinsic sympathomimetic activity
ISH	isolated systolic hypertension
IT	intrathecal
ITP	idiopathic thrombocytopenic purpura
IU	international units (this can be dangerous abbreviation because it may be read as "IV" for "intravenous")
IUD	intrauterine device
IV	intravenous; Roman numeral four; symbol for class 4 controlled substances
IVC	inferior vena cava; intravenous cholangiogram
IVDA	intravenous drug abuse
IVDU	injection drug use; intravenous drug use
IVF	intravenous fluids
IVIG	intravenous immunoglobulin
IVP	intravenous pyelogram; intravenous push
JODM	juvenile-onset diabetes mellitus
JRA	juvenile rheumatoid arthritis
JVD	jugular venous distension
JVP	jugular venous pressure
K	potassium
kcal	kilocalorie

KCl	potassium chloride
KOH	potassium hydroxide
KUB	kidney, ureter, and bladder
KVO	keep vein open
L	liter
LABA	long-acting beta agonist
LAD	left anterior descending; left axis deviation
LAO	left anterior oblique
LBBB	left bundle branch block
LBP	low-back pain
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LE	lower extremity
LES	lower esophageal sphincter
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LLE	left lower extremity
LLL	left lower lobe
LLQ	left lower quadrant (abdomen)
LMD	local medical doctor
LMP	last menstrual period
LMWH	low-molecular-weight heparin
LOS	length of stay
LP	lumbar puncture
LPN	Licensed Practical Nurse
LPT	Licensed Physical Therapist
LR	lactated Ringer's
LS	lumbosacral
LT_4	levothyroxine
LUE	left upper extremity
LUL	left upper lobe
LUQ	left upper quadrant
LUTS	lower urinary tract symptoms
LVH	left ventricular hypertrophy
MAP	mean arterial pressure
MAR	medication administration record
MB-CK	a creatine kinase isoenzyme
mcg	microgram
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	Medical Doctor
MDI	metered-dose inhaler
MDRD	modification of diet in renal disease
MEFR	maximum expiratory flow rate
mEq	milliequivalent
mg	milligram
MHC	major histocompatibility complex
MI	myocardial infarction; mitral insufficiency
MIC	minimum inhibitory concentration
mL	milliliter
MM	multiple myeloma; an isoenzyme of creatine phosphokinase
MMR	measles–mumps–rubella; midline malignant reticulosis
MOM	milk of magnesia
MPV	mean platelet volume
m/r/g	murmur/rub/gallop
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSE	methicillin-resistant *Staphylococcus epidermitis*
MS	mental status; mitral stenosis; musculoskeletal; multiple sclerosis; morphine sulfate
MSE	mental status exam
MSW	Master of Social Work
MTD	maximum tolerated dose
MTX	methotrexate
MVA	motor vehicle accident
MVI	multivitamin
MVR	mitral valve replacement; mitral valve regurgitation
MVS	mitral valve stenosis; motor, vascular, and sensory
N&V	nausea and vomiting
NAD	no acute (or apparent) distress
N/C	noncontributory; nasal cannula
NG	nasogastric
NGT	nasogastric tube; normal glucose tolerance
NIDDM	non–insulin-dependent diabetes mellitus
NIH	National Institutes of Health
NKA	no known allergies
NKDA	no known drug allergies
NHDA	nonketotic hyperosmolar acidosis
NL	normal
NOS	not otherwise specified
NPN	nonprotein nitrogen
NPO	nothing by mouth (*nil per os*)
NS	normal saline solution (0.9% sodium chloride solution); neurosurgery
NSAID	nonsteroidal anti-inflammatory drug
NSR	normal sinus rhythm
NSS	normal saline solution
NTG	nitroglycerin
NT/ND	nontender, nondistended
NVD	nausea/vomiting/diarrhea; neck vein distension; neovascularization of the disk; neurovesicle dysfunction; nonvalvular disease
N&V	nausea and vomiting
NYHA	New York Heart Association
O&P	ova and parasites
OA	osteoarthritis
OB	obstetrics
OCD	obsessive-compulsive disorder
OD	right eye (*oculus dexter*)
OGTT	oral glucose tolerance test
OPV	oral poliovirus vaccine
OR	operating room
OR×1	oriented to time
OR×2	oriented to time and place
OR×3	oriented to time, place, and person
OS	left eye (*oculus sinister*)
OSA	obstructive sleep apnea
OT	occupational therapy
OTC	over the counter
OU	each eye (*oculus uterque*)
P	pulse; plan; percussion; pressure
P&A	percussion and auscultation
P&T	peak and trough
PA	physician assistant; posteroanterior; pulmonary artery
PAC	premature atrial contraction
$Paco_2$	arterial carbon dioxide tension
Pao_2	arterial oxygen tension
PAOP	pulmonary artery occlusion pressure
PC	after meals (*post cibum*)
PCA	patient-controlled analgesia
PCI	percutaneous coronary intervention
PCKD	polycystic kidney disease
PCN	penicillin
PCP	*Pneumocystis carinii* pneumonia (also known as *Pneumocystis jirovecii* pneumonia); pneumocystis pneumonia; primary care physician; phencyclidine
PCWP	pulmonary capillary wedge pressure
PDE	paroxysmal dyspnea on exertion
PE	physical examination; pulmonary embolism
PEEP	positive end-expiratory pressure

PEFR	peak expiratory flow rate
PEG	percutaneous endoscopic gastrostomy; polyethylene glycol
Peg-IFN	pegylated interferon
PERL	pupils equal, reactive to light
PERRLA	pupils equal, round, and reactive to light and accommodation
PERRRLA	pupils equal, round, regular, and reactive to light and accommodation
PET	positron emission tomography
PFT	pulmonary function test
pH	hydrogen ion concentration
PH	past history; personal history; pinhole; poor health; pubic hair; public health
PHx	past history
PharmD	Doctor of Pharmacy
PID	pelvic inflammatory disease
PJD	*Pneumocystis jirovecii* pneumonia (also known as *Pneumocystis carinii* pneumonia)
PKU	phenylketonuria
PMH	past medical history
PMI	past medical illness; point of maximal impulse
PMN	polymorphonuclear leukocyte
PMS	premenstrual syndrome
PND	paroxysmal nocturnal dyspnea
Po	by mouth (*per os*)
Po_2	partial pressure of oxygen
POAG	primary open-angle glaucoma
POD	postoperative day
PPBG	postprandial blood glucose
ppd	packs per day
PPI	proton pump inhibitor
PPN	peripheral parenteral nutrition
PR	per rectum
PRBC	packed red blood cell
PRERLA	pupils round, equal, reactive to light and accommodation
PRN	when necessary, as needed (*pro re nata*)
PSA	prostate-specific antigen
PSH	past surgical history
PST	paroxysmal supraventricular tachycardia
PSVT	paroxysmal supraventricular tachycardia
PT	prothrombin time; physical therapy; patient
PTA	prior to admission; percutaneous transluminal angioplasty
PTCA	percutaneous transluminal coronary angioplasty
PTE	pulmonary thromboembolism
PTH	parathyroid hormone
PTSD	posttraumatic stress disorder
PTT	partial thromboplastin time
PUD	peptic ulcer disease
PVC	premature ventricular contraction
PVD	peripheral vascular disease
PVR	peripheral vascular resistance
PVT	paroxysmal ventricular tachycardia
q	every (*quaque*)
QA	quality assurance
qday	every day (*quaque die*)
QI	quality improvement
qid	four times daily (*quater in die*)
QNS	quantity not sufficient
qod	every other day
QOL	quality of life
QS	quantity sufficient
QTc	corrected QT interval
R&M	routine and microscopic
R&R	rate and rhythm
RA	rheumatoid arthritis; right atrium
RAAS	renin–angiotensin–aldosterone system
RBC	red blood cell
RCA	right coronary artery
RCM	right costal margin
RDA	recommended daily allowance
RDS	respiratory distress syndrome
RDW	red blood cell distribution width
REM	rapid eye movement; recent event memory
RES	reticuloendothelial system
RF	rheumatoid factor; renal failure; rheumatic fever
Rh	rhesus factor in blood
RHD	rheumatic heart disease
RLE	right lower extremity
RLL	right lower lobe
RLQ	right lower quadrant
RML	right middle lobe
RN	Registered Nurse
RNA	ribonucleic acid
R/O	rule out
ROM	range of motion
ROS	review of systems
RPh	Registered Pharmacist
RR	respiratory rate; recovery room
RRR	regular rate and rhythm
RRT	Registered Respiratory Therapist
RSV	respiratory syncytial virus
RT	radiation therapy
RUE	right upper extremity
RUL	right upper lobe
RUQ	right upper quadrant
RVH	right ventricular hypertrophy
S_1	first heart sound
S_2	second heart sound
S_3	third heart sound (ventricular gallop)
S_4	fourth heart sound (atrial gallop)
SA	sinoatrial
SABA	short-acting beta agonist
SAD	seasonal affective disorder
SAH	subarachnoid hemorrhage
Sao_2	arterial oxygen percent saturation
SBE	subacute bacterial endocarditis
SBFT	small bowel follow-through
SBGM	self-blood glucose monitoring
SBO	small bowel obstruction
SBP	systolic blood pressure
SC	subcutaneous; subclavian
SCr	serum creatinine
SEM	systolic ejection murmur
SG	specific gravity
SGOT (AST)	serum glutamic oxaloacetic transaminase (aspartate transaminase)
SGPT (ALT)	serum glutamic pyruvic transaminase (alanine transaminase)
SH	social history
SIADH	syndrome of inappropriate antidiuretic hormone secretion
SIDS	sudden infant death syndrome
SJS	Stevens-Johnson syndrome
SL	sublingual
SLE	systemic lupus erythematosus
SMA-6	sequential multiple analyzer for sodium, potassium, CO_2, chloride, glucose, and BUN
SMA-7	sequential multiple analyzer for sodium, potassium, CO_2, chloride, glucose, BUN, and creatinine

SMA-12	sequential multiple analyzer for glucose, BUN, uric acid, calcium, phosphorous, total protein, albumin, cholesterol, total bilirubin, alkaline phosphatase, SGOT, and LDH
SMA-23	includes the entire SMA-12 plus sodium, potassium, CO_2, chloride, direct bilirubin, triglyceride, SGPT, indirect bilirubin, R fraction, and BUN/creatinine ratio
SMBG	self-monitoring of blood glucose
SNF	skilled nursing facility
SNS	sympathetic nervous system
SOB	shortness of breath; see order book; side of bed
S/P	status post
SPF	sun protection factor
SQ	subcutaneous
SSKI	saturated solution of potassium iodide
SSRI	selective serotonin reuptake inhibitor
STAT	immediately; at once
STEMI	ST-segment elevated myocardial infarction
STD	sexually transmitted disease
SV	stroke volume
SVC	superior vena cava
SVRI	systemic vascular resistance index
SVR	supraventricular rhythm; systemic vascular resistance
SVT	supraventricular tachycardia
SW	social worker
Sx	signs
T	temperature
T_3	triiodothyroxine
T_4	thyroxine
T&A	tonsillectomy and adenoidectomy
T&C	type and crossmatch
TB	tuberculosis
TBG	thyroid-binding globulin
TBI	total-body irradiation; traumatic brain injury
TBW	total body weight
T bili	total bilirubin
TCA	tricyclic antidepressant
TCN	tetracycline
Tdap	tetanus, diphtheria, acellular pertussis vaccine
TEE	transesophageal echocardiogram
TFT	thyroid function test
TG	triglyceride
TIA	transient ischemic attack
TIBC	total iron-binding capacity
tid	three times daily (*ter in die*)
TLC	therapeutic lifestyle changes
TMJ	Temporomandibular joint
TMP-SMX	trimethoprim–sulfamethoxazole
TNTC	too numerous to count
TOD	target organ damage
TPN	total parenteral nutrition
TPR	temperature, pulse, respiration
T PROT	total protein
TSH	thyroid-stimulating hormone
TURP	transurethral resection of the prostate
Tx	treat, treatment
UA	urinalysis, uric acid
UC	ulcerative colitis
UE	upper extremity
UFH	unfractionated heparin
UGI	upper gastrointestinal
UOQ	upper outer quadrant
UPT	urine pregnancy test
URI	upper respiratory infection
USP	United States Pharmacopeia
UTI	urinary tract infection
UV	ultraviolet
VF	ventricular fibrillation
VLDL	very low-density lipoprotein
VO	verbal order
VOD	veno-occlusive disease
V_A/Q	ventilation–perfusion
VRE	vancomycin-resistant Enterococcus
VS	vital signs
VSS	vital signs stable
VT	ventricular tachycardia
VTE	venous thromboembolism
WA	while awake
WBC	white blood cell (count)
W/C	wheelchair
WDWN	well-developed, well-nourished
WHO	World Health Organization
WNL	within normal limits
W/U	workup
yo	year old
y	year

Appendix C: Glossary

2,3-Diphosphoglycerate: A compound in red blood cells that affects oxygen binding to and release from hemoglobin.

Ablation: Destruction of part or all of an organ or structure.

Abscess: Purulent collection of fluid separated from surrounding tissue by a wall consisting of inflammatory cells and adjacent organs.

Acanthosis nigricans: Increased thickness and hyperpigmentation of the outer cell layers of the skin; typically observed at areas of flexure.

Acaricide: A chemical that kills mites and ticks.

Acetylcholine: Neurotransmitter at synapses in the ganglia of the visceral motor system and a variety of sites within the central nervous system.

Achalasia: Disorder in which the esophageal sphincter is impaired, preventing normal swallowing and often causing reflux of contents and a feeling that something is caught in the throat.

Achlorhydria: Absence of free hydrochloric acid in the stomach.

Acinar cells: Cells in the pancreas responsible for the synthesis, secretion, and storage of certain digestive enzymes.

Action potential: A rapid change in the polarity of the voltage of a cell membrane from negative to positive and back to negative; a wave of electrical discharge that travels across a cell membrane.

Acute coronary syndromes: Ischemic chest discomfort at rest most often accompanied by ST-segment elevation, ST-segment depression, or T-wave inversion on the 12-lead electrocardiogram; caused by plaque rupture and partial or complete occlusion of the coronary artery by thrombus. Acute coronary syndromes include myocardial infarction and unstable angina.

Acute respiratory distress syndrome: Diffuse inflammatory condition of the lung resulting in damage of alveoli, surfactant production, innate immune system response, and dysregulation of hemostasis in the pulmonary tract.

Addiction: A primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Characterized by behaviors such as impaired control over substance use, compulsive use, continued use despite harm, and craving.

Adenoma: A non-malignant tumor of the epithelial tissue that is characterized by glandular structures.

Adenomatous polyposis coli: A gene associated with familial adenomatous polyposis, an inherited disorder characterized by the development of myriad polyps in the colon, often occurring in adolescents and young adults ages 15 to 25.

Adjuvant chemotherapy: Treatment given after primary surgical treatment and designed to eliminate any remaining cancer cells that are undetectable, with the goal of improving survival.

Adrenalectomy: Surgical removal of an adrenal gland.

Adverse drug reaction: Any unexpected, unintended, undesired, or excessive response to a medication that requires discontinuing the medication; requires changing the medication; requires modifying the dose (except for minor dosage adjustments); necessitates admission to the hospital; prolongs stay in a health care facility; necessitates supportive treatment; significantly complicates diagnosis; negatively affects prognosis; or results in temporary or permanent harm, disability, or death.

Aeroallergen: Airborne substance that causes an allergic response.

Afterload: The force against which a ventricle contracts that is contributed to by the vascular resistance, especially of the arteries, and by the physical characteristics (mass and viscosity) of the blood.

Ageism: Discrimination against aged persons.

Air embolus: An obstruction in a small blood vessel caused by air that is introduced into a blood vessel and carried through the circulation until it lodges in a smaller vessel.

Akathisia: Motor or subjective feelings of restlessness, often characterized by the urge to move limbs and inability to sit still.

Akinesia: Lack of movement.

Allodynia: Pain that results from a stimulus that does not normally cause pain.

Allogeneic: A transplant taking cells from one person and donating them to another.

Allogeneic hematopoietic stem cell transplant (HSCT): A procedure in which a patient receives hematopoietic stem cells from a genetically similar donor.

Allograft: Tissue or organ transplanted from a donor of the same species but different genetic makeup; recipient's immune system must be suppressed to prevent rejection of the graft.

Allograft survival: After the transplant procedure, when the transplanted organ continues to have some degree of function, from excellent to poor.

Allorecognition: Recognition of the foreign antigens present on the transplanted organ or the donor's antigen presenting cells.

Alopecia: Hair loss.

Ambulatory esophageal reflux monitoring: A telemetry capsule containing a tiny camera is swallowed, or a transnasal catheter is inserted to determine how often reflux is occurring as well as the incidence of abnormal esophageal acid exposure. The telemetry capsule provides about 48 hours of data, whereas the transnasal catheter provides about 24 hours of data.

Amenorrhea: The absence or discontinuation of regular menstrual periods. Abnormal cessation or absence of menses.

Ampulla of Vater: Dilation of the duodenal wall at the opening of the fused pancreatic and common bile ducts.

Amylin: A 37-amino acid polypeptide hormone that is secreted from the β-cells of the pancreas in response to nutrients. Mechanisms of action include slowing gastric emptying, suppressing postmeal glucagon secretion, and suppressing appetite.

Amyloid: Any of a group of chemically diverse proteins that are composed of linear non-branching aggregated fibrils.

Anaerobic: Living in the absence of oxygen.

Anaphylactic/anaphylaxis: Immediate, severe, potentially fatal hypersensitivity reaction induced by an antigen.

Anaphylactoid: An anaphylactic-like reaction, similar in signs and symptoms but not mediated by IgE. The drug causing this reaction produces direct release of inflammatory mediators by a pharmacological effect.

Anastomosis: The connection of two hollow organs to restore continuity after resection. A surgical connection made between two blood vessels.

Androgen deprivation therapy: Agents such as LHRH agonists, GnRH antagonist, and antiandrogens that are used to suppress testosterone levels to that consistent with medical castration (testosterone levels < 50 ng/mL).

Anergy: A reduction or lack of an immune response to a specific antigen.

Aneurysm: A blood-filled bulge which forms in the wall of a weakened blood vessel; if ruptured, may result in bleeding, shock, and/or other negative health outcome including mortality.

Angioedema: Swelling similar to urticaria (hives), but the swelling occurs beneath the skin instead of on the surface. It is characterized by deep swelling around the eyes and lips and sometimes of the hands and feet. If it proceeds rapidly, it can lead to airway obstruction and suffocation, and should therefore be treated as a medical emergency.

Angiogenesis: The formation of new blood vessels. Increased blood flow to deliver nutrients is required for tumor growth.

Angiography: Examination of the blood vessels using x-rays after injection of a radiopaque substance.

Anosmia: Loss of smell.

Anovulatory cycle: A menstrual cycle where ovaries fail to produce, mature, or release egg.

Anterior circulation: Blood supply to the anterior section of the brain supplied by the internal carotid arteries, anterior cerebral artery, and middle cerebral artery.

Anterograde amnesia: Inability to create new memories or recall the recent past.

Anticitrullinated protein antibodies: Autoantibodies directed against cyclic citrullinated peptide, a circular peptide (a ring of amino acids) containing the amino acid citrulline.

Anticoagulant: Any substance that inhibits, suppresses, or delays the formation of blood clots. These substances occur naturally and regulate the clotting cascade. Several anticoagulants have been identified in a variety of animal tissues and have been commercially developed for medicinal use.

Antiprotease: A substance that inhibits the enzymatic activity of a protease.

Aortic dissection: A serious condition in which there is a tear in the wall of the aorta.

Aortic stenosis: A condition in which the aortic valve becomes thickened or calcified leading to a narrowing of the aortic valve opening and restriction of blood flow from the left ventricle.

Aphakic: The absence of a lens in the eye.

Aphasia: Impairment of language affecting the ability to speak and to understand speech.

Aphthous ulcer: A small superficial area of ulceration within the gastrointestinal mucosa, typically found in the oral cavity.

Aplasia cutis: Congenital absence of skin, commonly affecting the scalp.

Apoptosis: Programmed cell death as signaled by the nuclei in normally functioning cells when age or state of cell health and condition dictates. A genetically directed process of cell self-destruction or programed cell death.

Arcuate scotoma: An arc-shaped area of blindness in the field of vision.

Arteriovenous malformation: A tangle of blood vessels, usually in the brain, that results in abnormal connections between arteries and veins; if ruptured, may result in hemorrhage.

Arthrocentesis: Puncture and aspiration of a joint. Certain drugs can be injected into the joint space for a local effect.

Articular: Related to the joints of the body.

Ascites: Accumulation of fluid within the peritoneal cavity.

Asterixis: Involuntary jerking movements, especially in the hands, best demonstrated by having the patient extend their arms in front of them, flex the hands upward, where a subsequent "flapping" can be seen; occurs primarily with various metabolic and toxic encephalopathic conditions, such as hepatic encephalopathy.

Astringent: A substance that causes tissues to constrict, resulting in a drying effect of the skin.

Atelectasis: Decreased or absent air in a partial or entire lung, with resulting loss of lung volume.

Atherosclerosis: Accumulation of lipids, inflammatory cells, and cellular debris in the subendothelial space of the arterial wall.

Atherosclerotic cardiovascular disease: Disease in which plaque builds up in vessels.

Atresia: Congenital absence of a normal opening or normally patent lumen.

Atrophic urethritis: Thinning and inflammation of the vaginal walls secondary to decline in estrogen, experienced by almost 50% of postmenopausal women.

Attenuated: Loss of intensity or virulence.

Aura: Visual, but sometimes sensory, motor, or verbal disturbance, usually occurring before a migraine or seizure.

Auspitz sign: Pinpoint bleeding that occurs when a psoriasis scale or lesion is peeled off of the skin.

Autologous: A transplant using one's own stem cells.

Autologous hematopoietic stem cell transplant (HSCT): A procedure in which hematopoietic stem cells are removed, stored, and then infused into the same patient.

Autoreceptor: Transmitter receptors on or near presynaptic terminals which are sensitive to the transmitter(s) released by the terminal itself.

Avolition: Inability to initiate and persist in goal-directed activities.

Azoospermic: Having no living spermatozoa in the semen, or failure of spermatogenesis.

Bacteremia: Presence of bacteria in the blood.

Barium enema: A diagnostic test using an x-ray to view the lower gastrointestinal tract (colon and rectum) after rectal administration of barium sulfate, a chalky liquid contrast medium.

Barrett esophagus: A change of the normal squamous epithelium of the distal esophagus to a metaplastic, columnar-lined epithelium, usually caused by prolonged exposure of the esophageal mucosa to gastric acid. The condition is associated with an increased risk of developing esophageal cancer.

Basal ganglia: Cluster of nerve cells deep in the brain that coordinate normal movement.

Bence–Jones proteins: Light chained immunoglobulins found in the urine.

β-Hydroxybutyric acid: A ketone body that is elevated in ketosis, is synthesized in the liver from acetyl-CoA, and can be used as an energy source by the brain when blood glucose is low.

β-Lactam allergy: Allergy to the β-lactam family, namely penicillins and cephalosporins, but may also include carbapenems.

β_2 microglobulin: A low molecular weight protein that may be elevated in multiple myeloma.

Bilateral salpingo-oophorectomy: Surgical removal of both ovaries and fallopian tubes.

Bile acids: The organic acids in bile. Bile is the yellowish-brown or green fluid secreted by the liver and discharged into the duodenum where it aids in the emulsification of fats, increases peristalsis, and retards putrefaction.

Biliary sludge: A deposit of tiny stones or crystals made up of cholesterol, calcium bilirubinate, and other calcium salts. The cholesterol and calcium bilirubinate crystals in biliary sludge can lead to gallstone formation.

Biopsy: The removal of cells or tissue for examination.

Bladder hypotonicity: Low elastic tension of the bladder.

Blast: An immature cell.

Blastospores: An asexual reproductive sphore formed by budding, often seen with yeast.

Blood urea nitrogen (BUN): A waste product in the blood produced from the breakdown of dietary proteins. The kidneys filter blood to remove urea and maintain homeostasis; a decline in kidney function results in an increase in BUN.

Body mass index: A calculation utilized to correct weight changes for height and is a direct calculation regardless of gender. It is the result of the weight in kilograms divided by the height in meters squared. If nonmetric measurements are used, it is the result of the weight in pounds multiplied by 703 and then that quantity divided by the product of height in inches squared.

Bouchard nodes: Hard, bony enlargement of the proximal interphalangeal (middle) joint of a finger or toe.

Boutonniere deformity: Joint deformity associated with rheumatoid arthritis that presents as flexion of the proximal interphalangeal joints with hyperextension of the distal interphalangeal joints.

Brachial plexus: Collection of nerves that arises from the spine at the base of the neck from nerves that supply parts of the shoulder, arm, forearm, and hand.

Brachytherapy: A form of radiotherapy where a sealed radiation source is placed inside or next to the area requiring treatment.

Bradycardia: Slower than normal heart rate.

Bronchiectasis: Chronic dilation of bronchi or bronchioles as a result of inflammatory disease or obstruction associated with heavy sputum.

Bullectomy: Surgical removal of one or more bullae (air spaces in the lung measuring more than one centimeter in diameter in the distended state).

Burst suppression: Electroencephalography pattern characterized by electrical brain activity alternating with periods of no activity.

Calcitonin: A hormone produced by the parafollicular cells of the thyroid gland; involved in helping to regulate levels of calcium and phosphate in the blood.

Calculi: An abnormal concretion (or stone) usually found in hollow organs or their passages (eg, kidney stone).

Capillary leak: Loss of intravascular volume into the interstitial space within the body.

Carcinogenesis: Production or origin of cancer.

Carcinoma: A malignant growth that arises from epithelium, found in skin or the lining of body organs. Carcinomas tend to infiltrate into adjacent tissue and spread to distant organs.

Carcinomatosis: Condition of having widespread dissemination of carcinoma (cancer) in the body.

Cardiac cachexia: Physical wasting with loss of weight and muscle mass caused by cardiac disease; a wasting syndrome that causes weakness and a loss of weight, fat, and muscle.

Cardiac index: Cardiac output normalized for body surface area (cardiac index = cardiac output/body surface area).

Cardiac output: The volume of blood ejected from the left side of the heart per unit of time:

Cardiac output (L/min) = Stroke volume (L) × heart rate (1/min)

Cardiac remodeling: Genome expression resulting in molecular, cellular and interstitial changes and manifested clinically as changes in size, shape, and function of the heart resulting from cardiac load or injury.

Cardiomyopathy: Diseases of the heart muscle in which the heart muscle becomes enlarged, thick, or rigid.

Carotid bruit: Abnormal sound heard when auscultating a carotid artery caused by turbulent blood flow, usually due to the presence of atherosclerotic plaques.

Carotids: The two main arteries in the neck.

Castration resistant prostate cancer: Prostate cancer that continues to progress despite suppression of typical hormonal growth signals (ie, despite androgen deprivation that achieves castration levels of testosterone).

Cataplexy: A sudden loss of muscle control with retention of clear consciousness that follows a strong emotional stimulus (eg, elation, surprise, or anger) and is a characteristic symptom of narcolepsy.

Catheterization: Insertion of a tubular medical device into canals, vessels, passageways, or body cavities to permit injection or withdrawal of fluids or to keep a passage open.

Causalgia: Persistent burning pain, allodynia, and hyperpathia following a traumatic nerve lesion.

Cavitary lesions: Gas or fluid filled areas of the lung in the center of a nodule observed through radiographic investigation.

CD4 and CD8: Protein markers predominantly found on the surface of T cells.

Cell-mediated immunity: An immune response that involves activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. Can be independent of antibody action.

Central pain: Pain that results from a lesion or dysfunction in the central nervous system.

Cervicitis: Inflammation of the cervix.

Chemokines: Any of a group of cytokines produced by various cells that stimulate chemotaxis in white blood cells.

Chemoprevention: Clinical application of pharmacologic agents to reduce the risk of developing certain malignancies. Use of drugs, vitamins, or other agents to reduce the risk of or delay the development or recurrence of cancer.

Chemoreceptor trigger zone: Located in the area postrema of the fourth ventricle of the brain. It is exposed to cerebrospinal fluid and blood and is easily stimulated by circulating toxins to induce nausea and vomiting.

Chemosis: Edema of the bulbar conjunctiva.

Cheyne–Stokes respiration: Pattern of breathing with gradual increase in depth (and sometimes in rate) to a maximum, followed by a decrease resulting in apnea; the cycles ordinarily are 30 seconds to 2 minutes in duration, with 5 to 30 seconds of apnea.

Chimeric: An individual, organ, or substance composed of substances with different genetic origins.
Chloasma: Melasma characterized by irregularly shaped brown patches on the face and other areas of the skin, often seen during pregnancy or associated with the use of oral contraceptives.
Chlorpromazine equivalents: Approximate dose equivalent of a first-generation antipsychotic to 100 mg of chlorpromazine (relative potency).
Cholecystitis: Inflammation of the gallbladder.
Cholelithiasis: Formation of stones in the gallbladder (gallstones).
Cholestasis: Reduced or lack of flow of bile, or obstruction of bile flow.
Cholesteatoma: A mass of keratinized epithelial cells and cholesterol resembling a tumor that forms in the middle ear or mastoid region.
Chorea: A type of dyskinesia with rhythmic dance-like movement.
Chronotropic: An effect that influences the rate of rhythmic movements (eg, heart rate).
Chvostek sign: Elicited by tapping on the proximal distribution of the facial nerve (adjacent to the ear). This will produce a brief spasm of the upper lip, eye, nose, or face in hypocalcemic patients.
Chylothorax: The presence of lymphatic fluid (chyle) in the pleural cavity.
Circadian rhythm: 24-hour cycles of behavior and physiology that are generated by endogenous biological clocks (pacemakers).
Cirrhosis: Hepatic fibrosis and regenerative nodules that have destroyed the architecture of the liver, scarring the liver tissues. Progressive scarring of the liver resulting in non-functional hepatocytes.
Clonal expansion: An immunologic response in which lymphocytes stimulated by antigen proliferate and amplify the population of relevant cells.
Closed comedo: A plugged hair follicle of sebum, keratinocytes, and bacteria that remains beneath the surface of the skin. Also referred to as a "whitehead."
Clotting cascade: A series of enzymatic reactions by clotting factors leading to the formation of a blood clot. The clotting cascade is initiated by several thrombogenic substances. Each reaction in the cascade is triggered by the preceding one and the effect is amplified by positive feedback loops.
Clotting factor: Plasma proteins found in the blood that are essential to the formation of blood clots. Clotting factors circulate in inactive forms but are activated by their predecessor in the clotting cascade or a thrombogenic substance. Each clotting factor is designated by a Roman numeral (eg, factor VII) and by the letter "a" when activated (eg, factor VIIa).
Clubbing: Proliferation of soft tissues, especially in the nail bed, which results in thickening and widening of finger and toe extremities.
Coalescence: Fusion of smaller lipid emulsion particles forming larger particles, resulting in destabilization of the emulsion.
Cocoon immunization: Vaccine strategy to protect an infant from disease by vaccinating those with expected close contact.
Cognitive deficit: An impairment in the mental process that affects the way a person interacts with their environment.
Collateral damage: Bacterial resistance to an antimicrobial that occurs when the antimicrobial is being used to treat a separate bacterial infection.
Colonocyte: Cell lining the colonic surface.
Colonoscopy: Visual examination of the colon using a lighted, lens-equipped, flexible tube (colonoscope) inserted into the rectum.
Colony-forming units: The number of microorganisms that form colonies when cultured and is indicative of the number of viable microorganisms in a sample.
Comedolytic: An agent that is able to break up or destroy a comedo.
Comorbidities: Multiple disease states occurring concurrently in one patient.
Complete response: In cancer, disappearance of all targeted lesions.
Complex regimen: Taking medications 3 or more times per day, or 12 or more doses per day.
Computed tomography: Radiography in which a three-dimensional image of a body structure is constructed by computer from a series of plane cross-sectional images made along an axis.
Concreteness: Inability to think in abstract terms. It may be a primary developmental defect or secondary to organic mental disorder or schizophrenia.
Congenital adrenal hyperplasia: A rare inherited condition resulting from a deficiency in cortisol and aldosterone synthesis with resulting excess androgen production. The clinical presentation depends on the variant of the condition but typically manifests as abnormalities in sexual development and/or adrenal insufficiency.
Conidia: Non-motile spores produced by fungi.
Conjunctival injection: Erythema of the conjunctiva.
Conjunctivitis: Inflammation of the conjunctiva.
Conjunctivitis medicamentosa: A drug-induced form of allergic conjunctivitis resulting from overuse of topical ocular vasoconstrictors.
Consolidation: Treatment that is given after cancer has disappeared following the initial therapy. Consolidation therapy is used to kill any cancer cells that may be left in the body.
Contiguous: Spread of infection via direct invasion of adjacent structures.
Continuous positive airway pressure (CPAP): A technique of assisting breathing by maintaining the air pressure in the lungs and air passages constant and above atmospheric pressure throughout the breathing cycle.
Cor pulmonale: Right-sided heart failure caused by lung disease.
Corneal arcus: Accumulation of lipid on the cornea.
Coronary artery bypass graft surgery: Surgical intervention to improve coronary blood flow by removing a vein from the leg and attaching one end to the aorta and the other end to the coronary artery distal to the atherosclerotic plaque. Alternatively, an artery from the inside of the chest wall may be used to bypass the coronary occlusion.
Cosyntropin: A synthetic version of adrenocorticotropic hormone.
Counterirritant: A substance that elicits a superficial inflammatory response with the objective of reducing inflammation in deeper, adjacent structures.
C-peptide: A peptide which is made when proinsulin is split into insulin and C-peptide. They split before proinsulin is released from endocytic vesicles within the pancreas, one C-peptide for each insulin molecule. C-peptide is the abbreviation for "connecting peptide." It is used to determine if a patient has type 1 or type 2 diabetes mellitus.
Creaming: Aggregation of lipid emulsion particles that then migrate to the surface of the emulsion can be reversed with mild agitation.
Creatinine: A waste product in the blood produced from the breakdown of protein by-products generated by muscle in the body or ingested in the diet. The kidneys filter blood to remove creatinine and maintain homeostasis; a decline in kidney function results in an increase in creatinine.

Crepitus: A grating sound or sensation typically produced by friction between bone-on-cartilage or bone-on-bone contact. It is also a crackling chest sound that is heard in pneumonia.

Cross-allergenicity: Sensitivity to one drug with activity to a different drug with a similar chemical structure.

Crypt abscess: Neutrophilic infiltration of the intestinal glands (crypts of Lieberkühn); a characteristic finding in patients with ulcerative colitis.

Cutis laxa: Hypereflacidity of the skin with loss of elasticity.

Cyanosis: A dark blue or purple discoloration of the skin and mucous membranes due to deficient oxygenation of the blood.

Cyclooxygenase: An enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and consists of two isoforms, generally abbreviated COX-1 and COX-2.

Cystitis: Inflammation of urinary bladder.

Cystocele: Herniation of the urinary bladder into the vagina. Herniation is abnormal protrusion of an organ through a defect or natural opening.

Cytokines: Regulatory proteins, such as interleukins and lymphokines, are released by cells of the immune system and act as intercellular mediators in the generation of an immune response. Soluble glycoproteins released by the immune system which act through specific receptors to regulate immune responses.

Cytomegalovirus (CMV) disease: This is the term used when patients who are already infected with CMV present with the classically associated symptoms that resemble a viral infection and may include fever, malaise, arthralgias, and others.

Cytomegalovirus (CMV) infection: This is the term used when a patient has anti-CMV antibodies in the blood, when CMV antigens are detected in infected cells, or when the virus is isolated from a culture.

Debridement: Removal of necrotic tissue to promote wound healing and reduce risk of further infection.

Delayed peak response: The effects of medication take longer than expected to initiate.

Delirium: Transient brain syndrome presenting as disordered attention, cognition, psychomotor behavior, and perception.

Delirium tremens (DTs): Symptom of alcohol withdrawal characterized by hallucinations, delirium, severe agitation, fever, elevations of blood pressure and heart rate, and possible cardiac arrhythmias.

Dematiaceous: Darkly pigmented colored spores or fungal hyphae.

Dennie-Morgan line: A line or fold below the lower eyelids; associated with atopy.

Dermatophyte: Any microscopic fungus that grows on the skin, scalp, and nails.

Desensitization: The process of giving a medication in a controlled and gradual manner, which allows the person to tolerate it temporarily without an allergic reaction.

Desquamation: Peeling or shedding of the epidermis (superficial layer of the skin) in scales or flakes.

Diabetes insipidus: An uncommon disorder that occurs when the kidneys pass an abnormally large volume of urine (3–20 quarts/day of urine versus the typical 1–2 quarts/day) that is dilute and odorless ("insipid"). Unrelated to diabetes mellitus, although both conditions cause frequent urination and constant thirst. Individuals with diabetes insipidus have normal blood glucose levels; however, their kidneys cannot balance fluid in the body.

Diabetic ketoacidosis: A reversible but life-threatening short-term complication primarily seen in patients with type 1 diabetes caused by the relative or absolute lack of insulin that results in marked ketosis and acidosis.

Dialysate: The physiologic solution used during dialysis to remove excess fluids and waste products from the blood.

Dialysis: The process of removing fluid and waste products from the blood across a semi-permeable membrane to maintain fluid, electrolyte, and acid–base balance in patients with kidney failure.

Diaphoresis: Sweating or profuse perspiration, generally as a symptom of a disease or an adverse drug effect.

Diarthrodial joint: A freely moveable joint (eg, knee, shoulder). Contrast with amphiarthrodial joint (a slightly movable joint; eg, vertebral joint) and synarthrodial joint (an unmovable joint; eg, fibrous joint).

Dilated cardiomyopathy: Ability of the heart to pump blood is decreased because the left ventricle is enlarged and weakened.

Diphasic dyskinesia: The motor fluctuations occur while the plasma levodopa concentrations are rising and when they are falling. In each dosing interval the patient may experience improvement, dyskinesia, and improvement (IDI) or dyskinesia, improvement, dyskinesia (DID).

Direct current cardioversion: The process of administering a synchronized electrical shock to the chest, the purpose of which is to simultaneously depolarize all of the myocardial cells, resulting in restoration of normal sinus rhythm.

Directly observed treatment: Method to increase adherence to medications when a patient is observed taking the medication by a health care worker.

Disease-free survival: Period of time from the end of treatment that the patient survives without signs or symptoms of the disease.

Disease progression: In cancer, at least a 20% increase in the sum of the longest diameter of target lesions from baseline, including new lesions discovered during treatment.

Disseminated erythrosquamous papules: Widespread or whole body red, scaly psoriatic lesions.

Disseminated intravascular coagulation (DIC): A thrombotic and hemorrhagic disorder marked by uncontrolled systemic coagulation resulting in thrombosis, which may lead to generalized bleeding due to the depletion of clotting factors and increased fibrinolysis.

DNA mismatch repair (dMMR) genes: Genes that control an intrinsic intracellular mechanism which corrects nucleotide insertion errors made during DNA replication, by excising the mismatched base pairs that escaped correction by the proofreading activities of DNA polymerases and replacing the mismatched bases with the correct ones.

Door-to-needle time: Time from arrival in hospital to drug administration in appropriate patients.

Dose density: The total amount of drug given in a fixed unit of time (usually 1 week), thus is a function of dose and frequency of administration.

D-test: Double disk diffusion microbiological testing which indicates the presence or absence of macrolide-induced resistance to clindamycin.

Ductus arteriosus: Shunt connecting the pulmonary artery to the aortic arch that allows blood from the right ventricle to bypass fetal lungs.

Duodenal enterocyte: Cells lining the duodenum, which is the first of three parts of the small intestine.

Dysarthria: Speech disorder due to weakness or incoordination of speech muscles; speech is slow, weak, and imprecise.

Dysentery: A number of disorders marked by inflammation of the intestines, especially of the colon, and attended by pain in the abdomen, tenesmus, and frequently stools containing blood and mucus.

Dysesthesia: An unpleasant abnormal sensation.

Dyskinesia: Abnormal involuntary movements (dystonia, chorea, and akathisia).

Dyslipidemia: Elevation of the total cholesterol, low density lipoprotein cholesterol or triglyceride concentrations, or a decrease in high density lipoprotein cholesterol concentration in the blood.

Dysmenorrhea: Crampy pelvic pain occurring with or just prior to menses. "Primary" dysmenorrhea implies pain in the setting of normal pelvic anatomy, while "secondary" dysmenorrhea is secondary to underlying pelvic pathology.

Dyspareunia: Pain during or after sexual intercourse.

Dyspepsia: Upper abdominal symptoms that may include pain or discomfort, bloating, feeling of fullness despite little food intake, unusual fullness after meals, nausea, loss of appetite, heartburn, regurgitation of food or acid, and belching.

Dysphagia: Painful or difficult swallowing, accompanied by a sensation of food being stuck in passage.

Dysphonia: Impairment of the voice or difficulty speaking.

Dyspnea: Difficult or labored breathing.

Dystonia: A type of dyskinesia. The movement is slow and twisting. It may be associated with painful muscle contractions or spasms.

Ebstein anomaly: Congenital heart defect in which the opening of the tricuspid valve is displaced towards the apex of the right ventricle.

Eburnation: A condition in which bone or cartilage becomes hardened and denser.

Ecchymosis: Passage of blood from ruptured blood vessels into subcutaneous tissue causing purple discoloration of the skin.

Eclampsia: Seizures associated with high blood pressure.

Ectopic pregnancy: Presence of a fertilized ovum outside of the uterine cavity.

Effector cells: Cells that become active in response to initiation of the immune response.

Ejection fraction: The fraction of the volume present at the end of diastole that is pushed into the aorta during systole.

Electroconvulsive therapy: Administration of electric current to the brain through electrodes placed on the head to induce seizure activity in the brain; used in the treatment of certain mental disorders.

Electroencephalography: The recording of brain waves via electrodes placed on the scalp or cortex.

Embolism: The sudden blockage of a vessel caused by a blood clot or foreign material which has been brought to the site by the flow of blood.

Embolization: The process by which a blood clot or foreign material dislodges from its site of origin, flows in the blood, and blocks a distant vessel.

Empiric: A strategy or treatment administered without definitive evidence of the cause, ie, often at the onset of symptoms or radiological findings.

Endometritis: Inflammation of the endometrium.

Endophthalmitis: Inflammation of intraocular fluid (vitreous and aqueous), usually due to infection.

Endoscopy: Visual inspection of the inside of hollow organs with an endoscope, mainly for diagnostic purposes; refers to procedures such as gastroscopy, duodenoscopy, colonoscopy, and sigmoidoscopy.

Endothelial cell: A single layer of cells surrounding the lumen of arteries.

Endovascular: Procedures involving insertion of a catheter containing medications or instruments into a blood vessel for the treatment of vascular disease.

End-stage liver disease: Liver failure that is usually accompanied by complications such as ascites or hepatic encephalopathy.

Enthesitis: Inflammation of the sites where tendons, ligaments, or fascia attach to bone.

Enuresis: Involuntary discharge of urine.

Eosinophilic asthma: Sub-phenotype of asthma with elevated tissue and sputum eosinophils, thickening of the basement membrane zone, and corticosteroid responsiveness. Criteria that have been used for medications to treat eosinophilic asthma include blood eosinophil count ≥ 150 cells/μL (0.150×10^9/L) or > 300 cells/μL (0.3×10^9/L) (400 cells/μL [0.4×10^9/L] for reslizumab) in the past year, sputum eosinophil count ≥ 3% (0.03), and exhaled nitric oxide concentration ≥ 50 ppb.

Epilepsy: A neurological disorder characterized by recurring motor, sensory, or psychic malfunction with or without loss of consciousness or convulsive seizures.

Epistaxis: Nasal hemorrhage with blood drainage through the nostrils; a nosebleed.

Erosive esophagitis: A severe form of gastroesophageal reflux disease (GERD) in which the mucous membrane lining the esophagus is inflamed with areas of erosion resulting from abnormal reflux of gastric acid.

Erythema nodosum: Inflammation of the fat cells under the skin resulting in termer red nodules or lumps.

Erythematous: Flushing of the skin caused by dilation of capillaries. Erythema is often a sign of inflammation and infection.

Erythrodermic psoriasis: Generalized erythema covering nearly the entire body surface area. Fever and malaise are common and, while quite rare, can be severe and even fatal; it is usually associated with a worsening of other forms of psoriasis.

Erythropoiesis stimulating agents: Agents developed by recombinant DNA technology that have the same biological activity as endogenous erythropoietin to stimulate erythropoiesis (red blood cell production) in the bone marrow.

Erythropoietin: A hormone primarily produced by the progenitor cells of the kidney that stimulates red blood cell production in the bone marrow. Lack of this hormone leads to anemia.

Esophageal manometry: Measurement of pressures and muscle contractions in the esophagus.

Esophageal stricture: Narrowing of the esophageal lumen resulting chronic inflammation and formation of scar tissue.

Esophageal varices: Dilated blood vessels in the esophagus.

Essential fatty acid deficiency: Deficiency of linoleic acid, linolenic acid, and/or arachidonic acid, characterized by hair loss, thinning of skin, and skin desquamation. Long-chain fatty acids include trienes (containing three double-bonds [eg, 5,8,11-eicosatrienoic acid [or Mead acid], trienoic acids]) and tetraenes (containing four double-bonds [eg, arachidonic acid]). Biochemical evidence of essential fatty acid deficiency includes a triene:tetraene greater than 0.2 and low linoleic or arachidonic acid plasma concentrations.

Exanthem: Eruption of the skin.

Excess body weight: Calculated as the difference between actual and ideal body weight.

Exfoliative dermatitis: Severe inflammation and peeling of the entire skin surface due to a reaction to certain drugs.

Exploratory laparotomy: Surgical incision into the abdominal cavity, performed to examine the abdominal organs and cavity in search of an abnormality and diagnosis.

External beam radiotherapy (EBRT): An external source of radiation is pointed at a particular part of the body.

Extraabdominal: Outside of the abdominal cavity.

Extraction ratio: Fraction of the drug entering the liver in the blood which is irreversibly removed.

Extrapyramidal symptoms (EPS): Adverse drug effects of medications such as phenothiazines. EPS include dystonia (involuntary muscle contractions), tardive dyskinesia (repetitive, involuntary movements), and akathisia (motor restlessness or anxiety).

Extravasation: Movement of fluid from inside a blood vessel into the surrounding tissues.

Facultative: An optional biological condition, not required for growth or survival.

Felty syndrome: An extra-articular manifestation of rheumatoid arthritis associated with splenomegaly and neutropenia.

Ferritin: A protein in the body that binds to iron; most of the iron stored in the body is bound to ferritin.

Festination: Walking with short, rapid, shuffling steps.

Fibrin: An insoluble protein that is one of the principal ingredients of a blood clot. Fibrin strands bind to one another to form a fibrin mesh. The fibrin mesh often traps platelets and other blood cells.

Fibrinolysis: A normal ongoing process that dissolves fibrin and results in the removal of small blood clots; hydrolysis of fibrin.

Fibroadenoma: A benign neoplasm which commonly occurs in breast tissue and is derived from glandular epithelium.

Fibrosis: Development of fibrous connective tissue in response to injury or damage.

Fluorescence in situ hybridization (FISH): A laboratory technique used to look at genes or chromosomes in cells and tissues. Pieces of DNA that contain a fluorescent dye are made in the laboratory and added to cells or tissues on a glass slide. When these pieces of DNA bind to specific genes or areas of chromosomes on the slide, they light up when viewed under a microscope with a special light.

Fistula: Abnormal connection between two internal organs (eg, arteriovenous fistula is a connection between an artery and a vein), or between an internal organ and the exterior or skin (eg, enterocutaneous fistula is a connection between the intestine and the skin).

Fistulogram: X-ray photograph (or radiograph) taken after injection of a contrast material or radiopaque material (material that will not allow passage of x-rays and will be visible in an x-ray photograph [or radiograph]).

Flexural psoriasis: Flexural psoriasis is characterized by lesions found in skin folds. These lesions tend to be erythematous plaques and are often found in the axillary, genital, perineal, intergluteal, and inframammary regions. While shiny, smooth, and deep red in color there may be skin fissures and the absence of the silvery scales.

Flight of ideas: A nearly continuous flow of rapid speech and thought that jumps from topic to topic, usually loosely connected.

Floppy iris syndrome: A syndrome of pupillary constriction, flaccid iris, and iris prolapse which can result in intraoperative complications during cataract surgery; associated with use of an α_1 adrenergic antagonist (eg, tamsulosin).

Flow cytometry: A method of measuring the number of cells in a sample, the percentage of live cells in a sample, and certain characteristics of cells, such as size, shape, and the presence of tumor markers on the cell surface. The cells are stained with a light-sensitive dye, placed in a fluid, and passed in a stream before a laser or other type of light. The measurements are based on how the light-sensitive dye reacts to the light.

Foam cell: Lipid-laden white blood cell.

Focal seizures: Seizures that start in a small area of the brain. They may stay localized or spread to involve larger areas or the entire brain.

Forced expiratory volume in the first second (FEV_1): The volume of air that a patient can forcibly exhale in the first second of forced exhalation after taking a maximal breath.

Forced vital capacity: The maximum volume of air that can be forcibly exhaled after taking a maximal breath.

Fraction of exhaled nitric oxide (FeNO): A noninvasive test that, when elevated, is an indicator of inflammation in the airways and likely responsiveness to inhaled corticosteroids.

Fragility fracture: A fracture resulting from a fall from standing height or less amount of trauma.

Frailty: Excess demand imposed upon reduced capacity; a common biological syndrome in the elderly.

Frank-Starling mechanism: Increase in stroke volume in response to an increase in volume of blood filling the heart (ie, end diastolic volume) when all other factors remain constant.

Freezing: A sudden but temporary inability to move.

Fremitus: Vibrations through the chest wall that may be detected through touch (tactile) or heard (vocal) through a stethoscope with certain spoken words (eg, "ninety-nine").

French scale: Scale used to measure external diameter of a feeding tube.

Fructooligosaccharide: Soluble fiber that is fermented by colonic bacteria to short-chain fatty acids (SCFAs).

Gadolinium: An intravenous contrast agent used with magnetic resonance imaging.

Gallstone (cholelithiasis): A solid formation in the gallbladder or bile duct composed of cholesterol and bile salts.

γ-Aminobutyric acid (GABA): An inhibitory neurotransmitter.

Gamma knife: A type of radiosurgery (radiation therapy) machine that acts by focusing low-dosage gamma radiation from many sources on a precise target.

Gastric bypass: A surgical procedure for weight loss that elicits its effectiveness through malabsorption and gastric volume limitation. The procedure involves full partitioning of the proximal gastric segment into a jejunal loop.

Gastritis: Inflammation of stomach lining.

Gastroparesis: A form of autonomic neuropathy involving nerves of the stomach. It may include nausea, vomiting, feeling full, bloating and lack of appetite. It may cause wide fluctuations in blood sugars due to insulin action and nutrient delivery not occurring at the same time.

Gastrostomy: Operative placement of a new opening into the stomach usually associated with feeding tube placement.

Generalized seizures: A seizure where the entire cerebral cortex is involved from the onset of the seizure.

Geniculate nucleus: The portion of the brain that processes visual information from the optic nerve and relays it to the cerebral cortex.

Genotype: The genetic constitution of an individual.

Geriatric syndrome: Age-specific presentations or differential diagnoses, including visual and hearing impairment, malnutrition and weight loss, urinary incontinence, gait impairment and falls, osteoporosis, dementia, delirium, sleep problems, and pressure ulcers; commonly seen conditions in older patients.

Gleason score: System of histological grading used in prostate cancer. Individual scores range from 2 to 5. The two highest scores from each sample are combined for a total score (up to 10). Higher scores indicate higher grade and more aggressive tumor.

Glomerular filtration rate (GFR): The volume of plasma that is filtered by the glomeruli per unit time, usually expressed as mL/min or mL/min/1.73 m^2 (and in some areas in SI units of mL/s or mL/s/m^2), which adjusts the value for body surface area. This is the primary index used to describe overall renal function.

Glomerulonephritis: Glomerular lesions that are characterized by inflammation of the capillary loops of the glomerulus. These lesions are generally caused by immunologic, vascular, or idiopathic diseases and lead to high blood pressure and possible loss of kidney function.

Glucagon: Hormone involved in carbohydrate metabolism that is produced by the pancreas and released when glucose levels in the blood are low. When blood glucose levels decrease, the liver converts stored glycogen into glucose, which is released into the bloodstream. The action of glucagon is opposite of insulin.

Gluconeogenesis: Formation of glucose from precursors other than carbohydrates especially by the liver and kidney using amino acids from proteins, glycerol from fats, or lactate produced by muscle during anaerobic glycolysis.

Glucosuria: Presence of glucose in the urine.

Glutamate: An excitatory amino acid found in the central nervous system.

Glycogenolysis: The process by which glycogen is broken down to glucose in body tissues.

Goiter: An enlargement of the thyroid gland, causing a swelling in the front part of the neck.

Gonioscopy: Examination of the anterior chamber angle. A gonioprism or Goldman lens is used to perform gonioscopic evaluation.

Graft-versus-host disease: A condition that results from donor immune cells attacking the normal tissue of a hematopoietic stem cell transplant recipient.

Graft-versus-tumor effect: An immune response directed at a patient's malignant cells that is the result of donor immune cell activation.

Grandiosity: Exaggerated sense of self-importance, ideas, plans, or abilities.

Granuloma: Organized collection of macrophages designed to wall off a foreign body or infectious pathogen that cannot be eliminated.

Gummatous: A small, soft swelling that is characteristic of the late stages of syphilis and generally occurs in the connective tissue of the liver, brain, testes, and heart.

Gut-associated lymphoid tissue: Lymphoid tissue, including Peyer patches, found in the gut that are important for providing localized immunity to pathogens.

Guttate psoriasis: Characterized by a heavy or light sprinkling of teardrop-like, salmon-pink papules covered with a fine scale. These lesions are found primarily on the trunk and proximal extremities.

Gynecomastia: Excessive development of the breasts in males.

HACEK: Group of fastidious gram-negative bacteria consisting of *Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.

Hashimoto Disease: Condition in which the immune system attacks the thyroid gland; may result in hypothyroidism. Symptoms may include fatigue, weight gain, pale or puffy face, feeling cold, joint and muscle pain, constipation, dry and thinning hair, heavy menstrual flow or irregular periods, depression, a slowed heart rate, and problems getting pregnant and maintaining pregnancy. It occurs more commonly in women than in men.

Health literacy: Degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.

Heberden nodes: Hard, bony enlargement of the distal interphalangeal (terminal) joint of a finger or toe.

Hematemesis: Vomiting blood from gastric or esophageal bleeding; in cirrhosis this is caused by variceal bleeding.

Hematochezia: Passage of stool that is bright red or maroon, usually because of bleeding from the lower gastrointestinal tract.

Hematogenous: Spread of infection via the blood stream.

Hematoma: A localized swelling in an organ or soft tissue that is filled with clotted or partially clotted blood resulting from a break in a blood vessel wall.

Hemiparesis: Weakness on one side of the body.

Hemisensory deficit: Loss of sensation on one side of the body.

Hemithorax: A single side of the trunk between the neck and the abdomen in which the heart and lungs are situated.

Hemoptysis: The expectoration of blood or blood-tinged sputum from the larynx, trachea, bronchi, or lungs.

Heparin-induced thrombocytopenia: A clinical syndrome of IgG antibody production against the heparin-platelet factor 4 complex occurring in approximately 1% to 5% of patients exposed to either heparin or low-molecular weight heparin. Results in excess production of thrombin, platelet aggregation, and thrombocytopenia (due to platelet clumping), often leading to venous and arterial thrombosis, amputation of extremities, and death.

Hepatic encephalopathy: Confusion and disorientation experienced by patients with advanced liver disease due to accumulation of ammonia in the bloodstream.

Hepatic steatosis: Accumulation of fat in the liver.

Hepatocellular carcinoma: Cancer of the liver.

Hepatorenal syndrome: Acute kidney injury occurring in individuals with disease of the liver or biliary tract due to decreased renal blood flow and conditions that damage both organs.

Hepatotoxicity: Toxicity to the liver causing damage to liver cells.

Herd immunity: The resistance to the spread of a contagious disease within a population, if a sufficiently high proportion of the people are immune to the disease, such as through vaccination.

Herniation: Abnormal protrusion of an organ or other structure through a defect or natural opening in a covering, membrane, muscle, or bone (eg, protrusion of the brain through the cranial wall).

Hesitancy: A decrease in the force of the stream of urine usually the result of an obstruction or stricture between the bladder and the external urethral orifice.

Heteroreceptor: A site on a neuron that binds a neurotransmitter other than that released by the neuron.

Heterotopic: Placing a transplanted organ into an abnormal anatomic location.

Heterozygous: Having different alleles at a gene locus.

Hiatal hernia: Protrusion of a portion of the stomach through the esophageal hiatus of the diaphragm.

Hirsutism: Excessive body and facial hair, especially in the female.

Histocompatibility: State of having antigenic similarities that prevent donor hematopoietic stem cells from being rejected by the recipient.

Homeostenosis: Impaired capability to withstand stressors and decreased ability to maintain physiological and psychosocial homeostasis; a state commonly found in elderly.

Homozygous: Having identical alleles at a gene locus.
Hormone receptor-positive: Expression of estrogen and/or progesterone receptors in breast cancer cells.
Hot flashes: A feeling of warmth that is commonly accompanied by skin flushing and mild to severe perspiration.
Human epidermal growth factor receptor type 2 (HER2)-positive: Tumor positivity is defined by immunohistochemistry (3+ when > 10% of the cells harbor complete membrane staining) and FISH (fluorescence in situ hybridization) (if the number of HER2 gene copies is > 6 or the HER2/chromosome 17 ratio is > 2).
Human leukocyte antigens (HLA): Groups of genes found on the major histocompatibility complex that contain cell-surface antigen presenting proteins. The body uses HLA to distinguish between self cells and non-self cells.
Humoral: Relating to the body fluids, especially with regard to immune responses involving antibodies in body fluids as distinct from cells.
Hydrocephalus: A condition marked by accumulation of cerebral spinal fluid in the brain resulting in increased pressure inside the skull.
Hydronephrosis: Swelling of the renal pelvis and calyces of the kidney due to a back-up of urine due to obstruction.
Hyperalgesia: An exaggerated intensity of pain sensation.
Hypercalcemia: Excessive amount of calcium in the blood.
Hypercalciuria: Excessive amount of calcium in the urine.
Hypercapnia: Excessive carbon dioxide in the bloodstream, typically caused by inadequate respiration.
Hypercoagulable state: A disorder or state of excessive or frequent thrombus formation; also known as thrombophilia.
Hyperemesis gravidarum: A rare disorder of severe and persistent nausea and vomiting during pregnancy that can result in dehydration, malnutrition, weight loss, and hospitalization.
Hyperglycemic hyperosmolar nonketotic syndrome: Severe increase in serum glucose concentration without the production of ketones, leading to an increase in serum osmolality and symptoms such as increased thirst, increased urination, weakness, fatigue, confusion, and in severe cases convulsions and/or coma.
Hyperopia: Farsightedness.
Hyperpigmentation: A common darkening of the skin which occurs when an excess of melanin forms deposits in the skin.
Hypertrichosis: Excessive growth of hair.
Hyphae: A long, branching multicellular filamentous form of a fungus.
Hypocretin: A wake-promoting hypothalamic neuropeptide whose deficiency is involved in the pathophysiology of narcolepsy.
Hypogammaglobulinemia: Reduced levels of antibodies.
Hypogonadism: A medical condition resulting from or characterized by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development. Associated with testosterone deficiency resulting from either testicular or pituitary/hypothalamic diseases. Presenting symptoms differ according to the timing of disease onset in relation to puberty.
Hypomimia: Lack of facial expression. Often termed masked face.
Hypophonia: Decreased voice volume.
Hypopituitarism: A clinical disorder characterized by complete or partial deficiency in pituitary hormone production.
Hypoxemia: Deficiency of oxygen in the blood.
Hypoxia: Deficiency of oxygen in body tissues.
Hysterectomy: An operation to remove a woman's uterus.
Immune reconstitution inflammatory syndrome (IRIS): A paradoxical clinical worsening of a known infection or the appearance of a new condition after initiating antiretroviral therapy in HIV-infected patients (or recovery from immunosuppression in non-HIV infected patients).
Immunoassay: A blood test for antibodies to antigens that worsen asthma, such as pollen, mold, or dust mites.
Immunogenicity: Ability of a substance to provoke an immune response.
Immunoglobulin G index: The ratio of immunoglobulin G to protein in the serum or cerebrospinal fluid.
Immunophenotyping: A process used to identify cells, based on the types of antigens or markers on the surface of the cell. This process is used to diagnose specific types of leukemia and lymphoma by comparing the cancer cells to normal cells of the immune system.
Immunotherapy: A type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.
Implantable cardioverter-defibrillator: A device implanted into the heart transvenously with a generator implanted subcutaneously in the pectoral area that provides internal electrical cardioversion of ventricular tachycardia or defibrillation of ventricular fibrillation.
Incretin effect: A greater insulin stimulatory effect after an oral glucose load than that caused by an intravenous glucose infusion. The majority of the effect is thought to be due to glucose-dependent insulinotropic peptide (GIP) and glucagon like peptide-1 (GLP-1). Patients with type 2 diabetes have a significant reduction of the incretin effect, implying that these patients either have decreased concentration of the incretin hormones, or a resistance to their effects. GLP-1 concentrations are reduced in patients with type 2 diabetes in response to a meal, while GIP concentrations are either normal or increased, suggesting a resistance to the actions of GIP, thus making GLP-1 a more logical target for therapeutic intervention.
Induction: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation.
Infantile spasms (West syndrome): A seizure syndrome in infants younger than 1 year. It is characterized by a specific electroencephalogram pattern and spasms or jitters.
Inotropic: Relating to or influencing the force of muscular contractions.
In-stent restenosis: Complex process following stent implantation resulting in smooth muscle cell proliferation within an implanted stent, renarrowing of the arterial lumen, and recurrent ischemia.
Insulin resistance: A decreased response to insulin found before or early in the diagnosis of type 2 diabetes mellitus.
International normalized ratio (INR): The ratio of the patient's clotting time to the clinical laboratory's mean reference value; normalized by raising it to the international sensitivity index (ISI) power to account for differences in thromboplastin reagents. Therefore, INR = (patient's prothrombin time/laboratory's mean normal prothrombin time)^{ISI}.
Interstitial nephritis: An acute inflammation of the kidney, often due to drugs; patients commonly present with fever, rash, and peripheral eosinophilia.
Intraabdominal: Within the abdominal cavity.
Intraarticular: Administered to or occurring in the space within joints.
Intraperitoneal: Within the peritoneal cavity.
Intravesicular: Situated or occurring within the bladder.

Intussusception: The prolapse of part of the intestine into the lumen of an immediately adjoining part. Blood supply to the telescoped region can be compromised leading to necrosis.
Iontophoresis: Introduction of a medication into tissue through use of an electric current.
Ipsilateral: Occurring on the same side.
Ischemia: Deficient supply of blood to a part(s) of the body.
Ischemic penumbra: Ischemic but still viable cerebral tissue. Typically a rim of mild to moderately ischemic tissue in between normally perfused tissue and the area of evolving infarction; may remain viable for several hours.
Jejunal entercocyte: Cells lining the jejunum, a section of the small intestine connecting the duodenum to the ileum.
Jejunostomy: Operative placement of a new opening into the jejunum, usually associated with feeding tube placement.
Jugular venous distention: Assessed with the patient laying at a 45 degree angle, and demonstrating a measurement of the right internal jugular vein that is more than 4 cm above the sternal angle; suggests systemic venous congestion and volume overload.
Juvenile myoclonic epilepsy: An epilepsy syndrome that typically occurs during teenage years and consists of generalized tonic-seizures and myoclonic jerks. Absence seizures may also occur with this syndrome.
Keratinization: The sloughing of epithelial cells in the hair follicle.
Keratinocytes: The predominant cell type in the outermost layer of the skin.
Keratitis: Infection of the cornea.
Keratoconjunctivitis sicca: An eye disease caused by eye dryness, which results from either decreased tear production or increased tear film evaporation. Also known as dry eye syndrome.
Kernicterus: Form of brain damage caused by excessive jaundice.
Ketosis: An abnormal increase of ketone bodies present in conditions of reduced or disturbed carbohydrate metabolism.
Korotkoff sounds: The noise heard over an artery by auscultation when pressure over the artery is reduced below the systolic arterial pressure.
Kyphosis: Abnormal curvature of the spine resulting in protrusion of the upper back; hunchback.
Lactose intolerance: The inability to digest lactose, a sugar found in milk products, resulting in diarrhea, bloating, and gas after ingestion.
Lagophthalmos: Poor closure of the upper eyelid.
Lamina cribrosa: A series of perforated sheets of connective tissue that the optic nerve passes through as it exits the eye.
Laminectomy: A surgical operation to remove the back of one or more vertebrae.
Laparoscopic: Abdominal exploration or surgery employing a type of endoscope called laparoscope.
Laparoscopic adjustable gastric banding: A surgical procedure for weight loss that elicits its effectiveness through gastric volume limitation. The procedure involves inserting a silicone band lined with an inflatable donut-shaped balloon around the neck of the stomach to be filled with isotonic liquid.
Laparotomy: Surgical opening of the abdominal cavity.
Left shift: An increase in the number of immature neutrophils (also referred to as bands). A left shift usually indicates infection or inflammation. The term originated in the days in which lab reports were written by hand and the bands were written on the left-hand side of the lab report. Also known as bandemia.
Lennox–Gastaut syndrome: An epilepsy syndrome that often appears early in life that consists of a distinct electroencephalogram pattern, mild to severe developmental delay, and multiple seizure types.
Lesch–Nyhan syndrome: A rare inherited gene mutation that results in accumulation of abnormally high uric acid levels.
Leukocytoclastic vasculitis: Acute cutaneous vasculitis characterized by purpura (especially of the legs) and histologically by exudation of neutrophils and sometimes fibrin around dermal venules, with extravasation of red blood cells.
Leukopenia: A condition where the number of circulating white blood cells are abnormally low due to decreased production of new cells, possibly in conjunction with medication toxicities.
Lewy bodies: Abnormal deposits of a protein called alpha-synuclein inside some nerve cells.
Lhermitte sign: Tingling or shock-like sensation passing down the arms or trunk when the neck is flexed.
Libido: Sexual drive or desire.
Ligament of Treitz: Landmark in the proximal portion of the jejunum beyond which it is preferred that postpyloric feedings be delivered to minimize aspiration.
Linea nigra: Dark vertical line that appears on the abdomen during pregnancy.
Linear accelerator: A device in which charged particles are accelerated in a straight line by successive impulses from a series of electric fields.
Lipophilic: Having affinity for fatty substances.
Lipoprotein lipase: Enzyme located in the capillary endothelium involved in the breakdown of intravenous lipid emulsion particles.
Livedo reticularis: Purple mottling of the skin.
Lower esophageal sphincter: A manometrically defined zone of the distal esophagus with an elevated basal resting pressure that prevents the reflux of gastric material from the stomach. It relaxes on swallowing to permit the free passage of food into the stomach.
Lymphangitis: Inflammation of lymphatic channels.
Lymphatic: The network of vessels carrying tissue fluids.
Lymphedema: Swelling, primarily in the appendages, caused by a blockage or disruption in the lymphatic system.
Lymphoproliferative: Of or related to the growth of lymphoid tissue.
Magnetic resonance imaging: A form of medical imaging that measures the response of the atomic nuclei of body tissues to high-frequency radio waves when placed in a strong magnetic field, and that produces images of the internal organs.
Major malformation: A defect that has either cosmetic or functional significance to the patient.
Maltodextrin: Easily digestible partially hydrolyzed starch.
Marcocytosis: Enlargement of red blood cells with near-constant hemoglobin concentration.
Mastalgia: Tenderness of the breasts.
Mastodynia: Pain in the breast.
Matrix metalloproteinases: Any of a group of enzymes, normally located in the extracellular space of tissue, that function to break down proteins (eg, collagen) and require zinc or calcium atoms as cofactors for enzymatic activity. Responsible for the degradation of connective tissue.
Meatal stenosis: Narrowing in the opening of the urethra.
Meconium: First intestinal discharge ("stool") of a newborn infant, usually green in color and consisting of epithelial cells, mucus, and bile.
Medication-assisted treatment: The use of medications with counseling and other behavioral therapies for the treatment of substance use disorders.
Melasma: Patchy skin pigmentation or dark skin discoloration, often seen during pregnancy.

Melena: Abnormally dark black, tarry feces containing blood (usually from gastrointestinal bleeding).
Menarche: The first menstrual cycle.
Meninges: Membranes surrounding the brain and spinal cord.
Meningismus: Symptoms similar to meningitis (nuchal rigidity, photophobia, and headache) but not caused by meningitis.
Mesial temporal lobe epilepsy: A common epilepsy syndrome manifested by seizures arising from the mesial temporal lobe of the brain, and is often associated with an anatomical change, described as hippocampal sclerosis.
Mesocortical pathway: A neural pathway that connects the ventral tegmentum to the cortex, particularly the frontal lobes. It is one of the major dopamine pathways in the brain.
Mesothelioma: A benign or malignant tumor affecting the lining of the chest or abdomen. Commonly caused by exposure to asbestos fibers.
Metabolic acidosis: A condition in the blood and tissues that is a consequence of an accumulation of lactic acid resulting from tissue hypoxia and anaerobic metabolism. It may also be caused by a decrease in the concentration of alkaline compounds (typically bicarbonate).
Metabolic syndrome: Constellation of cardiovascular risk factors related to hypertension, abdominal obesity, dyslipidemia, and insulin resistance diagnosed by the presence of at least three of the following criteria: increased waist circumference, elevated triglyceride concentrations, decreased high density lipoprotein (HDL) cholesterol or active treatment to raise HDL cholesterol, elevated blood pressure or active treatment with antihypertensive therapy, or elevated fasting glucose or active treatment for diabetes.
Metastasis: Cancer that has spread from the original site of the tumor.
Methemoglobinemia: A condition caused by elevated levels of methemoglobin in red blood cells, resulting in enhanced oxygen affinity in heme sites and reduced oxygen delivery to tissues; leads to hypoxia, cyanosis, shortness of breath, mental status changes, and dizziness. In severe cases, it can lead to seizures, coma, or death.
Microalbuminuria: Urinary excretion of small but abnormal amounts of albumin. Confirmed spot urine albumin to creatinine ratio of 30 to 300 mg/g (3.4–34 mg/mmol creatinine) is consistent with microalbuminuria. Considered an early sign of chronic kidney disease.
Microcytosis: A condition in which the erythrocytes are smaller than normal.
Micrognathia: Abnormal smallness of the jaws.
Micrographia: Small handwriting.
Microsatellite instability (MSI): The condition of genetic hypermutability that results from impaired DNA mismatch repair (MMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally.
Microvascular: Pertaining to the smaller vessels of the circulatory system such as capillaries, venules, and arterioles.
Microvascular pulmonary emboli: An obstruction in the small blood vessels in the lung caused by material (eg, blood clot, fat, air, foreign body) that is carried through the circulation until it lodges in another small vessel.
Micturition: Act of passing urine.
Minimum inhibitory concentration: The lowest concentration of a drug that visually inhibits the growth of a microorganism.
Minor malformation: Defect that has neither cosmetic nor functional significance to the patient.
Mixed mood features: Symptoms of mania and depression occurring simultaneously or in close juxtaposition. Criteria are either met for a manic/hypomanic episode and there are also at least three symptoms of depression, or criteria are met for a depressive episode with at least three manic/hypomanic symptoms.
Mobilization: A process by which medication(s) are used to promote the release of hematopoietic stem cells from the bone marrow to the peripheral blood for the purpose of collecting a sufficient amount of hematopoietic stem cells for a hematopoietic stem cell transplant.
Moebius syndrome: Rare congenital neurological disorder which is characterized by facial paralysis and affects eye movement.
Monoamine neurotransmitters: Serotonin, norepinephrine, dopamine.
Monoparesis: Slight or incomplete paralysis affecting a single extremity or part of one.
Monosodium urate: A crystallized form of uric acid that can deposit in joints leading to an inflammatory reaction and the signs and symptoms of gout.
Morphology: Structure and form of a cell.
Mucositis: Inflammatory, erosive, and/or ulcerative process inside the mouth, which is usually caused by radiation or chemotherapy.
Multiparity: Condition of having given birth to multiple children.
Muscularis mucosa: The thin layer of smooth muscle found in most parts of the gastrointestinal tract.
Mydriasis: Pupil dilation.
Myelin: A protein and phospholipid sheath that surrounds the axons of certain neurons. Myelinated nerves conduct impulses more rapidly than nonmyelinated nerves.
Myeloablative preparative regimen: Chemotherapy regimens with or without radiation that cause irreversible cytopenias without hematopoietic stem cell support.
Myelodysplastic syndrome: A type of cancer in which the bone marrow does not make enough healthy blood cells (white blood cells, red blood cells, and platelets) and there are abnormal cells in the blood and/or bone marrow.
Myelopathy: A neurologic deficit related to the spinal cord.
Myelosuppression: Reduction in white blood cells, red blood cells, and platelets.
Myocardial infarction: The formation of an infarct, an area of tissue death, due to a local lack of oxygen. Myocardial cell death secondary to prolonged ischemia.
Myocarditis: Inflammation of the heart muscle.
Myoglobinuria: The presence of myoglobin in urine.
Myonecrosis: Necrotic damage to muscle tissue.
Myopathy: Any disease of the muscle causing weakness, pain, and tenderness.
Myringotomy: A surgical incision made in the tympanic membrane to relieve pressure and drain fluid from the middle ear.
Myxedema: Hypothyroidism characterized by a relatively hard edema of subcutaneous tissue, with increased content of proteoglycans in the fluid; characterized by somnolence, slow mentation, dryness and loss of hair, increased fluid in body cavities such as the pericardial sac, subnormal temperature, hoarseness, muscle weakness, and slow return of a muscle to the neutral position after a tendon jerk.
Nail psoriasis: Characterized by pitting, onycholysis, hyperkeratosis, and an oil-drop sign.

Nasal scotoma: An area of blindness in the nasal portion of peripheral vision.
Nasolacrimal occlusion: The closing of the tear duct to decrease systemic absorption of a drug.
Natriuresis: Excretion of sodium in the urine.
Necrotizing enterocolitis: Medical condition seen in premature infants, where portions of the bowel undergo necrosis.
Nelson syndrome: A condition characterized by the aggressive growth of a pituitary tumor and hyperpigmentation of the skin.
Neoadjuvant therapy: Treatment given before the primary modality to downsize the tumor.
Nephrolithiasis: A condition marked by the presence of renal calculi (stones) in the kidney or urinary system.
Nephron: The working unit of the kidney that filters blood to remove fluid, toxins, and drugs. Each kidney contains approximately 1 million nephrons.
Nephrostomy: An artificial opening created between the kidney and the skin which allows for the urinary diversion directly from the upper part of the urinary system (renal pelvis).
Neuritic plaques: Extracellular deposits of amyloid beta with concentration markedly increased in the hippocampus, amygdala, and cerebral cortex. The plaque is thought to be formed through a cascade involving the formation of abnormally folded amyloid beta from amyloid precursor protein.
Neuritis: Inflammation of a nerve.
Neurofibrillary tangles: Aggregates of hyperphosphorylated tau protein which can disrupt cellular function and lead to cellular degeneration and death.
Neuropathic pain: Pain resulting from a lesion or dysfunction of the nervous system.
Neuropathy: An abnormal and usually degenerative state of the nervous system or nerves. Damage to the small and large nerves due to glycation end products, lack of blood and nutrients to the nerves, or chemical imbalances.
Neurotransmitters: Chemicals in the brain that allow the passage of a message between neurons or nerve cells.
Neutralizing antibodies: Antibodies that develop in response to a therapeutic agent that decrease the efficacy of the agent.
Nidus: A place in which something is formed or deposited; often used to refer to the site in which bacteria have lodged and multiply.
Nociception: Encoding and processing of noxious stimuli to the nervous system.
Nociceptors: Receptors for pain caused by injury from physical stimuli (mechanical, electrical, or thermal) or chemical stimuli (toxins); located in the skin, muscles, or in the walls of the viscera.
Nocturia: Urination that occurs during sleep, causing patients to awaken overnight.
Nocturnal polysomnography: Electrophysiologic assessment of human sleep minimally composed of electroencephalogram, electrooculogram, and electromyogram that allows determination of sleep stage, breathing events, and muscle movements.
Nodule: An abnormal small swelling or aggregation of cells in the body. When seen with rheumatoid arthritis, nodules are subcutaneous knobs over bony prominences or extensor surfaces.
Non-rapid eye movement (REM) sleep: A state of usually dreamless sleep that occurs regularly during a normal period of sleep with intervening periods of REM sleep and that consists of four distinct substages and low levels of autonomic physiological activity.
Nonbacterial thrombotic endocarditis: Endocarditis which consists of a sterile or noninfectious vegetation that has developed on the heart valve and may be visible on imaging tests.
Nonmyeloablative preparative regimen: Chemotherapy or chemotherapy/radiation regimens that cause minimal cytopenias and do not require hematopoietic stem cell support for hematopoietic cell recovery.
Nonpolyposis: Absence of polyps.
Nonprotein kilocalorie to nitrogen ratio: Numerical value derived from dividing kilocalories from carbohydrate plus fat by the number of grams of nitrogen in the diet (1 g of nitrogen represent about 6.25 g of protein).
Non–ST-segment elevation myocardial infarction: A type of myocardial infarction that is limited to the sub-endocardial myocardium and is smaller and less extensive than an ST-segment elevation myocardial infarction.
Noradrenergic: Neurons or receptors whose primary neurotransmitter is norepinephrine.
Nuchal rigidity: Inability to flex the neck forward due to neck muscle rigidity.
Nuclear factor kappa B (NF kappa B): Regulates cytokine production.
Nulliparity: Condition of not having given birth to a child.
Nystagmus: Rapid, involuntary movements of the eyes.
Odynophagia: Pain on swallowing solid food and fluids, which is often due to esophageal disease.
Off time: The time when the patient has poor control of their symptoms.
Off-label use: Use of a medication outside the scope of its approved, labeled use.
Oiling out: Continued coalescence of lipid emulsion particles, resulting in irreversible separation of the emulsion (also called "breaking" or "cracking" of the emulsion).
Oligoclonal immunoglobulin G bands: Small discrete bands in the gamma globulin region of fluid electrophoresis.
Oligohydramnios: Decreased amniotic fluid.
Oliguria: Reduced urine output; usually defined as less than 400 mL in 24 hours or less than 0.5 mL/kg/hour.
Omentumectomy: Excision of the double fold of peritoneum attached to the stomach and connecting it with abdominal viscera (omentum).
On time: The time when patient has good control of their symptoms.
Oncogenes: Genes found in the chromosomes of tumor cells whose activation is associated with the initial and continuing conversion of normal cells into cancer cells. Genes that cause transformation of normal cells into cancer cells by promoting uncontrolled cell growth and multiplication leading to tumor formation.
Open comedo: A plugged hair follicle of sebum, keratinocytes, and bacteria that protrudes from the surface of the skin and appears black or brown in color. Also referred to as a "blackhead."
Opsonization: The process by which an antigen is altered so as to become more readily and more efficiently engulfed by phagocytes.
Optic neuritis: Usually monocular central visual acuity loss and ocular/periorbital pain caused by demyelination of the optic nerve.
Oral glucose tolerance test: Used to measure the body's response to glucose; may be used to screen for type 2 diabetes and gestational diabetes.
Orchiectomy: Surgical removal of the testes.
Organification: Binding of iodine to tyrosine residues of thyroglobulin.
Orthopnea: Difficulty in breathing that occurs when lying down and is relieved upon changing to an upright position.

Orthostasis: Characterized by a drop in blood pressure when standing up from sitting or lying down, often causing lightheadedness and dizziness.

Orthostatic hypotension: Occurs when a person's systolic or diastolic blood pressure falls at least 20 mm Hg or 10 mm Hg, respectively, when a person suddenly changes from a lying or a sitting position to a standing position.

Orthotopic: Placing a transplanted organ into the normal anatomic location.

Osmolality: A measure of the number of osmotically active particles per unit solution, independent of the weight or nature of the particle.

Osmolar gap: The difference between the measured serum osmolality and the calculated serum osmolality.

Osteoblasts: Cells that secrete the matrix for bone formation.

Osteoclasts: Cells involved in bone resorption.

Osteomalacia: Softening of the bones.

Osteonecrosis: Death of bone tissue.

Osteopenia: Reduced bone density or mass.

Osteophytes: Bony outgrowths (also called bone spurs) into the joint space.

Osteoporosis: Disease of the bones characterized by a loss of bone tissue, resulting in brittle, weak bones that are susceptible to fracture (porous bones).

Ostomy: Surgical operation where part of the abdominal wall is opened and part of the intestine is connected to the opening for intestinal draining (eg, colostomy, ileostomy).

Otalgia: Ear pain or earache.

Ototoxicity: Damage to the hearing or balance functions of the ear by drugs or chemicals.

Ovulation: Periodic ripening and rupture of mature follicle and the discharge of ovum from the cortex of the ovary.

Palliative care: Pharmacologic and nonpharmacologic therapy to prevent or treat, as early as possible, the symptoms and side effects of the disease and treatment psychological, social, and spiritual problems too; with an overall goal of improving quality of life.

Palpable cord: The presence of an induration (cord) that is palpable, sometimes nodular, along the course of/or within the affected vein. Persistence of this cord when the extremity is raised suggests the presence of thrombus.

Pancolitis: Inflammation that involves the majority of the colon in patients with inflammatory bowel disease; often used interchangeably with extensive disease.

Pancreatic pseudocyst: A cyst-like space not lined by epithelium and contained within the pancreas.

Pancreatitis: Inflammation of the pancreas.

Panhypopituitarism: A clinical disorder characterized by complete deficiency in pituitary hormone production.

Pannus: Inflamed synovial tissue that invades and destroys articular structures. A sheet of inflammatory granulation tissue that invades the joint in rheumatoid arthritis after spreading from the synovial membrane. It eventually leads to fibrous ankylosis.

Papilledema: Swelling of the optic disc caused by increased intracranial pressure.

Paracentesis: Removal of ascitic fluid from the peritoneal space.

Paracentral scotoma: Blind spots near the center of the visual field.

Parasomnia: Undesirable physical or behavioral phenomena that occur predominantly during sleep. The most common parasomnias include sleepwalking, sleep talking, bruxism, enuresis, and REM sleep behavior disorder.

Parenchyma: The functional tissue of an organ as distinguished from connective and supporting tissue.

Parenteral nutrition: Delivery of nutrients via the intravenous route.

Paresthesia: An abnormal sensation, typically tingling or pricking ("pins and needles"), caused chiefly by pressure on or damage to peripheral nerves.

Partial response: In cancer, at least a 30% decrease in the sum of the longest diameter of target lesions from baseline.

Peak expiratory flow (PEF): The maximum flow rate of air leaving the lungs upon forced exhalation. Individualized best measurements are established for each patient using a handheld peak flow meter.

Pelvic inflammatory disease: Inflammation of the endometrium, uterine tubes, and pelvic peritoneum; often due to a sexually transmitted infection.

Percutaneous coronary intervention: A minimally invasive procedure whereby access to the coronary arteries is obtained through either the femoral or radial artery up the aorta to the coronary ostia. Contrast media is used to visualize the coronary artery stenosis using a coronary angiogram. A guidewire is used to cross the stenosis and a small balloon is inflated to break up atherosclerotic plaque and restore coronary artery blood flow. A stent is often deployed at the site to prevent acute closure and restenosis of the coronary artery. Newer stents are coated with antiproliferative drugs, such as paclitaxel, sirolimus, zotarolimus, or everolimus, which further reduce the risk of restenosis of the coronary artery.

Percutaneous endoscopic gastrostomy: Gastric feeding tube placed via endoscopic technique.

Percutaneous endoscopic jejunostomy: Jejunal feeding tube placed via endoscopic technique.

Performance status: An attempt to quantify cancer patients' general well-being and activities of daily life.

Pericarditis: Inflammation of the pericardial sac that surrounds the heart and the roots of the great blood vessels.

Perihilar: Just above the middle of the mediastinal surface and behind the cardiac impression of the lung.

Perimetry: Measurement of the field of vision.

Peripheral artery disease: Atherosclerosis of the peripheral arteries.

Peripheral vascular resistance: The sum of resistance to blood flow by systemic blood vessels.

Peritonitis: Acute inflammatory response of the peritoneal lining to microorganisms, chemicals, irradiation, or foreign-body injury.

Phagocytosis: The process of engulfing and ingesting an antigen by phagocytes.

Pharmacogenomics: The study of inherited genetic variations that dictate different drug responses. Pharmacogenomics explores the ways such variations can be used to predict responses to investigational products and plays an increasingly important role in drug discovery.

Phenotype: The visible or observable properties of an organism that are produced by the interaction of the genotype and the environment.

Pheochromocytoma: A tumor arising from chromaffin cells, most commonly found in the adrenal medulla. The tumor causes the adrenal medulla to hypersecrete epinephrine and norepinephrine resulting in hypertension and other signs and symptoms of excessive sympathetic nervous system activity. The tumor is usually benign but may occasionally be cancerous.

Phlebitis: Inflammation of a blood vessel (eg, vein).

Photochemotherapy: The use of psoralens in addition to ultraviolet rays for patients with a significant amount of body surface area affected (> 10%).
Photodynamic therapy: Treatment with drugs that become active when exposed to light.
Photophobia: Intolerance to bright light.
Phototherapy: The use of ultraviolet rays for patients with a significant amount of body surface area affected (> 10%).
Physical dependence: A state of adaptation that is manifested by a drug-class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.
Pilosebaceous unit: A hair follicle and the surrounding sebaceous glands.
Plaque psoriasis: The most common form of psoriasis and manifests as well-defined, sharply demarcated, erythematous plaques typically covered with silvery scales. These plaques are irregular, round to oval in shape, and are almost always found on the scalp, trunk, buttocks, and limbs.
Plasma cell: Antibody producing cells.
Pleocytosis: Increased cell count, particularly an increase in white blood cells count in a bodily fluid, such as cerebral spinal fluid.
Pleuritis: Inflammation of the lining (pleura) around the lungs.
Pneumatic otoscopy: A diagnostic technique involving visualization of the tympanic membrane for transparency, position, and color, and its response to positive and negative air pressure to assess mobility.
Pneumothorax: A condition that occurs when air leaks into the space between chest wall and lung. The air pocket exerts pressure against the lung causing it, or a portion of it, to "collapse." Often referred to as a collapsed lung.
Polycystic ovary syndrome: Condition in which women have many small cysts on their ovaries that can lead to hormone imbalances and irregular periods.
Polycythemia: An abnormal increase in the number of erythrocytes in the blood.
Polycythemia vera: A hematologic cancer that is slow-growing in which the bone marrow produces excess red blood cells.
Polydipsia: Excessive thirst.
Polymerase chain reaction: A laboratory method used to make many copies of a specific DNA sequence.
Polyphagia: Eating excessively large amounts of food at a meal.
Polypharmacy: Taking multiple medications concurrently.
Polyps: Any growth or mass protruding from a mucous membrane.
Polyuria: Excessive excretion of urine resulting in profuse micturition.
Posterior circulation: Blood supply to the posterior section of the brain through the vertebral, basilar, and posterior cerebral arteries (ie, brainstem, cerebellum, occipital lobe).
Prader–Willi syndrome: A genetic disorder characterized by short stature, mental retardation, low muscle tone, abnormally small hands and feet, hypogonadism, and excessive eating leading to extreme obesity.
Prebiotic: Substance that can be used to nourish beneficial microbes in the gut.
Prediabetes: An asymptomatic but abnormal state that precedes the development of clinically evident diabetes.
Preemptive: Therapy administered prior to evidence of active disease (fever, radiological findings) but based on a positive biomarker or microbiological test.
Preload: The stretched condition of the heart muscle at the end of diastole just before contraction; volume in the left ventricle at the end of diastole estimated by the pulmonary artery occlusion pressure (also known as the pulmonary artery wedge pressure or pulmonary capillary wedge pressure).
Priapism: A prolonged, painful erection lasting more than 4 hours. Considered a medical emergency.
Primary amenorrhea: Absence of menses by age 15 in the presence of normal secondary sexual development or within 5 years of thelarche (if occurs before age 10).
Probiotics: Dietary supplements containing potentially beneficial bacteria that promote health by stimulating optimal mucosal immune responses.
Proctitis: Inflammation confined to the rectum in patients with inflammatory bowel disease.
Proctosigmoiditis: Inflammation involving the sigmoid colon and rectum in patients with inflammatory bowel disease.
Prodrome: A symptom indicating the onset of a disease.
Progenitor: A primitive cell.
Prognostic factors: Biological or clinical markers associated with survival independent of therapy.
Progression-free survival: The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the progression-free survival is one way to see how well a new treatment works.
Prolapse: The dropping, falling, sinking, or sliding of an organ from its normal position or location in the body.
Prophylaxis: Therapy administered in the absence of active disease (fever, radiological findings) or a positive biomarker or microbiological test.
Proptosis: Forward displacement of the eyeball.
Prostaglandin: Any of a large group of biologically active, carbon-20, unsaturated fatty acids that are produced by the metabolism of arachidonic acid through the cyclooxygenase pathway.
Prostate specific antigen (PSA): Protein produced by columnar secretory cells in the prostate that plays a role in the liquefaction of seminal fluid. Serum PSA levels greater than 10 ng/mL are associated with prostate cancer.
Prostatectomy: An operation to remove the prostate gland and tissues surrounding it.
Proctitis: Inflammation of the rectum.
Prostatic hyperplasia: Benign enlargement of the prostate gland.
Prostatism: A syndrome associated with outlet obstruction at the bladder neck, and most commonly caused by benign prostatic hypertrophy.
Protease: Any of numerous enzymes that catalyze the breakdown of proteins.
Protectant: An agent that forms an occlusive barrier between the skin and surrounding moisture.
Proteinuria: The presence of measurable amounts of protein in the urine, which is often indicative of glomerular or tubular damage in the kidney.
Proteoglycan: Any one of a class of glycoproteins of high molecular weight that are found in the extracellular matrix of connective tissue. They are made up mostly of carbohydrate consisting of various polysaccharide side chains linked to a protein and resemble polysaccharides rather than proteins with regard to their properties.
Proteosome: An enzyme complex that degrades intracellular proteins.

Prothrombin time: A measure of coagulation representing the amount of time required to form a blood clot after the addition of thromboplastin to the blood sample; also known as Quick test.

Prothrombotic state: A state of high coagulation of the blood.

Protooncogenes: Normal genes that are present in all normal cells and regulate cell function and replication, and through some genetic alteration caused by carcinogens, change into oncogenes.

Pruritus: Localized or generalized itching due to irritation of sensory nerve endings.

Pseudohyphae: Chains of easily disrupted fungal cells; not a true hypha.

Pseudophakic: Presence of a lens after cataract extraction.

Pseudopolyp: An area of hypertrophied gastrointestinal mucosa that resembles a polyp and contains non-malignant cells.

Psoralens: Compounds that act as photosensitizing compounds.

Psoriatic arthritis: Inflammatory arthropathy associated with psoriasis. This condition is characterized by stiffness, pain, swelling, and tenderness around the joints and ligaments.

Pulmonary artery catheter: An invasive device used to measure hemodynamic parameters directly, including cardiac output and pulmonary artery occlusion pressure; calculated parameters include stroke volume and systemic vascular resistance.

Pulmonary artery occlusion pressure: A hemodynamic measurement obtained via catheter placed into the pulmonary artery used to evaluate patient volume status within the left ventricle.

Pulmonary embolus: An obstruction of the pulmonary artery or one of its branches by material that originated elsewhere in the body. The embolic material is often either thrombus, air, tumor, or adipose tissue.

Pulmonary hypertension: An elevation in the pulmonary arterial pressure that can lead to right ventricular failure and heart failure symptoms.

Pulse oximetry: A noninvasive method of measuring arterial oxygen saturation. A pulse oximeter is a small device placed on a finger or earlobe that reads reflected light from capillary blood and estimates oxygen saturation.

Pulsus paradoxus: A large fall in systolic blood pressure and pulse volume during inspiration or an abnormal variation in pulse volume during respiration in which the pulse becomes weaker with inspiration and stronger with expiration.

Punding: Stereotyped behavior with repetitive movement or actions. An adverse reaction to dopaminergic therapy.

Purified protein derivative: An extract of Mycobacterium tuberculosis used for intradermal injection to determine if a patient has been previously exposed based on immune response.

Purkinje fibers: Specialized myocardial fibers that conduct impulses from the atrioventricular node to the ventricles.

Purpura: A small hemorrhage of the skin, mucous membrane, or serosal surface.

Purulent: Containing, consisting of, or being pus.

Pustular psoriasis: Collection of neutrophils is great enough to be seen clinically. May be generalized or localized. Often characterized by widespread sterile pustules and erythema.

Pyuria: Presence of pus in urine when voided.

Quality indicators: A list of indicators used by long-term care facility administrators and government overseers to identify potential problems in patient care.

Quality of life: Perceived physical and mental health over time.

Radon: A chemically inert, radioactive gaseous element produced by the decay of radium.

Rales: Abnormal rattling or cracking sounds heard when listening to breath sounds through a stethoscope; caused by air passing through fluid in the bronchioles; sign of pulmonary edema.

Rapid cycling: Four or more mood episodes (major depressive, manic, or hypomanic) within 1 year.

Rapid eye movement (REM) sleep: A state of sleep that recurs cyclically several times during a normal period of sleep and that is characterized by increased neuronal activity of the forebrain and midbrain, by depressed muscle tone, and especially in humans by dreaming, rapid eye movements, and vascular congestion of the sex organs.

Receptor editing: A process that occurs during the maturation of B cells, which are part of the adaptive immune system. This process forms part of central tolerance to attempt to change the specificity of the antigen receptor of self-reactive immature B-cells, to rescue them from programmed cell death, called apoptosis.

Rectal prolapse: Externally visible sinking of the rectum through the anal sphincter.

Recurrence: A relapse that occurs after a clear-cut recovery.

Regurgitation: The effortless and nonprojectile passage of refluxed gastric contents into the pharynx or mouth.

Relapse: The return of symptoms, satisfying the full syndrome criteria, after a patient has responded, but prior to recovery.

Remission: Patient has no or minimal symptoms of disease. In the case of cancer, in partial remission, some but not all signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although cancer still may be in the body.

Renin-angiotensin-aldosterone system: The hormonal system controlled mainly by the kidneys and adrenal glands that regulates blood pressure, blood volume, and electrolyte balance.

Resistance-associated substitution: Resistance to a drug resulting in decrease antiviral activity caused by an amino acid change in the viral protein.

Respiratory disturbance index: A summary measure that quantifies the number of apneas, hypopneas, and respiratory effort-related arousals per hour of sleep.

Response: A predefined reduction of symptoms from baseline that generally results in significant functional improvement.

Response inhibition: Ability to stay on task or the ability to think before acting.

Reticulocytes: Immature blood cells that mature into erythrocytes.

Retinopathy: Occurs when the microvasculature nerve layer that provides blood and nutrients to the retina is damaged, and can cause blindness.

Retrograde ejaculation: Semen flows to the bladder instead of the urethra.

Retrograde pyelography: Injection of a radiocontrast agent into the ureters to visualize the ureter and kidney with fluoroscopy or radiography.

Reverse transcriptase: Enzyme that catalyzes the formation of DNA from an RNA template in reverse transcription.

Rhabdomyolysis: Destruction of skeletal muscle.

Rheumatic fever: A rare, acute immune-mediated disease that occurs mainly in children and young adults that is characterized by fever, arthritis, and inflammation of the pericardium and heart valves; it is associated with untreated or undertreated group A streptococcal disease.

Rheumatoid factors: Antibodies reactive with the Fc region of IgG.

Rhonchi: Abnormal, rumbling sounds heard on auscultation of an obstructed airway. They are more prominent during expiration and may clear somewhat on coughing.
Rubefacient: A substance that produces redness of the skin.
Salicylism: A toxic syndrome caused by excessive doses of acetylsalicylic acid (aspirin), salicylic acid, or any other salicylate product. Signs and symptoms may include severe headache, nausea, vomiting, tinnitus (ringing in the ears), confusion, increased pulse, and increased respiratory rate.
Scleritis: Inflammation of the outer layer of the eyeball (sclera).
Scotoma: A spot in the visual field in which vision is absent or deficient.
Secondary amenorrhea: Absence of menses for 3 cycles or 6 months in a previously menstruating woman.
Seizure: A sudden electrical disturbance of the cerebral cortex, when a population of neurons fires rapidly and repetitively for seconds to minutes, and electrical discharges are excessively rapid, rhythmic, and synchronous.
Sentinel lymph node: The first lymph node to which cancer is likely to spread from the primary tumor.
Septic emboli: A detached, traveling intravascular mass of infected tissue. An infected emboli containing the causative organism that breaks off from a vegetation or cardiac foci, which then travels to various areas of the body resulting in significant complications.
Sequestra: A fragment of dead bone detached from healthy bone.
Seropositive: Showing a positive reaction to a test on blood serum for a disease.
Severe myoclonic epilepsy of infancy: Resistant epilepsy that occurs in the first year of life of previously healthy children.
Sialorrhea: Drooling.
Sigmoidoscopy: Visual inspection of the sigmoid colon and rectum with a flexible tube called a sigmoidoscope.
Sleep apnea: The temporary stoppage of breathing during sleep; can be caused by narrowing of the airways resulting from swelling of soft tissue.
Sleep latency: The amount of time it takes to fall asleep.
Sleeve gastrectomy: A surgical treatment for weight loss that involves constructing a small gastric "sleeve" but cutting vertically and removing up to 90% of the stomach.
Slit-lamp biomicroscope: An instrument that allows for the microscopic examination of the cornea, anterior chamber lens, and posterior chamber.
Source control: Removal of primary source of infection through surgery, drainage, or removal of infected material.
Spasticity: Feelings of stiffness and involuntary muscle contractions or sudden movements.
Spirometry: Measurement by means of a spirometer of the air entering and leaving the lungs.
Sputum smear: Microscopic examination on a glass slide of material produced from the lungs usually collected through coughing.
Stable disease: In cancer, neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.
Status epilepticus: Continuous seizure activity lasting more than 5 minutes or two or more seizures without complete recovery of consciousness.
Steatohepatitis: A severe form of liver disease caused by fat deposition in the liver, characterized by hepatic inflammation that may rapidly progress to liver fibrosis and cirrhosis.
Steatorrhea: Passage of fat in large amounts in the feces, due to failure to digest and absorb it.
Steatosis: Infiltration of liver cells with fat.
Stent retriever: Thrombectomy devices used to trap a thrombus between the arterial wall and stent to allow rapid restoration of blood flow. The stent is pulled back to remove the thrombus.
Stenting: Placement of a stent (a metal or plastic tube) to allow blood flow through an artery.
Stevens–Johnson syndrome: A severe expression of erythema multiforme (also known as erythema multiforme major). It typically involves the skin and the mucous membranes, with the potential for severe morbidity and even death.
Stimulant: Any amphetamine or amphetamine-like substance (methylphenidate) that causes an increase in dopaminergic and norepinephrine activity in the brain resulting in lessening of hyperactivity, impulsiveness, and/or inattentiveness.
Stomatitis: Inflammation of mucous membranes in the mouth.
Stricture: An abnormal narrowing of a body passage, especially a tube or a canal.
Stroke volume: The amount of blood ejected from the heart during systole.
ST-segment elevation myocardial infarction: A type of myocardial infarction that typically results in an injury that transects the thickness of the myocardial wall.
Subchondral: Situated beneath and supporting cartilage.
Substance use disorder: The recurrent use of a substance and the pathological pattern of behaviors that result from substance use, including significant impairment in health, disability, or failure to meet obligations at home, work, or school.
Substantia nigra: The area in the brainstem with highly pigmented cells that make dopamine.
Subtrochanteric: Below the trochanter (the bony protrusion at the end of the femur where the hip and thigh muscles attach).
Suspending agent: An additive used in the compounding of oral liquid medications to suspend drug particles throughout a liquid and enables resuspension of particles by agitation (eg, shaking well).
Swan neck deformity: Joint deformity associated with rheumatoid arthritis that presents as flexion of the distal interphalangeal joints with hyperextension of the proximal interphalangeal joints.
Sympathomimetics: Drugs that mimic the effects of stimulating adrenergic sympathetic nerves.
Synechia: Adhesions or abnormal attachment of the iris to another structure. Peripheral anterior synechia refers to occurrence of synechia with the trabecular meshwork.
Synergism: Combination of agents (eg, bacteria, drugs) increasing the activity or severity greater than the sum of the individual effects.
Synovitis: Inflammation of the synovial membrane, often in combination with pain and swelling of the affected joint.
Synovium: The membrane lining the internal surfaces of joints.
Systemic inflammatory response syndrome: A complex pathophysiologic response to an insult such as infection, trauma, burns, pancreatitis, and/or other injuries.
T2-weighted magnetic resonance imaging: A setting of the magnetic resonance imaging machine that shows water and similar fluids such as cerebrospinal fluid as a bright signal.
Tachycardia: An abnormally rapid heart rate.
Tachyphylaxis: Rapidly diminishing response to successive doses of a drug, rendering it less effective.
Tachypnea: Faster than normal respiratory rate.
Tachypneic: Rapid breathing indicated by a rate of greater than 20 breaths per minute.
Tachysystole: More than five contractions in 10 minutes, averaged over a 30-minute window.

Tangentiality: Abandoning one's ideational objective in pursuit of thoughts peripheral to the original goal. Used to describe a thought and speech pattern wherein the individual never gets to the point or answers the question.

Tardive dyskinesia: A chronic disorder of the nervous system characterized by involuntary jerky or writhing movements of the face, tongue, jaws, trunk, and limbs, usually developing as a late occurring side effect of prolonged treatment with antipsychotic drugs.

Targeted therapy: A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells.

Tendinosis: Tendon degeneration without accompanying inflammation.

Tenesmus: Difficulty with bowel evacuation despite the urgency to defecate.

Teratogenic: Causing malformation in the development of the embryo or fetus.

Terminal secretions: The noise produced by the oscillatory movements of secretions in the upper airways in association with the inspiratory and expiratory phases of respiration. It is also known as "death rattle".

Tetany: A condition marked by intermittent muscular spasms, caused by malfunction of the parathyroid glands and a consequent deficiency of calcium.

Thelarche: Onset of breast development.

Third spacing: Fluid moving from the intravascular space into the interstitial or "third" space or into a body cavity.

Thought-blocking: Speech is halted, often in mid-sentence, and then picked up later, usually at another point in the thought process.

Thrombin: An enzyme formed from prothrombin which converts fibrinogen to fibrin and also activates platelets. It is the principal driving force in the clotting cascade.

Thrombocytopenia: A condition whereby the number of circulating platelets are abnormally low due to decreased production of new cells, possibly secondary to medication toxicities.

Thrombocytosis: Increased number of platelets in the blood.

Thrombogenesis: The process of forming a blood clot.

Thrombolysis: The process of enzymatically dissolving or breaking apart a blood clot.

Thrombolytic: An enzyme that dissolves or breaks apart blood clots.

Thrombophlebitis: Inflammation of a blood vessel (eg, vein) associated with the stimulations of clotting and formation of a thrombus (or blood clot).

Thromboplastin: A substance that triggers the coagulation cascade. Tissue factor is a naturally occurring thromboplastin and is used in the prothrombin time test.

Thrombosis: A condition in which blood changes from a liquid to a solid state and produces a blood clot.

Thrombotic thrombocytopenic purpura: Condition characterized by formation of small clots within the circulation resulting in the consumption of platelets and a low platelet count.

Thrombus: Blood clot attached to the vessel wall and consisting of platelets, fibrin, and clotting factors. A thrombus may partially or completely occlude the lumen of a blood vessel compromising blood flow and oxygen delivery to distal tissue.

Thyroglobulin: A thyroid hormone-containing protein, usually stored in the colloid within the thyroid follicles.

Thyroid peroxidase: Enzyme that catalyzes the organification and coupling steps of thyroid hormone synthesis.

Thyroiditis: Inflammation of the thyroid gland.

Thyrotoxicosis: A syndrome caused by elevated levels of thyroid hormone. Thyrotoxicosis is often caused by hyperthyroidism, a condition in which the thyroid gland produces excessive levels of thyroid hormone.

Tocolytic: Medication used to stop premature labor.

Tonometry: A method by which the cornea is indented or flattened by an instrument. The pressure required to achieve corneal indentation or flattening is a measure of intraocular pressure.

Tophi: Collections of monosodium urate crystals that develop in tissues and generally appear as firm nodules under the skin.

Topoisomerase-I: Enzymes that cut one of the two strands of double-stranded DNA, relax the strand, and reanneal the strand.

Torsade de pointes: Very rapid ventricular tachycardia characterized by a gradually changing QRS complex in the electrocardiogram; may change into ventricular fibrillation.

Total abdominal hysterectomy and bilateral salpingo-oophorectomy: Surgical removal of the uterus, fallopian tubes, and ovaries which results in immediate menopause.

Toxic epidermal necrolysis: A life-threatening skin disorder characterized by blistering and peeling of the top layer of skin.

Toxoid: Bacterial toxin which has been inactivated.

Transcranial magnetic stimulation: A technique that involves the use of electrical coils on the head to generate a brief magnetic field which reaches the cerebral cortex.

Transesophageal echocardiogram: Procedure (Doppler ultrasound) used to generate an image of the heart via sound waves, via a probe introduced into the esophagus (rather than the traditional transthoracic view) to obtain a better image of the left atrium.

Transferrin saturation: The ratio of serum iron and total iron-binding capacity, multiplied by 100.

Translocation: Movement of viable bacteria from gastrointestinal tract into other areas of the body.

Transmural: Existing or occurring across the entire wall of an organ or blood vessel.

Transsphenoidal pituitary microsurgery: Surgery through the nasal cavity to access the pituitary gland through the sphenoid bone.

Transthoracic echocardiogram: A Doppler ultrasound to visualize the heart through placing the device on the patient's chest or abdomen; views may be limited by the size of the vegetation or patient's body habitus.

Traveler's diarrhea: An acute infectious diarrhea that afflicts travelers during or immediately upon return and is due to ingestion of contaminated food or beverages resulting in diarrhea and other gastrointestinal symptoms.

Trigeminal neuralgia: A disorder of the fifth cranial (trigeminal) nerve characterized by excruciating paroxysms of pain in the face.

Troponins T or I: Proteins found predominately in the myocardium. Troponin I and T are released into the blood from the myocytes at the time of myocardial cell necrosis secondary to infarction. These biochemical markers become elevated and are used in the diagnosis of myocardial infarction.

Trousseau sign: Elicited by inflating a blood pressure cuff on the patient's upper arm, whereby hypocalcemic patients will experience tetany of the wrist and hand as evidenced by thumb adduction, wrist flexion, and metacarpophalangeal joint flexion.

Trypsin: A proteolytic enzyme formed in the small intestine from trypsinogen by the action of enteropeptidase, which once activated hydrolyzes peptides, amides, and esters.

Tuberoeruptive xanthomas: Small yellow-red raised papules usually presenting on the elbows, knees, back, and buttocks.

Tubulointerstitial: Involving the tubules or interstitial tissue of the kidneys.

Tumor lysis syndrome: A syndrome resulting from cytotoxic therapy, occurring generally in aggressive, rapidly proliferating lymphoproliferative disorders. It is characterized by combinations of hyperuricemia, lactic acidosis, hyperkalemia, hyperphosphatemia, and hypocalcemia.

Tumor suppressor genes: A gene that suppresses growth of cancer cells.

Tympanocentesis: Puncture of the tympanic membrane with a needle to aspirate middle ear fluid.

Tympanostomy tube: Small plastic or metal tube surgically inserted in the eardrum to keep the middle ear aerated and improve hearing in patients with chronic middle ear effusion.

Uhthoff phenomenon: Acute worsening of multiple sclerosis symptoms on exposure to heat because high body temperatures may exceed the capacitance of the demyelinated nerve and conduction may fail.

Ultrasound: An imaging method that uses high-frequency sound waves to produce images of structures within the body.

Unknown-onset seizures: Seizures where the onset (ie, focal or generalized) cannot be determined.

Unstable angina: Pathogenically similar to non-ST segment myocardial infarction but without muscle damage, therefore troponins are not elevated.

Uremia: A condition that results from accumulation of metabolic waste products and endogenous toxins in the body resulting from impaired kidney function. Symptoms of uremia include nausea, vomiting, weakness, loss of appetite, and mental confusion.

Urethral stricture: Narrowing of the urethra.

Urgency: A compelling desire to void, which is difficult to defer.

Uricosuric: Pertaining to, characterized by, or promoting renal excretion of uric acid.

Urticaria: Itchy, raised, swollen areas on the skin, also known as hives.

Uterine tachysystole: Uterine hyperstimulation with frequent contractions, hypertonus and non-reassuring fetal heart rate pattern.

Uveitis: An inflammation of the uvea. Uveal structures include the iris, the ciliary body, and the choroid.

Valsalva maneuver: A forceful attempt at exhalation while keeping the mouth and nose closed.

Valvular heart disease: Damage or defects in one or more of the heart valves, disrupting blood flow into and out of the heart. The most common valves affected are the aortic and mitral valves. Valvular stenosis is a narrowing of the valve opening restricting the forward flow of blood. Valvular regurgitation or insufficiency occurs when there is inadequate closure of the valve leaflets leading to blood "leaking" backward.

Vasculitis: Inflammation of the walls of blood vessels.

Vasomotor symptoms: Menopausal symptoms that include both hot flashes (flushes) and night sweats for which women most commonly seek therapy.

Vasopressors: Medications that cause constriction of blood vessels, increase in vascular resistance, and increase in blood pressure.

Vegetation: Infectious mass comprised of protein, cellular components, and microorganisms attached to the endocardial surface of a heart valve which may be visualized on an echocardiogram.

Ventilation/perfusion ratio (V_A/Q): A comparison of the proportion of lung tissue being ventilated by inhaled air to the rate of oxygenation of pulmonary blood.

Ventricular depolarization: Change in the membrane potential of a ventricular myocyte, resulting in loss of polarization. Under normal conditions, depolarization of ventricular myocytes is followed by ventricular contraction.

Vertigo: Sensation of spinning or feeling out of balance.

Vesicants: Chemotherapy drugs that cause significant tissue damage if extravasation occurs.

Virilization: Production or acquisition of virilism, which is masculine characteristics.

Viscoelastic testing: Point-of-care testing devices utilizing thromboelastography principles to evaluate clot formation and dissolution.

Volvulus: Twisting of the intestine causing obstruction and possible necrosis.

Vulvovaginal atrophy: Thinning of vaginal tissue due to a lack of estrogen stimulation.

Wernicke syndrome: Neurologic condition caused by thiamine deficiency and characterized by mental confusion, ataxia, and ophthalmoplegia.

Wheeze: A high-pitched whistling sound caused by air moving through narrowed airways. Wheezes are usually heard at the end of expiration but may be heard during inspiration and expiration in acute severe asthma.

White coat hypertension: A persistently elevated average office blood pressure of greater than 140/90 mm Hg and an average awake ambulatory reading of less than 135/85 mm Hg.

Wild-type virus: The phenotype of naturally occurring, nonmutated strain of the HIV virus.

Wilson disease: A disorder of copper metabolism, characterized by cirrhosis of the liver and neurological manifestations.

Xanthomas: Firm raised nodules composed of lipid-containing histocytes.

Xerostomia: Unusual dryness of the mouth.

ZAP-70 expression: An intracellular tyrosine kinase found in CLL B-cells.

Zymogen: An inactive protein precursor of an enzyme that is converted into an active form.

Appendix D: Prescription Writing Principles

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According to the International Monetary Systems (IMS) Health Report, 4 billion prescriptions were written and dispensed in the United States in 2016. Seventy-seven percent of those were digital prescriptions.[1] This reflects a need for prescribers and dispensers to fully understand prescriptive privileges and rational prescribing.[2] The following outlines principles of pharmacotherapy, including general considerations of prescribing, rational prescribing of medications, types of prescription orders, safe prescribing practices including the importance of handwriting and electronic prescribing, adverse event reporting, and medication education.

It is essential that the prescriber and dispenser familiarize themselves with professional guidelines, state laws, and federal laws. In addition, they must understand the components of rational prescribing. Table D–1 provides key elements a prescriber should understand as well as useful resources.

TYPES OF PRESCRIPTION ORDERS

Prescription orders can be provided in a variety of ways by authorized prescribers. Outpatient prescriptions may be written, verbally authorized by phone, faxed, or provided via electronic means. All outpatient prescriptions are subject to federal regulations and contain the same basic components. Laws and regulations for outpatient prescription requirements can vary from state to state, so prescribers should be knowledgeable of all applicable laws. The basic components of a prescription are listed below as well as numbered in Figure D–1.[3]

1. Prescriber information: name, address, and phone number
2. Prescriber's signature and prescriptive authority number or Drug Enforcement Administration (DEA) number (if applicable)
3. Patient information: full name and address, and weight and age if appropriate
4. Date the prescription was written
5. Superscription (Rx symbol), meaning "you take" or "recipe"
6. Inscription: medication being prescribed (name of medication, strength, and dose)
7. Signa, sig, or signature: directions to the patient (eg, take one tablet daily)
8. Subscription: dispensing instructions to the pharmacist (number, quantity, or volume to dispense)
9. Number of refills allowed
10. Generic substitution requirement: "DAW (dispense as written)" or "no substitution" if brand name medication only is desired

Further regulations are in place for prescriptions written for controlled substances. In addition to the above elements, prescriptions for controlled substances must also include the patient's full name and address as well as the full name, address, and DEA number of the prescriber. Stricter regulations exist for schedule II-controlled substances compared with schedules III and V. Schedule II prescriptions must be written and can only be provided orally in an emergency situation. However, with advancements in security capabilities of electronic medical records (EMR), the DEA amended this to provide an option to issue schedule II prescriptions electronically. Federal and state rules must be followed. In cases where federal and state laws conflict, the stricter law must be adhered to.[4] Refills are prohibited with schedule II prescriptions.[5] Schedule III and IV prescriptions may be refilled up to five times within 6 months of when the prescription was issued.

Orders listed in the medical record for hospitalized patients are not considered prescriptions and are not subject to the same requirements. Typically medical record orders include:

- Patient identifiers including name, account number
- Prescriber name
- Medication name, dose, route, and frequency of administration
- Date and time of order
- Prescriber signature
- If the order was given verbally, the person reducing the order to writing must sign the order and the ordering provider countersign.

Electronic prescribing has become common practice because of government incentives aimed at moving health records to electronic databases with the goal of improving health care processes.[6] Principles discussed previously in regard to requirements of a prescription hold true for electronic orders; however, additional considerations must be taken to ensure safe prescribing habits. A brief list of potential barriers and benefits is summarized in Table D–2.

Electronic prescribing is no longer a projection of the future but instead is becoming the norm. With appropriate use of this technology, patients are provided with safer and more efficient care.

Omission of any of the above-discussed elements on a prescription order can be considered erroneous and poses a danger to patient care. Responsibility lies with the prescriber as well as the pharmacist dispensing the medication to ensure prescriptions are accurate and appropriate for each patient.

Table D–1

Pharmacotherapy Principles

Pharmacotherapy Principle	Description	Online Resources
Prescriptive privileges	Dictated by federal and state law Scope of practice and formularies vary by profession. Physicians, nurse practitioners, physician assistants, and dentists all have varying scopes of practice, which may include formularies or supervising prescribers. Each provider must become familiar with his or her profession's scope of practice. Pharmacology courses in program of study and continuing education required	
	Prescribing legend drugs requires board examination and National Provider Identifier (NPI)	https://nppes.cms.hhs.gov/NPPES/Welcome.do
	Prescribing controlled substances requires DEA registration number	http://www.justice.gov/dea/
Rational prescribing	Ensure necessity of medication Obtain pertinent history • Health history: comorbidities or contraindications (ie, pregnancy, hepatic failure, or renal failure) • Medication history: prior and current prescription, OTC, or herbal use; drug allergies or sensitivities; compliance issues • Family and social history	
	Select correct medication • It is important to know the following components of each medication when prescribing or dispensing: • Pharmacokinetics • Pharmacodynamics • Drug interactions • Drug-disease interactions • Interdisciplinary collaboration when necessary	http://www.jointcommission.org/

DEA, Drug Enforcement Administration; OTC, over the counter.

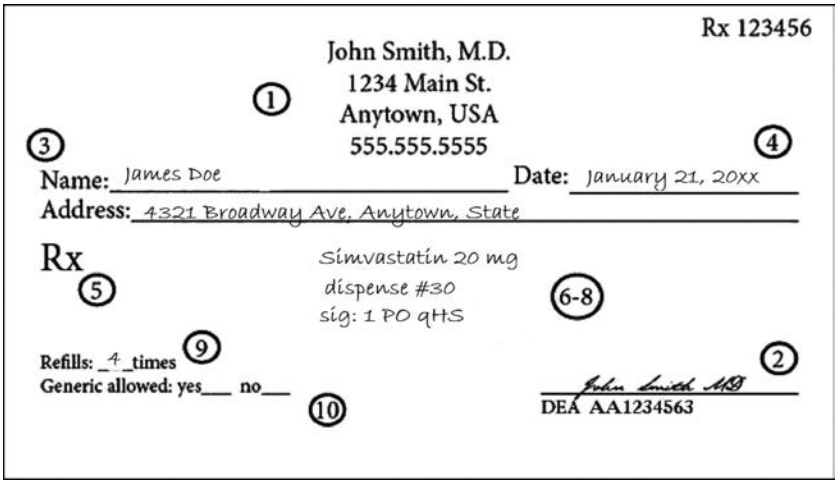

FIGURE D–1. Example of a prescription.

Table D–2

Electronic Prescribing[7-9]

Benefits	Barriers
Reduce medication errors	Cost of software programs
Reduce adverse drug events	Lack of financial benefit seen immediately
Improves efficiency	Lack of software standardization
Improved recognition of drug–drug and drug–disease interactions	Indirect costs: training personnel, reduced patient visits during training period
Improved recognition of medication allergy cross-sensitivity	Clinician resistance: worry of worsening relationship with patient, negative impact on workflow, and fears of restrictions on prescribing habits
Enhanced prescriber knowledge of patient adherence	
Enhanced prescriber knowledge of insurance coverage for medications	

SAFE PRESCRIBING PRACTICES

Safe prescribing should be a priority of all healthcare providers. To avoid inappropriate use of medications, prescribers should take careful consideration in writing clear and descriptive prescriptions. This ensures appropriate communication among the interdisciplinary health care team.

A thorough understanding of the medication prescribed, including its expected risks and benefits, should be realized by the prescriber ensuring appropriate drug selection. Providers must also be able to recognize and avoid common errors related to prescription writing. These errors include sound-alike/look-alike medications and inappropriate use of shorthand language and abbreviations. The Joint Commission, as well as the Institute for Safe Medication Practices (ISMP), has collected common examples of these errors seen during the ordering process. Common examples are described in Tables D–3 and D–4.

Table D–3

Sound-Alike/Look-Alike Medications[10,a]

Medication Name	Misinterpreted Medication Name
acetoHEXAMIDE	aceta**ZOLAMIDE**
chlordiazePOXIDE	chlorpro**MAZINE**
CISplatin	**CARBO**platin
ePHEDrine	**EPINEPH**rine
hydrALAZINE	hydr**OXY**zine
LORazepam	**ALPRAZ**olam
NIFEdipine	ni**CAR**dipine
RABEprazole	**ARIP**iprazole
risperiDONE	r**OPINIR**ole
sulfADIAZINE	sulfa**SALA**zine
valACYclovir	val**GAN**ciclovir
Zantac	Xanax

[a]For additional information, please see http://www.ismp.org/tools/confuseddrugnames.pdf.

Table D–4

Error-Prone Abbreviations[10,a]

Abbreviation	Anticipated Meaning	Misinterpretation	Correction
µg	Microgram	Mistaken as "mg"	Use "mcg"
IJ	Injection	Mistaken as "IV" or "intrajugular"	Use "injection"
q.d. or QD	Every day	Mistaken as q.i.d., especially if the period after the "q" or the tail of the "q" is misunderstood as an "i"	Use "daily"
U	Units	May appear as a µ or 0	Use "units"
IU	International Units	IV (intravenous)	Use "units"
bid, tid, qid	Twice daily, three times daily, four times daily	Depending on handwriting, may be misinterpreted a number of ways	Write out the words "twice daily," etc
biw, tiw, qiw	Twice weekly, three times weekly, four times weekly	Two times per day, three times per day, four times per day	Write out the words "twice weekly," etc
Dose Designation	**Anticipated Meaning**	**Misinterpretation**	**Correction**
Trailing zero after decimal point (eg, 4.0 mg)	4 mg	Mistaken as 40 mg if the decimal point is not seen	Do not use trailing zeros for doses expressed in whole numbers
No leading zero before a decimal point (eg, .8 mg)	0.8 mg	Mistaken as 8 mg if the decimal point is NOT seen	Use zero before a decimal point when the dose is less than a whole unit
Large doses without properly placed commas (eg, 100,000 units;1000000 units)	100,000 units 1,000,000 units	100,000 has been mistaken as 10,000 or 1,000,000; 1,000,000 has been mistaken as 100,000	Use commas for dosing units at or above 1000 or use words such as 100 "thousand" or 1 "million" to improve readability
Drug Name Abbreviation	**Anticipated Meaning**	**Misinterpretation**	**Correction**
AZT	Zidovudine (Retrovir)	Mistaken as azathioprine or aztreonam	Use complete drug name
MS, MSO_4	Morphine sulfate	Mistaken as magnesium sulfate	Use complete drug name
PCA	Procainamide	Mistaken as patient-controlled analgesia	Use complete drug name
T3	Tylenol with codeine No. 3	Mistaken as liothyronine	Use complete drug name
Stemmed Drug Names	**Anticipated Meaning**	**Misinterpretation**	**Correction**
"Nitro" drip	Nitroglycerin infusion	Mistaken as sodium nitroprusside infusion	Use complete drug name
"IV Vanc"	Intravenous vancomycin	Mistaken as Invanz	Use complete drug name
Symbol	**Anticipated Meaning**	**Misinterpretation**	**Correction**
×3d	For 3 days	Mistaken as three doses	Use "for 3 days"
&	And	Mistaken as "2"	Use "and"
°	Hour	Mistaken as a zero (eg, q2° seen as q 20)	Use "hr," "h," or "hour"

[a]For additional information, please see https://www.ismp.org/Tools/errorproneabbreviations.pdf.

Other commonly used medical abbreviations used in prescription writing can be found in Appendix B: Common Medical Abbreviations.

Adverse Event Reporting

Adverse events may occur related to inappropriate prescribing, dispensing, or administering medications. Inappropriate prescribing may be avoided by ensuring care is taken to determine all pertinent patient-related issues are discussed during the encounter. Additionally, appropriate interdisciplinary care where multiple health care providers are evaluating and treating the patient's problem may help avoid adverse events from occurring. Inappropriate dispensing and administration may be avoided through use of clear order entry that undergoes multiple checks by a variety of providers before a prescription reaches the patient. Movement to electronic prescribing has helped eliminate many issues with misinterpreting handwritten orders; however, should they still be encountered, providers should take care to very legibly write prescriptions. If any questions remain upon receipt of a questionable order, verification should occur with the writing provider by the dispensing pharmacist. If adverse events related to medication use are determined, the health care provider who discovers the event is responsible for reporting it. The Food and Drug Administration's reporting system for such adverse events is MedWatch https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home.[11] This online database archives medication-related adverse events, and providers are able to report errors seen in clinical practice.

Medication Education

After a prescription has been written, counseling patients on newly prescribed therapies is an essential responsibility of the prescriber and pharmacist. The patient should be made aware of the rationale for drug use, the dose, route, and frequency at which they should administer the medication and expectations of the prescribed drug. Expectations should include risks and benefits to avoid patient confusion about side effects or efficacy measures. Thorough discussion with the patient about the selected medication therapy may identify contraindications previously unknown or a patient history of failure or success with the selected agent in the past.

CONCLUSION

Multiple principles must be exercised for appropriate drug delivery from the bedside to the patient. As a health care provider, understanding these processes helps to ensure safe medication prescribing.

REFERENCES

1. Volume of electronic prescriptions continues to rise. Medscape. Available from: https://www.medscape.com/viewarticle/867572. Accessed December 5, 2017.
2. Total number of retail prescription drugs filled at pharmacies. Kaiser Family Foundation. Available from: www.kff.org/health-costs/state-indicator/total-retail-rx-drugs/?currentTimeframe=0&sortModel=%7B"colId":"Location","sort":"asc"%7D. Accessed July 27, 2017.
3. Enz SL, Ockerman AV. The prescription. In: Allen LV, ed. Remington: The Science and Practice of Pharmacy, 22nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013: 1955–1970.
4. Electronic prescribing for controlled substances. U.S. Department of Justice Drug Enforcement Administration Diversion Control Division. Available from: https://www.deadiversion.usdoj.gov/ecomm/e_rx/index.html. Accessed December 5, 2017.
5. Section IX—Valid prescription requirements. Office of Diversion Control. Available from: http://www.deadiversion.usdoj.gov/pubs/manuals/pharm2/pharm_content.htm. Accessed July 27, 2017.
6. Slight SP, Berner ES, Galanter W, et al. Meaningful use of electronic health records: experiences from the field and future opportunities. Eysenbach G, ed. JMIR Med Inform. 2015;3(3):e30.
7. Lapane KL, Rosen RK, Dube C. Perceptions of e-prescribing efficiencies and inefficiencies in ambulatory care. Intern J Med Informatics. 2011;80 39–46.
8. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: asystematic review. J Am Med Informatics Assn. 2008;15:585–600.
9. ISMP's list of confused drug names. Institute of Safe Medication Practices:©2014 Available from: https://www.ismp.org/recommendations/confused-drug-names-list. Accessed July 22, 2018.
10. ISMP's list of error-prone abbreviations, symbols, and dose designations. Institute of Safe Medication Practices:©2013 Available from: http://ismp.org/tools/errorproneabbreviations.pdf. Accessed July 27, 2017.
11. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. U.S. Food and Drug Administration. ©2011. Available from: http://www.fda.gov/Safety/MedWatch/default.htm. Accessed July 27, 2017.

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Common Laboratory Tests

The following table is an alphabetical listing of some common laboratory tests and their reference ranges for adults as measured in plasma or serum (unless otherwise indicated). Reference values differ among laboratories, so readers should refer to the published reference ranges used in each institution. For some tests, both the Système International Units and Conventional Units are reported.

Laboratory Test	Conventional Units	Conversion Factor	Système International Units
Acid phosphatase			
Male	2–12 U/L	16.7	33–200 nkat/L
Female	0.3–9.2 U/L	16.7	5–154 nkat/L
Activated partial thromboplastin time (aPTT)	25–40 seconds		
Adrenocorticotropic hormone (ACTH)	15–80 pg/mL or ng/L	0.2202	3.3–17.6 pmol/L
Alanine aminotransferase (ALT, SGPT)	7–53 U/L	0.01667	0.12–0.88 µkat/L
Albumin	3.5–5.0 g/dL	10	35–50 g/L
Albumin:creatinine ratio (urine)		0.113	
Normal	< 30 mg/g creatinine		< 3.4 mg/mmol creatinine
Microalbuminuria	30–300 mg/g creatinine		3.4–34 mg/mmol creatinine
Proteinuria	> 300 mg/g creatinine		> 34 mg/mmol creatinine
or	or		
Normal			
Male	< 18 mg/g creatinine	0.113	< 2.0 mg/mmol creatinine
Female	< 25 mg/g creatinine	0.113	< 2.8 mg/mmol creatinine
Microalbuminuria			
Male	18–180 mg/g creatinine	0.113	2.0–20 mg/mmol creatinine
Female	25–250 mg/g creatinine	0.113	2.8–28 mg/mmol creatinine
Proteinuria			
Male	> 180 mg/g creatinine	0.113	> 20 mg/mmol creatinine
Female	> 250 mg/mmol creatinine	0.113	> 28 mg/mmol creatinine
Alcohol			
See under Ethanol			
Aldosterone			
Supine	< 16 ng/dL	27.7	< 444 pmol/L
Upright	< 31 ng/dL	27.7	< 860 pmol/L
Alkaline phosphatase			
10–15 years	130–550 IU/L	0.01667	2.17–9.17 µkat/L
16–20 years	70–260 IU/L	0.01667	1.17–4.33 µkat/L
> 20 years	38–126 IU/L	0.01667	0.63–2.10 µkat/L
α-Fetoprotein (AFP)	< 15 ng/mL	1	< 15 mcg/L
α-1-Antitrypsin	80–200 mg/dL	0.01	0.8–2.0 g/L
Amikacin, therapeutic			
Peak	15–30 mg/L	1.71	25.6–51.3 µmol/L
Trough	≤ 8 mg/L	1.71	≤ 13.7 µmol/L
Amitriptyline	80–200 ng/mL or mcg/L	3.605	288–721 nmol/L
Ammonia (plasma)	15–56 mcg/dL	0.5872	9–33 µmol/L
Amylase	25–115 U/L	0.01667	0.42–1.92 µkat/L
Androstenedione	50–250 ng/dL	0.0349	1.7–8.7 nmol/L
Angiotensin-converting enzyme	15–70 units/L	16.67	250–1167 nkat/L
Anion gap	7–16 mEq/L	1	7–16 mmol/L
Anti–double-stranded DNA (anti-ds DNA)	Negative		
Anti-HAV	Negative		
Anti-HBc	Negative		
Anti-HBs	Negative		
Anti-HCV	Negative		
Anti-Sm antibody	Negative		
Antinuclear antibody (ANA)	Negative		
Apolipoprotein A-1			
Male	95–175 mg/dL	0.01	0.95–1.75 g/L
Female	100–200 mg/dL	0.01	1.0–2.0 g/L
Apolipoprotein B			
Male	50–110 mg/dL	0.01	0.5–1.10 g/L
Female	50–105 mg/dL	0.01	0.5–1.05 g/L
Aspartate aminotransferase (AST, SGOT)	11–47 IU/L	0.01667	0.18–0.78 µkat/L
β_2-Microglobulin	< 0.2 mg/dL	10	< 2 mg/L
Bicarbonate	22–26 mEq/L	1	22–26 mmol/L
Bilirubin			
Total	0.3–1.1 mg/dL	17.1	5.1–18.8 µmol/L
Direct	0–0.3 mg/dL	17.1	0–5.1 µmol/L
Indirect	0.1–1.0 mg/dL	17.1	1.7–17.1 µmol/L
Bleeding time	3–7 minutes	60	180–420 seconds
Blood gases (arterial)			
pH	7.35–7.45	1	7.35–7.45
PO_2	80–105 mm Hg	0.133	10.6–14.0 kPa
PCO_2	35–45 mm Hg	0.133	4.7–6.0 kPa
HCO_3	22–26 mEq/L	1	22–26 mmol/L
O_2 saturation	≥ 95%	0.01	≥ 0.95
Blood urea nitrogen (BUN)	8–25 mg/dL	0.357	2.9–8.9 mmol/L
B-type natriuretic peptide (BNP)	0–99 pg/mL	1	0–99 ng/L
		0.289	0–29 pmol/L
B-type natriuretic peptide, N-terminal fragment (NT-proBNP)	0–299 pg/mL	1	0–299 ng/L
		0.118	0–35 pmol/L
BUN-to-creatinine ratio	10:1–20:1		40:1–100:1
C-peptide	0.51–2.70 ng/mL	331	170–894 pmol/L
		0.331	0.17–0.89 nmol/L
C-reactive protein	< 0.8 mg/dL	10	< 8 mg/L
CA-125	< 35 units/mL	1	< 35 kU/L
CA 15–3	< 30 units/mL	1	< 30 kU/L
CA 19–9	< 37 units/mL	1	< 37 kU/L
CA 27.29	< 38 units/mL	1	< 38 kU/L
Calcium			
Total	8.6–10.3 mg/dL	0.25	2.15–2.58 mmol/L
	4.3–5.16 mEq/L	0.50	2.15–2.58 mmol/L
Ionized	4.5–5.1 mg/dL	0.25	1.13–1.28 mmol/L

(*Continued*)

Laboratory Test	Conventional Units	Conversion Factor	Système International Units
	2.26–2.56 mEq/L	0.50	1.13–1.28 mmol/L
Carbamazepine, therapeutic	4–12 mg/L	4.23	17–51 µmol/L
Carboxyhemoglobin (nonsmoker)	< 2%	0.01	< 0.02
Carcinoembryonic antigen (CEA)			
Nonsmokers	< 2.5 ng/mL	1	< 2.5 mcg/L
Smokers	< 5 ng/mL	1	< 5 mcg/L
CD4 lymphocyte count	31%–61% of total lymphocytes	0.01	0.31–0.61 of total lymphocytes
CD8 lymphocyte count	18%–39% of total lymphocytes	0.01	0.18–0.39 of total lymphocytes
Cerebrospinal fluid (CSF)			
Pressure	75–175 mm H_2O	0.0098	0.74–1.72 kPa
Glucose	40–70 mg/dL	0.0555	2.2–3.9 mmol/L
Protein	15–45 mg/dL	0.01	0.15–0.45 g/L
White blood cell (WBC) count	< 10/mm^3	10^6	< 10 × 10^6/L
Ceruloplasmin	18–45 mg/dL	10	180–450 mg/L
Chloride	97–110 mEq/L	1	97–110 mmol/L
Cholesterol			
Desirable	< 200 mg/dL	0.0259	< 5.18 mmol/L
Borderline high	200–239 mg/dL	0.0259	5.18–6.19 mmol/L
High	≥ 240 mg/dL	0.0259	≥ 6.2 mmol/L
Chorionic gonadotropin (β-hCG)	< 5 mIU/mL	1	< 5 IU/L
Clozapine, minimum trough	300–350 ng/mL or mcg/L	3.06	918–1071 nmol/L
		0.00306	0.92–1.07 µmol/L
CO_2 content	22–30 mEq/L	1	22–30 mmol/L
Complement component 3 (C3)	70–160 mg/dL	0.01	0.70–1.60 g/L
Complement component 4 (C4)	20–40 mg/dL	0.01	0.20–0.40 g/L
Copper	70–150 mcg/dL	0.157	11–24 µmol/L
Cortisol (fasting, morning)	5–25 mcg/dL	27.6	138–690 nmol/L
Creatine kinase			
Male	30–200 IU/L	0.01667	0.50–3.33 µkat/L
Female	20–170 IU/L	0.01667	0.33–2.83 µkat/L
MB fraction	0–7 IU/L	0.01667	0.0–0.12 µkat/L
Creatinine clearance (CrCl)	85–135 mL/min/1.73 m^2	0.00963	0.82–1.30 mL/s/m^2
		0.01667	1.41–2.25 mL/s/1.73 m^2
Creatinine			
Male 4–20 years	0.2–1.0 mg/dL	88.4	18–88 µmol/L
Female 4–20 years	0.2–1.0 mg/dL	88.4	18–88 µmol/L
Male (adults)	0.7–1.3 mg/dL	88.4	62–115 µmol/L
Female (adults)	0.6–1.1 mg/dL	88.4	53–97 µmol/L
Cyclosporine			
Renal, cardiac, liver, or pancreatic transplant	100–400 ng/mL or mcg/L	0.832	83–333 nmol/L
Cryptococcal antigen	Negative		
D-dimers	< 250 ng/mL	1	< 250 mcg/L
Desipramine	75–300 ng/mL or mcg/L	3.75	281–1125 nmol/L
Dexamethasone suppression test (DST) (overnight), 8:00 am cortisol	< 5 mcg/dL	27.6	< 138 nmol/L
DHEAS (dehydroepiandrosterone sulfate)			
Male	170–670 mcg/dL	0.0272	4.6–18.2 µmol/L
Female			
Premenopausal	50–540 mcg/dL	0.0272	1.4–14.7 µmol/L
Postmenopausal	30–260 mcg/dL	0.0272	0.8–7.1 µmol/L
Digoxin, therapeutic (heart failure)	0.5–0.8 ng/mL or mcg/L	1.28	0.6–1.0 nmol/L
Therapeutic (atrial fibrillation)	0.8–2.0 ng/mL or mcg/L	1.28	1.0–2.6 nmol/L
Erythrocyte count (blood)			
See under red blood cell (RBC) count			
Erythrocyte sedimentation rate (ESR)			
Westergren			
Male	0–20 mm/h		
Female	0–30 mm/h		
Wintrobe			
Male	0–9 mm/h		
Female	0–15 mm/h		
Erythropoietin	2–25 mIU/mL	1	2–25 IU/L
Estradiol			
Male	10–36 pg/mL	3.67	37–132 pmol/L
Female	34–170 pg/mL	3.67	125–624 pmol/L
Ethanol, legal intoxication (depends on location)	≥ 50–100 mg/dL	0.217	≥10.9–21.7 mmol/L
	≥ 0.05–0.1%	217	≥10.9–21.7 mmol/L
Ethosuximide, therapeutic	40–100 mg/L or mcg/mL	7.08	283–708 µmol/L
Factor VIII or factor IX			
Severe hemophilia	< 1 IU/dL	0.01	< 0.01 IU/mL
Moderate hemophilia	1–5 IU/dL	0.01	0.01–0.05 IU/mL
Mild hemophilia	> 5 IU/dL	0.01	> 0.05 IU/mL
Usual adult levels	60 to 140 IU/dL	0.01	0.60–1.40 IU/mL
Ferritin			
Male	20–250 ng/mL	1	20–250 mcg/L
		2.25	45–562 pmol/L
Female	10–150 ng/mL	1	10–150 mcg/L
		2.25	22–337 pmol/L
Fibrin degradation products (FDP)	2–10 mg/L		
Fibrinogen	200–400 mg/dL	0.01	2.0–4.0 g/L
Folate (plasma)	3.1–12.4 ng/mL	2.266	7.0–28.1 nmol/L
Folate (RBC)	125–600 ng/mL	2.266	283–1,360 nmol/L
Follicle-stimulating hormone (FSH)			
Male	1–7 mIU/mL	1	1–7 IU/L
Female			
Follicular phase	1–9 mIU/mL	1	1–9 IU/L
Midcycle	6–26 mIU/mL	1	6–26 IU/L
Luteal phase	1–9 mIU/mL	1	1–9 IU/L
Postmenopausal	30–118 mIU/mL	1	30–118 IU/L
Free thyroxine index (FT_4I)	6.5–12.5		
Gamma glutamyltransferase (GGT)	0–30 U/L	0.01667	0–0.50 µkat/L
Gastrin (fasting)	0–130 pg/mL	1	0–130 ng/L
Gentamicin, therapeutic (traditional dosing)			
Peak	4–10 mg/L	2.09	8.4–21 µmol/L
Trough	≤ 2 mg/L	2.09	≤ 4.2 µmol/L
Globulin	2.3–3.5 g/dL	10	23–35 g/L
Glucose (fasting, plasma)	65–109 mg/dL	0.0555	3.6–6.0 mmol/L
Glucose, 2-hour postprandial blood (PPBG)	< 140 mg/dL	0.0555	< 7.8 mmol/L
Granulocyte count	1.8–6.6 × 10^3/mm^3	10^6	1.8–6.6 × 10^9/L

(Continued on back inside cover)

Laboratory Test	Conventional Units	Conversion Factor	Système International Units
Growth hormone (fasting)			
Male	< 5 ng/mL	1	< 5 mcg/L
Female	< 10 ng/mL	1	< 10 mcg/L
Haptoglobin	60–270 mg/dL	0.01	0.6–2.7 g/L
Hepatitis B surface antigen, extracellular form (HBeAg)	Negative		
Hepatitis B surface antigen (HbsAg)	Negative		
Hepatitis B virus (HBV) DNA	Negative		
Hematocrit			
Male	40.7%–50.3%	0.01	0.407–0.503
Female	36.1%–44.3%	0.01	0.361–0.443
Hemoglobin (blood)			
Male	13.8–17.2 g/dL	10	138–172 g/L
		0.621	8.56–10.68 mmol/L
Female	12.1–15.1 g/dL	10	121–151 g/L
		0.621	7.51–9.36 mmol/L
Hemoglobin A1c	4.0%–6.0%	0.01	0.04–0.06
		[a]	20–42 mmol/mol hemoglobin
Heparin			
Via protamine titration method	0.2–0.4 units/mL		
Via antifactor Xa assay	0.3–0.7 units/mL		
High-density lipoprotein (HDL) cholesterol	> 35 mg/dL	0.0259	> 0.91 mmol/L
Homocysteine	3.3–10.4 µmol/L		
Ibuprofen			
Therapeutic	10–50 mcg/mL	4.85	49–243 µmol/L
Toxic	≥ 100 mcg/mL	4.85	≥ 485 µmol/L
Imipramine, therapeutic	100–300 ng/mL or mcg/L	3.57	357–1071 nmol/L
Immunoglobulin A (IgA)	85–385 mg/dL	0.01	0.85–3.85 g/L
Immunoglobulin G (IgG)	565–1765 mg/dL	0.01	5.65–17.65 g/L
Immunoglobulin M (IgM)	53–375 mg/dL	0.01	0.53–3.75 g/L
Insulin (fasting)	2–20 µU/mL or mU/L	7.175	14.3–143.5 pmol/L
International normalized ratio (INR), therapeutic	2.0–3.0 (2.5–3.5 for some indications)		
Iron			
Male	45–160 mcg/dL	0.179	8.1–28.6 µmol/L
Female	30–160 mcg/dL	0.179	5.4–28.6 µmol/L
Iron-binding capacity (total)	220–420 mcg/dL	0.179	39.4–75.2 µmol/L
Iron saturation	15%–50%	0.01	0.15–0.50
Itraconazole			
Trough, therapeutic	0.5–1 mcg/mL or mg/L	1.42	0.7–1.4 µmol/L
Lactate (plasma)	0.7–2.1 mEq/L	1	0.7–2.1 mmol/L
	6.3–18.9 mg/dL	0.111	0.7–2.1 mmol/L
Lactate dehydrogenase (LDH)	100–250 IU/L	0.01667	1.67–4.17 µkat/L
Lead	< 25 mcg/dL	0.0483	< 1.21 µmol/L
Leukocyte count	3.8–9.8 × 10^3/mm^3	10^6	3.8–9.8 × 10^9/L
Lidocaine, therapeutic	1.5–6.0 mcg/mL or mg/L	4.27	6.4–25.6 µmol/L
Lipase	< 100 IU/L	0.01667	1.67 µkat/L
Lithium, therapeutic	0.5–1.25 mEq/L	1	0.5–1.25 mmol/L
Low-density lipoprotein (LDL) cholesterol			
Target for very high-risk patients	< 70 mg/dL	0.0259	< 1.81 mmol/L
Desirable LDL level and target for high-risk patients (optimal)	< 100 mg/dL	0.0259	< 2.59 mmol/L
Above desirable	100–129 mg/dL	0.0259	2.59–3.34 mmol/L
Borderline high risk	130–159 mg/dL	0.0259	3.36–4.11 mmol/L
High risk	160–189 mg/dL	0.0259	4.14–4.89 mmol/L
Very high risk	≥ 190 mg/dL	0.0259	≥ 4.91 mmol/L
Luteinizing hormone (LH)			
Male	1–8 mIU/mL	1	1–8 IU/L
Female			
Follicular phase	1–12 mIU/mL	1	1–12 IU/L
Midcycle	16–104 mIU/mL	1	16–104 IU/L
Luteal phase	1–12 mIU/mL	1	1–12 IU/L
Postmenopausal	16–66 mIU/mL	1	16–66 IU/L
Lymphocyte count	1.2–3.3 × 10^3/mm^3	10^6	1.2–3.3 × 10^9/L
Magnesium	1.3–2.2 mEq/L	0.5	0.65–1.10 mmol/L
	1.58–2.68 mg/dL	0.411	0.65–1.10 mmol/L
Mean corpuscular volume (MCV)	80.0–97.6 $µm^3$	1	80.0–97.6 fL
Mononuclear cell count	0.2–0.7 × 10^3/mm^3	10^6	0.2–0.7 × 10^9/L
Nortriptyline, therapeutic	50–150 ng/mL or mcg/L	3.797	190–570 nmol/L
Osmolality (serum)	275–300 mOsm/kg	1	275–300 mmol/kg
Osmolality (urine)	250–900 mOsm/kg	1	250–900 mmol/kg
Parathyroid hormone (PTH), intact	10–60 pg/mL or ng/L	0.107	1.1–6.4 pmol/L
PTH, N-terminal	8–24 pg/mL or ng/L		
PTH, C-terminal	50–330 pg/mL or ng/L		
Phenobarbital, therapeutic	15–40 mcg/mL or mg/L	4.31	65–172 µmol/L
Phenytoin, therapeutic (total concentration)	10–20 mcg/mL or mg/L	3.96	40–79 µmol/L
Phosphate	2.5–4.5 mg/dL	0.323	0.81–1.45 mmol/L
Platelet count	140–440 × 10^3/mm^3	10^6	140–440 × 10^9/L
Potassium (plasma)	3.3–4.9 mEq/L	1	3.3–4.9 mmol/L
Prealbumin (adult)	19.5–35.8 mg/dL	10	195–358 mg/L
Primidone, therapeutic	5–12 mcg/mL or mg/L	4.58	23–55 µmol/L
Procainamide, therapeutic	4–10 mcg/mL or mg/L	4.25	17–42 µmol/L
Progesterone			
Male	13–97 ng/dL	0.0318	0.4–3.1 nmol/L
Female			
Follicular phase	15–70 ng/dL	0.0318	0.5–2.2 nmol/L
Luteal phase	200–2500 ng/dL	0.0318	6.4–79.5 nmol/L
Prolactin	< 20 ng/mL	1	< 20 mcg/L
		43.5	< 870 pmol/L
Prostate-specific antigen (PSA)	< 4 ng/mL	1	< 4 mcg/L
Protein, total	6.0–8.0 g/dL	10	60–80 g/L
Prothrombin time (PT)	10–12 seconds		
Quinidine, therapeutic	2–5 mcg/mL or mg/L	3.08	6.2–15.4 µmol/L
Radioactive iodine uptake (RAIU)	< 6% in 2 hours		
Red blood cell (RBC) count (blood)			
Male	4–6.2 × 10^6/mm^3	10^6	4–6.2 × 10^{12}/L
Female	4–6.2 × 10^6/mm^3	10^6	4–6.2 × 10^{12}/L
Pregnant			
Trimester 1	4–5 × 10^6/mm^3	10^6	4–5 × 10^{12}/L
Trimester 2	3.2–4.5 × 10^6/mm^3	10^6	3.2–4.5 × 10^{12}/L
Trimester 3	3–4.9 × 10^6/mm^3	10^6	3–4.9 × 10^{12}/L
Postpartum	3.2–5 × 10^6/mm^3	10^6	3.2–5 × 10^{12}/L

(*Continued*)

Laboratory Test	Conventional Units	Conversion Factor	Système International Units
Red blood cell distribution width (RDW)	11.5%–14.5%	0.01	0.115–0.145
Reticulocyte count			
Male	0.5%–1.5% of total RBC count	0.01	0.005–0.015
Female	0.5%–2.5% of total RBC count	0.01	0.005–0.025
Retinol-binding protein (RBP)	2.7–7.6 mg/dL	10	27–76 mg/L
Rheumatoid factor (RF) titer	Negative		
Salicylate, therapeutic	150–300 mcg/mL or mg/L	0.00724	1.09–2.17 mmol/L
	15–30 mg/dL	0.0724	1.09–2.17 mmol/L
Sirolimus (renal transplant)	4–20 ng/mL	1	4–20 mcg/L
		1.094	4–22 nmol/L
Sodium	135–145 mEq/L	1	135–145 mmol/L
Tacrolimus			
Renal, cardiac, liver, or pancreatic transplant	5–20 ng/mL	1	5–20 mcg/L
		1.24	6.2–24.8 nmol/L
Testosterone (total)			
Men	300–950 ng/dL	0.0347	10.4–33.0 nmol/L
Women	20–80 ng/dL	0.0347	0.7–2.8 nmol/L
Testosterone (free)			
Men	9–30 ng/dL	0.0347	0.31–1.04 nmol/L
Women	0.3–1.9 ng/dL	0.0347	0.01–0.07 nmol/L
Theophylline			
Therapeutic	5–15 mcg/mL or mg/L	5.55	28–83 µmol/L
Toxic	20 mcg/mL or mg/L or more	5.55	111 µmol/L or more
Thiocyanate	Toxic level unclear; units are mcg/mL or mg/L	17.2	µmol/L
Thrombin time	20–24 seconds		
Thyroglobulin	< 42 ng/mL	1	< 42 mcg/L
Thyroglobulin antibodies	Negative		
Thyroxine-binding globulin (TBG)	1.2–2.5 mg/dL	10	12–25 mcg/L
Thyroid-stimulating hormone (TSH)	0.35–6.20 µIU/mL	1	0.35–6.20 mIU/L
TSH receptor antibodies (TSHRab)	0–1 units/mL		0–1 kU/L
Thyroxine (T_4)			
Total	4.5–12.0 mcg/dL	12.87	58–154 nmol/L
Free	0.7–1.9 ng/dL	12.87	9.0–24.5 pmol/L
Thyroxine index, free (FT_4I)	6.5–12.5		
TIBC—see Iron binding capacity (total)			
Tobramycin, therapeutic			
Peak	4–10 mcg/mL or mg/L	2.14	8.6–21.4 µmol/L
Trough	≤ 2 mcg/mL or mg/L	2.14	≤ 4.3 µmol/L
Transferrin	200–430 mg/dL	0.01	2.0–4.3 g/L
Transferrin saturation	30%–50%	0.01	0.30–0.50
Triglycerides (fasting)	< 160 mg/dL	0.0113	< 1.81 mmol/L
Triiodothyronine (T_3)	45–132 ng/dL	0.0154	0.69–2.03 nmol/L
Triiodothyronine (T_3) resin uptake	25%–35%		
Uric acid	3–8 mg/dL	59.48	178–476 µmol/L
Urinalysis (urine)			
pH	4.8–8.0		
Specific gravity	1.005–1.030		
Protein	Negative		
Glucose	Negative		
Ketones	Negative		
RBC	1–2 per low-power field		
WBC	< 5 per low-power field		
Valproic acid, therapeutic	50–100 mcg/mL or mg/L	6.93	346–693 µmol/L
Vancomycin, therapeutic			
Peak	20–40 mcg/mL or mg/L	0.690	14–28 µmol/L
Trough	10–20 mcg/mL or mg/L	0.690	7–14 µmol/L
Trough for central nervous system infections	15–20 mcg/mL or mg/L	0.690	10–14 µmol/L
Vitamin A (retinol)	30–95 mcg/dL	0.0349	1.05–3.32 µmol/L
Vitamin B_{12}	180–1000 pg/mL	0.738	133–738 pmol/L
Vitamin D_3, 1,25-dihydroxy	20–76 pg/mL	2.4	48–182 pmol/L
Vitamin D_3, 25-hydroxy	10–50 ng/mL	2.496	25–125 nmol/L
Vitamin E (*α*-tocopherol)	0.5–2.0 mg/dL	23.22	12–46 µmol/L
WBC count	4–10 × 10^3/mm^3	10^6	4–10 × 10^9/L
WBC differential (peripheral blood)			
Polymorphonuclear neutrophils (PMNs)	50%–65%	0.01	0.50–0.65
Bands	0%–5%	0.01	0–0.05
Eosinophils	0%–3%	0.01	0–0.03
Basophils	1%–3%	0.01	0.01–0.03
Lymphocytes	25%–35%	0.01	0.25–0.35
Monocytes	2%–6%	0.01	0.02–0.06
WBC differential (bone marrow)			
PMNs	3%–11%	0.01	0.03–0.11
Bands	9%–15%	0.01	0.09–0.15
Metamyelocytes	9%–25%	0.01	0.09–0.25
Myelocytes	8%–16%	0.01	0.08–0.16
Promyelocytes	1%–8%	0.01	0.01–0.08
Myeloblasts	0%–5%	0.01	0–0.05
Eosinophils	1%–5%	0.01	0.01–0.05
Basophils	0%–1%	0.01	0–0.01
Lymphocytes	11%–23%	0.01	0.11–0.23
Monocytes	0%–1%	0.01	0–0.01
Zinc	60–150 mcg/dL	0.153	9.2–23.0 µmol/L

[a]Hemoglobin A1c (mmol/mol hemoglobin) = (Hemoglobin A1c (%) – 2.15) × 10.929.

References:

Medscape. Brain-Type Natriuretic Peptide (BNP). http://emedicine.medscape.com/article/2087425-overview. Accessed October 26, 2014.

Jacobs DS, Oxley DK, DeMott WR (eds.). (2001) Laboratory Test Handbook (5th ed.). Hudson OH: Lexi-Comp, Inc.

Young DS, Huth EJ (eds.). (1998) SI Units for Clinical Measurement. Philadelphia, PA: American College of Physicians. Reviewed and updated by Edward W. Randell.